

Immunity, Hypoxia and Metabolism - the ménage à trois of cancer: implications for immunotherapy

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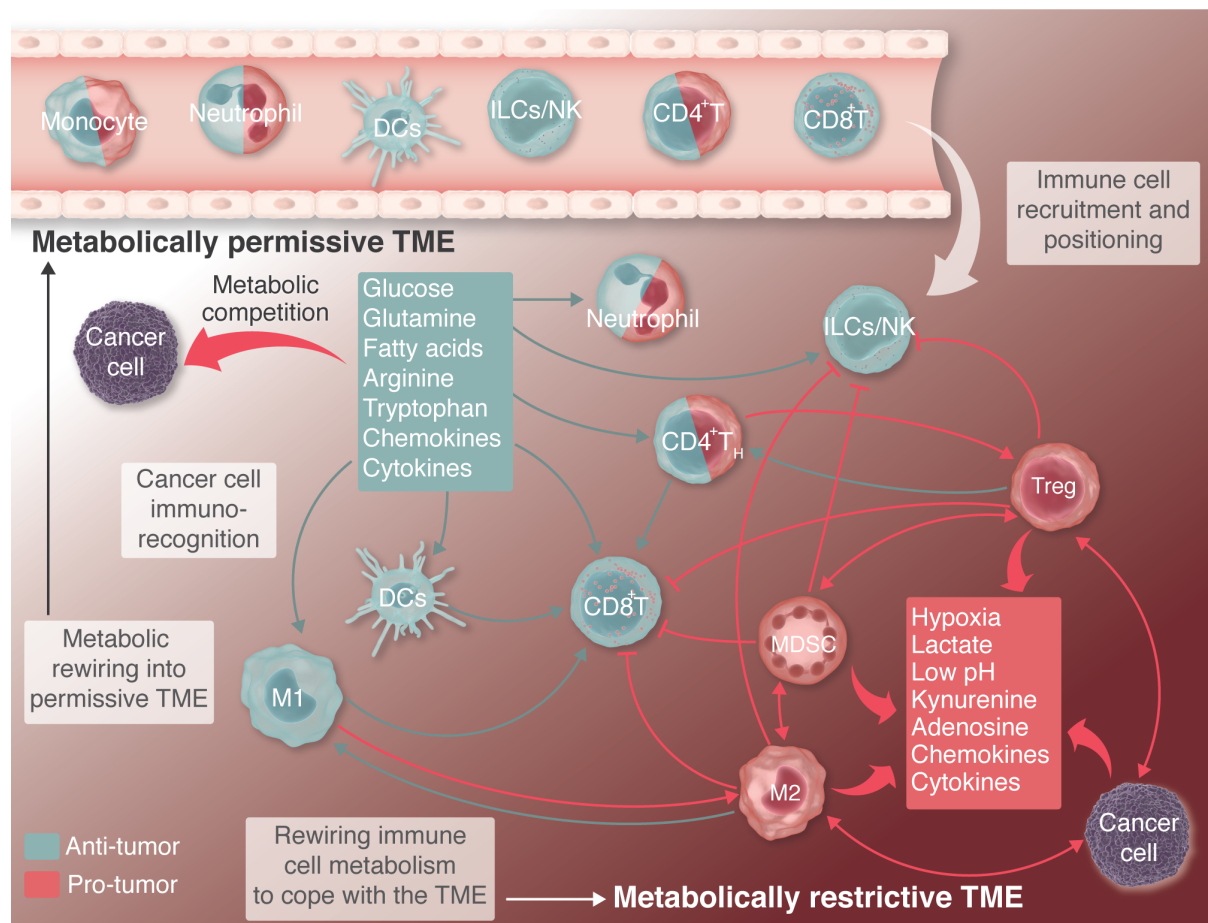
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Abstract

It is generally accepted that metabolism is able to shape the immune response. Only recently we are gaining awareness that the metabolic crosstalk between different tumor compartments strongly contributes to the harsh tumor microenvironment (TME) and ultimately impairs immune cell fitness and effector functions. The major aims of this review are: *i)* to provide an overview on the immune system in cancer; *ii)* to position oxygen shortage and metabolic competition as the ground of a restrictive TME and as important players in the anti-tumor immune response; *iii)* to define how immunotherapies affect hypoxia/oxygen-delivery and the metabolic landscape of the tumor and *iv)* vice versa, how oxygen and metabolites within the TME impinge on the success of immunotherapies. By analyzing preclinical and clinical endeavors, we will discuss how a metabolic characterization of the TME can identify novel targets and signatures that could be exploited in combination with standard immunotherapies and can help to predict the benefit of new and traditional immunotherapeutic drugs.

Graphical abstract



Call-out box for clinicians

Metabolism strongly shapes the interplay between cancer cells and immune cells, modulating the anti-tumor immune response. Most cancer cells adopt glycolytic metabolism with subsequent production of lactate and acidification of the tumor microenvironment (TME), which is associated with several parameters of aggressiveness, including immune evasion. The similarities in the metabolic pathways between cancer cells and several anti-tumor immune cells promote the establishment of a harsh metabolic competition in the TME and also pose some challenges to the use of metabolic targets in the clinic. Moreover, cancer cell metabolic changes can alter the expression of immune checkpoint proteins, which can either be stimulatory (e.g. CD40L) or inhibitory (e.g. PD-L1) and could contribute to cancer cell evasion from the immune system. Immune checkpoint inhibitors (ICIs) have been highly investigated in recent years, with the use of antibodies that block T cell co-inhibitory receptors or ligands. Among them, CTLA4, PD-1, and PD-L1 are the most explored across different

cancer types, including advanced melanoma, non–small cell lung carcinoma, renal cell carcinoma, bladder cancer and lymphoma.

I. Intertwined relationship between inflammation, hypoxia and metabolism in the tumor

Tumors are not only composed of cancer cells but also of the tumor microenvironment (TME), which comprises tumor-associated stromal cells (namely tumor-infiltrating immune cells, cancer-associated fibroblasts (CAFs) and endothelial cells), the extracellular matrix and a wide range of metabolites and cytokines. The TME represents most of the tumor mass and actively participates in tumorigenesis (441). Immune cells engage the TME since the early beginning of tumorigenesis. Tumors evolve through different phases that profoundly impact the recruitment and phenotype of tumor-infiltrating immune cells (section II). In turn, the dynamic tumor immune landscape deeply influences tumor progression, dissemination and response to therapy (sections III and VIII-X). Besides immune cells, CAFs are a key component of the TME and, in most cases but not all, they have pro-tumorigenic and immunosuppressive properties. A detailed analysis of this population is out of the scope of this review and, therefore, we refer the interested readers to other extensive recent reviews (74, 123, 337).

Blood vessels provide oxygen and nutrients, remove byproducts of cellular metabolism and are one of the main transport routes for immune cells and disseminating cancer cells. As tumors grow, pre-existing blood vessels fail to sufficiently perfuse the tumor. Consequently, oxygen levels drop (ranging from nearly anoxia to 8% O₂ in the most oxygenated areas) and an hypoxic and nutrient-poor environment is established where metabolic byproducts and immunosuppressive modulators accumulate (98). Hypoxia is rapidly sensed by the O₂/prolyl hydroxylases (PHD)/Von Hippel Lindau (VHL) axis, which induces the stabilization of the α subunit of hypoxia inducible factors (HIF-1 α or HIF-2 α) and the subsequent activation of a gene signature that orchestrates the cellular adaptation to hypoxia (section V) (532). Hypoxia triggers angiogenesis, namely the formation of new blood vessels, rewires cell metabolism and modulates the expression of several immunomodulatory molecules, thereby shaping immune cell infiltration and phenotype (161, 532, 563). Importantly, since HIFs can be stabilized by O₂-independent stimuli and immune cells are also sensitive to other hypoxia-driven signals (i.e. low pH, cytokines and nutrient fluctuations), the intrinsic effect of HIF-1 α does not always meet the global effect of hypoxia. Thus, the integration of HIF-mediated responses together with other hypoxia-driven signals and intercellular crosstalks are key to understand the biology of immune cells in hypoxia (section V).

In the past decade it has become evident that immune cell phenotypes are linked to distinct metabolic profiles and that interfering with metabolism can profoundly impact immune cell function. Moreover, the nutrient scarcity in some areas of the TME imposes a harsh metabolic competition that, together with tumor acidosis and the build-up of metabolic byproducts, further impact the metabolic and functional reprogramming of cancer cells and tumor-associated stromal cells (sections VI-IX) (116). Thus, hypoxic areas can be regarded as metabolic niches within the tumor that strongly fine-tune the tumor-associated immune response.

Numerous studies have been carried out aiming to reveal correlations between immune cell infiltration and patient prognosis. However, it is becoming clear that **i)** the overall number of tumor-infiltrating immune cells does not always offer a precise indication of disease outcome, **ii)** the phenotype of immune cells can overrule their abundance, **iii)** positioning of immune cell subsets in specific niches can actually provide a better tool to predict progression and therapy response (17, 54, 99, 159, 241-243, 402, 702, 761, 786, 794). The segregation of distinct immune cell subsets between different tumor niches also suggests that their localization and phenotype is dictated by a match between their metabolic demands, oxygen levels, nutrient availability and cytokine composition (section V) (17, 54, 242, 243, 379, 402, 786, 794). In sum, it is not the cell type but rather the specific immune skewing and its localization what is important to define disease outcome and progression. With this regard, although we are well aware that other components (i.e., antigenicity of the tumor or organ-specific cues (616)) can participate to this fate, we believe that the metabolic imprinting of the niche where the immune cells are located will emphasize their anti-tumor or pro-tumor functions, leading to the need of better defining the “metabolic immune niches” of the tumor.

Overall, cancer cell escape from innate and adaptive immunity as well as the success of anti-cancer therapies are widely influenced by hypoxia and cell metabolism and, therefore, to unravel how these processes control immune cell activation and differentiation in the TME deserve much more attention. Starting from a general overview on the role of the immune system in cancer (section II), its impact on the success of conventional therapies (section III) and how to exploit the reactivation of immune responses for therapeutic purposes (section IV, VIII-X), in this review we will surf on the wave of how hypoxic and metabolic changes within the TME impact on the overall immune landscape and

fitness (sections V-VII), how they affect the success of immunotherapeutic treatments and how targeting hypoxia and metabolism may sensitize refractory tumors to immunotherapy (sections VIII and IX).

II. The immune system in cancer

Whether the immune system is capable of controlling the development of malignant tumors has been one of the most controversial questions in Immunology. Macfarlane Burnet and Lewis Thomas first proposed the concept of cancer immunosurveillance, that is, that lymphocytes could recognize and eliminate nascent cancer cells and, therefore, that the immune system actively prevents tumor formation (76, 691). However, this concept remained a longstanding debate for several decades due to the lack of substantial experimental evidence supporting their hypothesis. Importantly, the immunosurveillance theory failed to explain why some tumors undergo immune escape and become resistant to elimination by the immune system. Later on, Robert Schreiber and colleagues embedded immunosurveillance in a broader concept termed the cancer immunoediting theory, which encompasses the dual host-protecting and tumor-sculpting effects of the immune system on tumor development (192). The cancer immunoediting theory postulates that, in cases which immunosurveillance is not successful, the immune system favors the prevalence of non-antigenic cancer cells with an enhanced ability to survive and to evade the immune system recognition. Besides this, inflammation may promote cell transformation as, in fact, 25% of cancer cases are associated with chronic inflammation of diverse origins (146, 201).

The immune system requires several steps to initiate and amplify anti-tumor immunity and all these steps together are known as the anti-tumor immune cycle (121). This cycle starts with the release of neo-antigens from dead or dying cancer cells, which are captured and processed by antigen-presenting cells (APCs) for presentation or cross-presentation on MHC-II or MHC-I molecules, respectively. After loaded with antigens, APCs migrate to the draining lymph nodes to prime and activate T cells. Antigen-educated T cells then exit the lymph node and infiltrate into the tumor. Tumor antigen-specific CD8⁺ T cells (or CTLs) can recognize cancer cells through TCR-MHC-I signal. In addition, tumor antigen-specific CD4⁺ T cells also exert immune responses by communicating with APCs

residing in the tumors. Upon recognition of cancer cells, CTLs kill cancer cells and release effector molecules to restrain tumor growth. These processes can release more tumor-associated antigens to enhance the anti-tumor immune responses and amplify the anti-tumor immune cycle.

Nowadays it is conceived that different subsets of immune cells can exert pro- or anti-tumor roles and that the skewing towards these opposing phenotypes is susceptible to environmental stimuli within the niche they occupy (*Figure 1*). Thus, identifying the functions and effects of different tumor-infiltrating immune cells during tumorigenesis and understanding the mechanisms underlying their abundance, distribution and phenotypes are key to elucidate how the immune system contributes to the clinical therapeutic outcomes and to envisage strategies to favor an anti-tumor immune response.

II.I The innate immune system in cancer

The innate immune system comprises macrophages, dendritic cells, neutrophils, MDSCs and, although wrapped in some controversy, innate lymphoid cells (ILCs). In the context of cancer, the innate immune system is quickly recruited to the nascent tumor, where it recognizes damage-associated molecular patterns (DAMPs) through pattern recognition receptors (PPRs) and, in turn, initiates and shapes the actions of the adaptive immune system. Therefore, the activation of innate immune system and the coordination between innate and adaptive immune cells are critical to launch efficient and effective immune responses against cancer, tissue damage and infections. Nevertheless, the innate immune system can also promote tumor initiation due to its ability to induce inflammatory responses. Here we will summarize the major types of innate immune cells and their contribution in tumor progression and anti-tumor immunity.

II.I.I Macrophages in cancer

Macrophages are very plastic cells display a wide range of phenotypes in response to the environmental stimuli they receive (497). The two extremes are represented by M1 or classically activated macrophages and M2 or alternatively activated macrophages, arising from stimulation with LPS and IFN- γ or with IL-4, respectively (497) (*Figure 1*). While long-lived tissue-resident macrophages arise from embryonic precursors, the majority of tumor-associated macrophages

(TAMs) differentiate from circulating monocytes (490). STAT1 and STAT6 are necessary for the polarization into M1 and M2 macrophages, respectively (497).

GM-CSF, IFN- γ , TNF- α , TGF- β and TLR agonists typically induce macrophage differentiation or polarization into M1-like macrophages. M1-like macrophages can produce inflammatory cytokines (i.e. IL-1, IL-6, IL-12 and TNF- α) and effector molecules (i.e. iNOS/NOS2) and efficiently present antigens to T cells (*Figure 1*) (497). Thus, M1-like macrophages can promote anti-tumor T_H1 and T_H17 immune responses. Moreover, IFN- γ triggers the tumoricidal activity and further induces secretion of CXCL9 and CXCL10 by TAMs, which support the recruitment of cytotoxic CD8⁺ T cells and halt tumor progression. On the other hand, IL-4, IL-13, IL-10 and M-CSF typically induce macrophage differentiation or polarization into M2-like macrophages. M2-like macrophages express higher levels of anti-inflammatory cytokines (i.e. IL-10, IL-6, TGF- β), scavenging receptors (CD206, CD204), pro-angiogenic molecules (VEGF-A) and proteases (MMP9), which allow them to promote T_H2 immune responses (*Figure 1*). Whereas in the context of inflammation M2 macrophages serve to maintain homeostasis and promote tissue repair, in the tumor context they favor immune escape, tumor growth and metastasis.

In tumors, cancer cells produce various cytokines and chemokines, such as colony-stimulating factor 1 (CSF1), VEGF-A, CCL2, and CXCL12, to recruit macrophages (687). Recruited macrophages in the TME tend to polarize into M2-like or mixed M1/M2 phenotypes, supporting angiogenesis, tumor progression and metastasis. The pro-angiogenic functions of TAMs and a subset of perivascular TIE2⁺ monocytes and macrophages are carried out, in part, by the release of VEGF-A (162, 402, 675) and several proteases, including matrix metalloproteinases and cathepsin, which degrade the extracellular matrix and increase VEGF-A bioavailability (107, 189, 258, 334). TAMs can suppress CD8⁺ T cell infiltration and cytotoxicity through the expression of inhibitory ligands (i.e. PD-L1 and PD-L2 (371, 374)), ARG1 or NOS2 activity (186, 588-591, 684) and the CCL22-mediated recruitment of T_{regs} (153). Importantly, hypoxia fine-tunes the M2 phenotype of macrophages (384) and accumulation of macrophages in hypoxia promotes their pro-angiogenic and T cell suppressing capacity (99).

High density of TAMs in tumors is generally considered to associate with poor clinical survival in human cancer patients (794, 797). However, in some cases such as in colorectal cancer high TAM density correlates with good prognosis ((70) and references therein). This apparent discrepancy illustrates that, as introduced above, the sublocalization of macrophages within different tumor niches may account for a pro- or an anti-tumor function (99, 104, 489, 786). In this line, re-educating TAMs to acquire M1-like phenotype has been suggested to be an attractive strategy to alleviate the immunosuppressive features of the TME and lead to tumor regression in pre-clinical models.

II.I.II Dendritic cells in cancer

Tumor-infiltrating dendritic cells (TIDCs) capture and process tumor-associated antigens from dying cancer cells. Matured TIDCs then migrate to draining lymph nodes, where they prime and activate T cells (121).

There are two major subsets of DCs in the TME, plasmacytoid DCs (pDCs) and conventional DCs (cDCs), which derive from the common DC progenitor (CDP) but differ in morphology and functions (*Figure 1*) (459). pDCs were originally described to respond to viral infections by the production of type I interferon. In the tumor context pDCs support T_{regs} function via Sema4A and IDO production, among others, and thus are considered to be immunosuppressive and promote tumor progression and metastasis ((168, 391, 647), reviewed in (474)), although they have been less studied than cDCs. FLT3L and GM-CSF participate in the differentiation of both cDC1 and cDC2. cDCs can be further divided into cDC1 and cDC2 based on their functions and surface marker expression pattern (136, 459). cDC1 express XCR1 and CD8 α in the lymphoid organs or CD103 within peripheral tissues and require the transcription factors IRF8, BATF3, and ID2 for their development (136, 459, 496). On the other hand, cDC2 express CD11b and SIRP α , and require the transcription factor IRF4, ZEB2 and Notch2 for their development (136, 459, 496) (*Figure 1*). cDC1 are necessary to elicit an MHC-I-mediated anti-tumor CD8 $^{+}$ T cell response and secrete IL-12 to support T cell effector functions, while cDC2 seem to participate in the MHC-II-mediated activation of CD4 $^{+}$ T cells, although their role in tumor development is still less studied (302, 332). In addition, cDC1 attract CD8 $^{+}$ T cells through production of CXCL9 and CXCL10 (671). It has been recently shown that CCL4 production

by cancer cells is required for the infiltration of anti-tumor cDC1s and CD8⁺ T cells (670). Moreover, prostaglandin E2 production can impair the recruitment of cDC1s into tumors by impairing natural killer (NK) cell-mediated CCL5 production (65). These findings reveal the critical role of cDC1s on tumor growth control.

In the context of immunotherapy, cDC1s are required to promote anti-tumor effects upon PD-1 blockade and efficient adoptive T cell transfer therapy (72, 615, 618, 671). Moreover, the efficiency of cDC1 or cDC2 vaccination in murine tumor models depends on their immune contexture. While cDC1 vaccination enhances CD8⁺ T cell anti-tumor performance, vaccination with cDC2 enhanced T_H17 differentiation and the skewing of TAMs into an anti-tumor M1-like phenotype (383). Notably, the gene signatures of cDC1 positively correlate with survival of human cancer patients in different tumor types, including, breast cancer, head and neck squamous cell carcinoma, and lung adenocarcinoma (65). More studies are required to describe the actual role of cDC2 in tumor development.

II.I.III Neutrophils and myeloid derived suppressive cells (MDSCs) in cancer

Neutrophils are a subset of myeloid cells often referred to as polymorphonuclear granulocytes due to their lobulated nuclei and cytoplasmic granules. STAT3 is the main transcription factor governing neutrophil formation (539) (*Figure 1*). Tumor-derived factors stimulate granulopoiesis as well as neutrophil release from the bone marrow. Despite neutrophil maturation is normally completed inside the bone marrow, tumors can exert such pressure that undifferentiated immature progenitors are prematurely released (101, 132, 610, 735). MDSCs comprises a heterogeneous group of Gr1⁺ immature myeloid cells that exhibit immunosuppressive functions and are only found in pathological conditions such as chronic infection, autoimmunity and cancer (239, 376, 685) (*Figure 1*). MDSCs have been subdivided into two different subtypes based on their morphology: mononuclear MDSC (M-MDSC), which resemble monocytes and may give rise to TAMs (489), and polymorphonuclear MDSC (PMN-MDSC), which are similar to neutrophils (488). Importantly, the term “myeloid-derived suppressive cell” remains very controversial because it suggests that these cells can only be immunosuppressive, colliding with the dynamic nature of myeloid cells, and also due to the technical difficulties to unequivocally distinguish MDSC subsets from neutrophils, monocytes and TAMs

(685). For instance, the anti-Gr1 antibody used to define MDSCs recognizes both Ly-6G and Ly-6C antigens, which are also found on mature neutrophils (Ly-6G^{high} Ly-6C^{med}) and monocytes (Ly-6G^{low} Ly-6C^{med/high}); and some MDSCs express F4/80, like TAMs, or CSF1R, like monocytes (134, 685). Moreover, MDSCs share other surface molecules, intracellular proteins and strategies to promote immunosuppression with neutrophils, monocytes and TAMs (239, 556). In this review we will use the same nomenclature as in the original work cited.

Far from being static and short-lived cells after maturation, neutrophils are now regarded as environment-responding cells that can carry out both pro- and anti-tumor functions. Generally, it is believed that neutrophils oppose tumor growth in early stages but, as tumors progress and under certain therapies, tend to support tumor growth and metastasis ((257, 472) and reviewed in (134)). Similar to other myeloid cells, intratumoral neutrophils can be divided between anti-tumor “N1-like” and pro-tumor “N2-like” neutrophils (*Figure 1*). IFN- β and HGF support the anti-tumor roles of N1 neutrophils (14, 220, 323, 772), while TGF- β and G-CSF are the main cytokines supporting the pro-tumor roles of N2 neutrophils (233, 735). In this line, circulating neutrophils in cancer can be divided into high density anti-tumor neutrophils and low density pro-tumor neutrophils and MDSCs (610). More evidence is required to better define these polarization states and to clarify if they really represent two phenotypes of mature neutrophils or if they refer to rather immature cells.

Neutrophils play a key tumor-promoting role in models of inflammation-induced carcinogenesis (201, 327, 646). MDSCs and neutrophils continuously produce reactive oxygen species (O₂⁻, H₂O₂, ONOO⁻) and nitric oxide (NO) that hinder T cell infiltration and activation and lead to T cell apoptosis (132, 478) high levels of ARG1, which promotes T cell cycle arrest by depleting L-arginine in the TME (588-591). Moreover, MDSCs express immunosuppressive cytokines (i.e. IL-10 and TGF- β) and PD-L1 to inhibit effector T cells function, induce T_{regs} activation and promote NK cell anergy (403, 511, 537) and facilitate T_{regs} tumor infiltration in a CCR5-dependent manner (633). MDSCs and neutrophils promote cancer cell proliferation and angiogenesis via the secretion of pro-angiogenic molecules, such as VEGF-A, FGF and Bv8 (103, 654, 655) and matrix remodeling enzymes (i.e. elastase and MMP9) (305, 518). Finally, neutrophils can form neutrophil extracellular traps (NETs), a mixture of DNA, histones and anti-microbial peptides that trap and kill microorganisms and that have

been associated with several pro-tumor mechanisms (reviewed in (139)). In contrast, anti-tumor and anti-metastatic neutrophils can induce cancer cell killing in a H₂O₂ and NO-mediated mechanism (220, 263) and secrete TNF- α (14).

The presence of circulating or tumor-associated neutrophils (TANs) is associated to poor prognosis (649, 688) and poor therapy outcome (257) in bronchoalveolar carcinoma (46), glioma (230), metastatic melanoma (634), metastatic renal cell carcinoma (26), and pancreatic cancer (579). In contrast, elevated numbers of TANs in patients with advanced gastric carcinoma correlated with a low mortality rate (96). Targeting the recruitment of pro-tumor neutrophils or MDSCs or promoting neutrophil anti-tumor functions could be an attractive strategy for alleviating anti-tumor immunity.

II.I.IV Innate lymphoid cells in cancer

Innate lymphoid cells (ILCs) are a recently discovered group of immune cells with some analogy to T cell subsets at the functional level. Unlike T cells, ILCs are activated by cytokines and as a result of a balance of activating and inhibitory signals in an antigen-independent manner since they do not express antigen receptors (TCR/CD3⁻). Based on the expression of a particular set of surface markers and transcription factors as well as functional features, ILCs can be divided into three subtypes: conventional NK/ILC1s, ILC2s and ILC3s (194, 669) (*Figure 1*). The ILC subtypes fulfill non-redundant functions and play a pivotal role in the pathogenesis of inflammatory diseases. However, recent findings indicate an ambiguous role for different ILCs in the context of cancer.

II.I.IV.I Group 1 ILCs in cancer

Group1 ILCs include conventional natural killer (NK) cells and non-NK ILC1s. Group 1 ILCs are characterized by constitutive expression of the transcription factor T-bet and the release of T_H1 cytokines such as IFN- γ and TNF- α in response to IL-12, IL-15 and IL-18 (52, 235). ILC1s can be further subdivided based on the expression of the IL-7 receptor (CD127), T-bet, and Eomes (665) (*Figure 1*).

NK cells can be identified by the expression of the surface marker CD56 in humans, NK1.1⁺ in some murine strains (such as C57BL/6 but not in BALB/c), or NKp46⁺ in both species (86). NK cells possess unique cytotoxic functions and the ability to fight cancer cells without prior sensitization (19).

Whether an NK cell stays put or eliminates a target cell depends on the balance of signals coming from activating and inhibitory signals. NK cells can kill cells that downregulate inhibitory MHC class I molecules, including both cancer cells and non-transformed cells (731). Alternatively, NK cells attack cancer cells that still express MHC-I but express enough stress ligands for activating NK cell activating receptors (108, 179, 574). The most thoroughly studied activating receptors in the context NK cell responses against malignant cells are NKG2D, the natural cytotoxicity receptors (NCRs), DNAM1 and CD16 (483). Mature NK cells are morphologically characterized as lymphocytes with large cytoplasmic granules that contain perforin (that causes membrane-disruption) as well as granzymes (a family of proteolytic enzymes) (734). Upon NK cell activation these granules are exocytosed and target cells are lysed (372). An alternative way of NK cell-mediated killing is executed by so-called death ligands on the NK cell surface, namely FAS ligand and TNF-related apoptosis-inducing ligand (TRAIL) (736), which leads to caspase-dependent apoptosis in target cells (662). In addition, activated NK cells can secrete cytokines and chemokines which then orchestrate the recruitment and the response of other cells of the innate and adaptive immune system (731). Several studies revealed a key role for NK cells in tumor immunosurveillance and limitation of metastasis in mice and humans (483). However, some tumors undertake several routes to escape from NK cell-mediated immunosurveillance. Noteworthy, if the tumor is not completely eradicated, NK cell-mediated killing will contribute to tumor editing and immune escape. Indeed, Balsamo et al. have demonstrated that after initial NK cell-mediated killing, the residual melanoma cells develop resistance to IL-2-activated NK cells. The resistance mechanism depends on NK cell-derived IFN- γ and involves upregulation of inhibitory HLA class I molecules as well as decreased expression of activating NKG2D ligands on melanoma cells (34).

In contrast to the well accepted anti-tumor role of conventional NK cells, a role for the involvement of non-NK cell ILC1s in tumor immunity is just emerging. Non-NK ILC1s have been reported to be anti-tumor based on their ability to secrete the effector cytokines IFN- γ and TNF- α in response to the anti-tumor cytokine IL-12 (91, 357, 705). Both cytokines induce strong anti-tumor immune responses via enhanced recruitment and stimulation of other immune cells (84, 580, 754). Moreover, IFN- γ and TNF- α can lead to vessel growth inhibition (or disruption) and apoptosis of cancer cells, independent

of host immune cells (41, 71, 173, 180). On the other hand, IFN- γ and TNF- α can promote inflammation in murine models and these pro-inflammatory functions may foster tumor growth and the expression of growth factors and angiogenic molecules (31, 665, 745, 792). Recent studies revealed that tumor-derived TGF- β can promote the conversion of anti-tumor NK cells into ILC1s in a SMAD4-dependent manner, which, strikingly, resulted in pro-tumor and pro-metastatic effects (143, 244). Thus, although ILC1s seem to primarily inhibit tumor formation and progression, this effect might be context and tumor-dependent.

II.IV.II Group 2 ILCs in cancer

ILC2s protect against infections with helminths and viruses in tissues with a barrier function like the gut, lung and skin (594). In addition, ILC2s are characterized by constitutive expression of the transcription factor GATA3 and secretion of the type 2 cytokines IL-5 and IL-13 in response to IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) (19, 194). Owing to the fact that type 2 cytokines create a TME that inhibits anti-tumor immunity, ILC2 are considered to be pro-tumorigenic (*Figure 1*). IL-13 drives polarization of tumor-associated macrophages towards an immunosuppressive M2 phenotype that fosters tumor progression, is also involved in generation of MDSCs and may support apoptosis resistance, proliferation and migration of carcinoma cells (278, 494). Noteworthy, ILC2-derived IL-13 is also a major driver of organ fibrosis, namely in the liver and lung, which predisposes for subsequent malignant transformation (283, 454). Further support for the tumor-promoting role of ILC2s comes from studies that identify ILC2s as a major source for the Th2 cytokine IL-4 (516, 551). Thus, ILC2-derived IL-4 secretion is likely to further promote tumor progression. In contrast, IL-5 secreted by ILC2 may prevent tumorigenesis indirectly via enhanced eosinophil recruitment (317). In general, intratumoral accumulation of eosinophils is correlated with an improved prognosis (425). Consequently, ILC2-derived IL-5 prevents pulmonary metastasis in the B16F10 melanoma model (317).

In summary, the existing experimental evidence indicates that ILC2-derived cytokines promote tumorigenesis, particularly in epithelial tissues with a barrier function, where ILC2s are abundantly present.

II.IV.III Group 3 ILCs in cancer

ILC3s depend on the transcription factor ROR γ t and secrete IL-17 and IL-22 in response to IL-23. ILC3s subsets are heterogeneous and are most abundantly found in mucosal layers and mucosa-associated lymphoid tissues, where they are crucial for mounting adequate immune responses against bacteria and fungi, as well as in orchestrating homeostasis and repair of epithelial barriers (75). However, ILC3s in the gut lung and skin have been shown to drive IL-23-mediated chronic inflammation. Murine ILC3s are further subcategorized by the surface expression of chemokine receptor CCR6 and the NCR NKp46 (669). The role of ILC3s in tumor immunity and tumorigenesis is debated controversially (*Figure 1*). Whereas some studies suggest anti-tumor activity, studies on tumors that are driven by inflammation indicate a pro-tumorigenic effect of ILC3s, which might reflect the heterogeneity of ILC3s subsets. NCR⁺ ILC3s are able to secrete a set of chemokines and pro-inflammatory cytokines that are likely to be involved in the formation of tertiary lymphoid structures and improved tumor immune surveillance in patients with non-small cell lung cancer (95). Moreover, in a model of IL-12-overexpressing melanoma, ILC3s showed anti-tumor functions in a mechanism independent of their signature cytokines (199). Instead, ILC3s fostered the expression of adhesion molecules in the tumor vasculature and the recruitment of other immune cells (199). On the other hand, based on the numerous reports that describe a tumor-promoting role for IL-23, ILC3s as downstream effectors are believed to be pro-tumorigenic in a IL-17 or IL-22-dependent manner (113, 310, 352).

In summary, the role of ILC3s in tumor initiation and progression remains ambiguous and incompletely understood. Moreover, it seems that the pro- or anti-tumor effects might be exerted by distinct ILC3 subsets in a cytokine-dependent or independent manner.

II.II The adaptive immune system in cancer

The adaptive immune system, including T cells and B cells, provides antigen-specific immune responses against tumors by recognizing tumor antigens presented on cancer cells or antigen-presenting cells (APCs) (77, 704). T cells are divided into subsets based on their T cell receptor (TCR) chain, co-receptor and cytokine expression profile. During development in the thymus, T cell

precursors commit into two T cell lineages, $\alpha\beta$ T cells or $\gamma\delta$ T cells, expressing different TCR chains. $\alpha\beta$ T cells (T cells from now on) are further subdivided into $CD4^+$ T cells and $CD8^+$ cytotoxic T cells (CTLs) according to their co-receptor expression. Activation of $CD4^+$ and $CD8^+$ T cells occurs upon TCR ligation to tumor antigens presented on major histocompatibility complex class II (MHC-II) and class I (MHC-I) molecules, respectively. MHC-II complexes are expressed by professional APCs, whereas MHC-I complexes are expressed by all nucleated cells. Influenced by the cytokine milieu, $CD4^+$ T cells differentiate into T_{H1} , T_{H2} , T_{H17} or T_{regs} subsets, which are controlled by distinct molecular programs and differ in their functions and cytokine expression profile (*Figure 1*). Although other helper T cell subsets (i.e. T_{H3} , T_{H9} , T_{H22}) have recently been discovered, their role in tumor biology is still unclear and thus will not be included in this review. After the primary immune response, most T cells undergo apoptosis to allow the resolution of the immune response. Nevertheless, a fraction of T cells remains and gives rise to memory T cells (553). Memory T cells respond faster to a second antigen exposure and can undergo proliferation and deploy their effector functions more effectively (326). In the last years, a new subtype of $CD8^+$ memory T cell has been discovered, resident memory T cells (T_{RM}), which holds a promising anti-tumor capacity (10, 248, 449). T_{RM} are long-lived non-circulating cells that reside in the tissue where they were originated. T_{RM} are characterized by CD69 and CD103 expression, respond faster to antigen re-exposure and have a superior cytotoxic capacity than other types of memory T cells (10, 326). In the clinical arena, using memory CTLs instead of naïve or effector CTLs holds promise for an improved and long-lasting anti-tumor effect that locally protects from recurrence (10, 57).

A detailed analysis of the current knowledge on B cells and $\gamma\delta$ T cells is out of the scope of this review. Thus, we refer the interested readers to other extensive recent reviews on B cells (622, 748) or $\gamma\delta$ T cells (658). In this section, we will focus on the tumor-promoting or tumoricidal effects of the distinct T cell subsets and we will describe different dysfunctional states that compromise T cell function.

II.II.I Type 1 T helper cells (T_{H1}) in cancer

Type 1 T helper cells (T_{H1}) promote host protective immunity against intracellular pathogens as well as malignant cells. T_{H1} cells express transcription factor T-bet and produce high amounts of IFN- γ , IL-2 and TNF- α in response to IL-12 (*Figure 1*). T-bet supports differentiation program and immune responses of T_{H1} cells, including macrophage activation, cell-mediated immunity and phagocyte-dependent protective responses. IFN- γ and TNF- α secreted by T_{H1} cells are also involved in anti-tumor and anti-angiogenic activities (144, 493, 568). In addition, IFN- γ and TNF- α are required for cytokine-mediated activation and regulation of tumor-specific CTLs (210) and are reported to induce cancer cell senescence (39). Intriguingly, IFN- γ also provides positive feedback mechanism to support T_{H1} cell differentiation and lineage stability by activating STAT1. STAT1-deficient mice decreased IFN- γ production and failed to reject immunogenic tumors. In contrast, STAT1-deficient mice increased T_{H2} polarization of CD4⁺ T cells (209, 339). Moreover, IFN- γ can antagonize the production of immunosuppressive cytokines, including TGF- β and IL-10, an action that has been considered to support anti-tumor immune responses (187, 198). In addition to their effect on immune and cancer cells, T_{H1} cells have recently been reported to support vascular normalization in tumor through secretion of IFN- γ (696). Thus, tumor-specific T_{H1} cells can restrain tumor progression (275).

II.II.II Type 2 T helper cells (T_{H2}) in cancer

T_{H2} cells support humoral immune responses and host immunity against extracellular pathogens and play a significant role in induction and persistence of allergic responses and asthma. T_{H2} cells express the transcription factor GATA3 and produce IL-4, IL-5 and IL-13 in response to IL-4 (*Figure 1*). In contrast to T_{H1} cells, cytokines produced by T_{H2} cells exhibit tumor-promoting activities. T_{H2} can induce T cell anergy, inhibit T cell mediated cytotoxicity and promote the immunosuppressive functions of other immune cells. In many tumor types, elevated IL-4 and IL-13 in the TME can polarize TAMs into M2 pro-tumor phenotype, which hampers anti-tumor immune responses, promoting stromal cell formation, angiogenesis and the secretion of immunosuppressive cytokines TGF- β and IL-10 (170, 656). Human clinical data indicated that higher intratumoral T_{H2} cell infiltration reduced patient survival rate in pancreatic cancer patients and other tumor types (159).

II.II.III Type 17 T helper cells (T_H17) in cancer

Type 17 T helper cells (T_H17) owe their name to their ability to produce IL-17 (289, 541) and play critical roles in autoimmunity and in host protection against bacterial and fungal infections (365). T_H17 differentiation is induced by IL-6, IL-22, IL-23 and TGF- β and regulated by the transcription factors STAT3 and orphan receptor ROR γ t. In addition to IL-17, T_H17 also exert their immune responses by producing other cytokines, including IL-21, IL-22 and GM-CSF. Despite the contributions of T_H17 in gut homeostasis and autoimmunity are well established, the role of T_H17 cells in cancer remains controversial since they are reported to have both pro-tumor and anti-tumor effects (20) (*Figure 1*). IL-17A has been reported to promote tumor angiogenesis (780), but other T_H17 cytokines, such as IL-21 and IL-22, were shown to display anti-angiogenic effects (756). In addition to cytokines secreted by conventional T_H17 cells, tumor-infiltrating T_H17 cells could have distinct cytokine profiles that could be influenced by the stage of tumorigenesis and tumor types (252). Indeed, tumor-infiltrating T_H17 cells have been reported to express IL-17 and IFN- γ (“T_H1-like” T_H17 cells) or IL-17 and IL-10 (“T_{regs}-like” T_H17) cells, which exhibit distinct effector and regulatory functions and have different impacts on tumorigenesis (20). Intriguingly, T_H17 cells can differentiate into T_H1 or T_{regs} and vice versa in a process that is, at least in part, governed by hypoxia and metabolism (sections V.II.I and VII.II.I). The balance and plasticity between T_H17 cells and T_{regs} have been reported to have the correlation of patient clinical cancer stage and associated with tumor progression (448). In lung cancer, T_H17 cells cooperate with T_{regs} to promote lung cancer progression and metastasis (190, 447). In contrast, in ovarian cancer patients, T_H17 exhibit a polyfunctional effector T cell phenotype to stimulate recruitment of effector T cells into the TME by promoting CXCL9 and CXCL10 production in tumors, and induce expression of chemokines for type I immune responses in recruiting effector T cells (370). Yet, TNF- α induced the secretion of IL-17 by T_H17 cells and elicited the recruitment of neutrophils that supported tumor progression (119). Again, this highlights the potential pro- and anti-tumor effects of T_H17 cells.

II.II.IV Regulatory T cells (T_{regs}) in cancer

Regulatory T cells (T_{regs}) play a crucial role in maintaining immune homeostasis and self-tolerance and preventing autoimmune disease. TGF- β can induce T_{regs} polarization. T_{regs} are characterized by the expression of the transcription factor Foxp3, which is key for T_{regs} development and function and is considered as a lineage-specific marker for T_{regs} . Unlike other $CD4^+$ helper T cells, T_{regs} exhibit immunosuppressive activities through different mechanisms. Foxp3 suppresses IL-2 production in T_{regs} , but T_{regs} constitutively express the high-affinity IL-2 receptor α chain (CD25) (*Figure 1*). Thus, T_{regs} sustain their survival by competing for IL-2 with other T lymphocytes and this competition could further hamper proliferation and survival of effector T cell subsets. Migration of T_{regs} into tumors is mediated by their chemokine receptors CCR4, CCR5, and CXCR1 (183). Once in the tumor, T_{regs} also upregulate the expression of co-inhibitory receptors, including CTLA4, programmed cell death protein 1 (PD-1), T cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte activation gene-3 (LAG-3), inducible T cell co-stimulator (ICOS), and glucocorticoid-induced TNFR family related gene (GITR). The expression of these co-inhibitory receptors on T_{regs} dampens the anti-tumor functions of effector T cells, as well as potentially promote T_{regs} generation (509). For instance, CTLA4 competes for binding to CD80 and CD86 on antigen-presenting cells (APCs) with the co-stimulatory receptor CD28. Since CTLA4 has a higher affinity for CD80/CD86 than CD28, it impairs T cell activation by reducing CD28-mediated co-stimulatory signal in other T cells (137). Moreover, T_{regs} dampen immune responses in both T cells and APCs by producing immunosuppressive cytokines, such as IL-10 and TGF- β (744). The stability and function of intratumoral T_{regs} is maintained by pDC-derived Semaphorin 4A (Sema4A) signaling through neuropilin 1 (Nrp1) on T_{regs} (168).

In humans, various tumor types such as breast (422), ovarian (153), lung (555) and gastric (554) cancer, show high levels of T_{regs} either in circulation or intratumoral, or a low $CD8^+/T_{\text{regs}}$ ratio, which correlate with a poor clinical prognosis. In contrast, a few studies provided evidence that T_{regs} may also be associated with improved clinical outcome in head and neck (29) and colorectal carcinoma (614). In general, tumor-infiltrating T_{regs} promote tumor immune evasion and development of the immunosuppressive TME through their abilities to dampen anti-tumor immune responses.

II.II.V CD8⁺ cytotoxic T cells (CTLs) in cancer

CD8⁺ cytotoxic T cells (CTLs) express CD8, composed of one CD8 α and one CD8 β chain. CTLs play an important role in immunity against intracellular pathogens and tumor immunosurveillance. After being primed by APC in the lymphatic organs, CTLs become activated and gain the ability to eliminate infected or malignant cells upon recognition of peptides presented by MHC-I. Upon recognition of the peptide-MHC-I complex, effector CTLs secrete cytokines, including TNF- α and IFN- γ , to activate macrophages and cell-mediated immunity. Moreover, effector CTLs can directly lyse target cells by producing and releasing cytotoxic granules containing perforin and granzymes. Perforin is a glycoprotein, which can form pores on target cell membrane (527). These pores allow granzymes, a serine proteases, to enter the target cells, cleave proteins inside these cells and induce their programmed cell death (126). In addition, effector CTLs express Fas ligand (FasL) on the cell surface, which binds Fas expressed on the surface of target cells. Fas-FasL interaction stimulates caspase cascade activation and engagement of apoptosis in Fas-expressing target cells (*Figure 1*). Clinical observations and retrospective studies suggest that high densities of infiltrating CTLs in the TME, or a high CD8⁺/T_{regs} ratio, associates with better clinical outcomes, including prolonged survival and higher response rates to cancer immunotherapy, in many different tumor types, such as melanoma (697), breast (437), ovarian (624), renal (499), colorectal (243, 358), pancreatic (237), and lung cancer (342).

II.II.VI Dysfunctional T cell states: ignorance, tolerance, anergy, exhaustion and senescence

As a result of the intensity and duration of antigen exposure, the cytokine and metabolic milieu as well as the intercellular crosstalk within the TME, T cells may exhibit a series of dysfunctional states, namely ignorance, tolerance, anergy, exhaustion and senescence, that compromise their anti-tumor function (reviewed in (149, 631, 692, 762)). The term ignorance refers to a state in which naïve T cells fail to recognize their cognate antigen that can be either *i*) physically sequestered, *ii*) have low expression or *iii*) be scarcely cross-presented. As a result, the T cell remains in its naïve status with the possibility to be still activated in the right circumstances and conditions. Tolerant T cells, on the other hand, are (self-) antigen antigen-experienced cells that have been inefficiently primed and is

associated to a dysregulated expression of effector molecules, master transcription factors, chemokine receptors, exhaustion-associated markers and cell cycle-associated genes (631). Therefore, tolerant T cells are unable to undergo clonal expansion even if antigen re-stimulation takes place under optimal conditions, but yet may retain a degree of effector function (631). The development of peripheral tolerance is a physiological mechanism to prevent autoimmunity, but it can also arise in pathological conditions such as cancer. CD8⁺ T cell tolerance can occur when tumor antigens derive from tissue-specific genes (i.e. prostate-specific antigen PSA and melanocyte glycoprotein PMEL) or from overexpressed wild type genes (i.e. c-MET proto-oncogene). Anergy is an hyporesponsive state that arises as a result of *in vitro* stimulation in the absence of co-stimulatory or cytokine signals or of *in vivo* sub-optimal stimulation. Anergy is characterized not only by an impaired proliferation, as in tolerant T cells, but also by defective IL-2 production (638). Exhaustion is a state of hyporesponsiveness due to the combination of a persistent antigen stimulation with the absence of CD4⁺ T helper stimulation and an immunosuppressive environment. It is the most common situation encountered by tumor-infiltrating T cells. Exhausted T cells have a decreased proliferation, impaired effector function and increased expression of inhibitory receptors (PD-1, LAG3, Tim3, CTLA4, among others) (762). While anergy occurs within a few days after TCR stimulation, exhaustion may take up to several weeks. Finally, senescent T cells display a shortening of telomere length as a result of ageing after several rounds of division, a reduction of CD28 expression and undergo an irreversible cell cycle arrest (149). Importantly, tolerance, anergy and exhaustion are reversible states that could potentially be targeted by immunotherapies while senescence is irreversible. With this respect, it is relevant not only to define whether tumors are “cold” or “hot”, but also to characterize the fitness of tumor-infiltrating T cells in order to find tailored strategies to reverse T cell dysfunction. In other words, hot tumors with senescent or anergic T cells would require a different approach than hot tumors characterized by exhausted T cells.

III. Positive and negative involvement of the immune system in the success of therapeutic approaches such as chemotherapy and radiotherapy

Conventional therapies, such as chemotherapy and radiotherapy, are widely used in clinical cancer treatment. Chemotherapy drugs eliminate cancer cells through inhibition of DNA replication and synthesis, induction of DNA damage or prevention of cell mitosis. Radiation causes DNA damage, including single-strand and double-strand breaks. In addition to a direct effect on cancer cells, localized radiation or systemic chemotherapy can initiate cell death-induced immune responses, namely immunogenic cell death (ICD), and induce production of inflammatory cytokines and chemokines, leading immune cells infiltration and reprogramming the TME to exert a potent anti-tumor immunity (169, 217, 397) (reviewed in (240, 758)). Mechanistically, dying cancer cells release immunogenic tumor antigens and emit danger-associated molecular patterns (DAMP). The liberation of DAMPs, such as calreticulin, ATP, and high-mobility group protein B1 (HMGB1), stimulate phagocytosis and enhance APCs activation. Dying cancer cells also release DNA and RNA in the cytosol. DNA triggers cGAS-STING pathway, whereas RNA induces toll-like receptors (TLRs), RIG-I-like receptors (RLRs) signals. The activation of those pathways induces type-I IFN expression, which is essential for DC activation and function. Hence, radiotherapy- or chemotherapy-induced ICD leads to DCs maturation and migration to the draining lymph node, where they prime tumor antigen-specific T cells and initiate systemic immune responses. Additionally, type-I IFN in tumors can further stimulate recruitment effector CD8⁺ T cells and anti-tumor responses of those recruited effector T cells (171, 405, 758, 771). Very few standard chemotherapeutics elicit ICD (i.e. anthracyclines, oxaliplatin, mitoxantrone, among others) (191, 240). Thus, drug combinations with the potential to enhance ICD and to revive the anti-tumor function of the immune system, for instance metabolism-targeting agents with tolerogenic chemotherapies, would hold promising effects.

In addition to the activation of T1DC-CTL-mediated anti-tumor immune responses, conventional therapies also trigger chemokine production on cancer cells to recruit T cells. Radiotherapy induces the expression of T cell attracting chemokines, including CXCL9, CXCL10, CXCL1, and CXCL16 (450, 456) and chemotherapy promotes T cell infiltration in the TME by stimulating expression of CXCL9, CXCL10, and CCL5 in cancer cells (303). Moreover, cytotoxic chemotherapy can alleviate

the immunosuppressive features of the TME through the elimination of immunosuppressive cells. For instance, low dose cyclophosphamide and gemcitabine selectively ablate T_{regs} or MDSCs and dampen production of the immune suppressive cytokines, such as IL-4, IL-10 and IL-13 (390, 430, 650). These findings pave the foundations for several pre-clinical and clinical studies in which treating cancer-bearing mice or patients with cyclophosphamide in combination with cancer vaccine achieve higher response rates (388, 725, 740). Even though conventional therapies can augment T cell responses, there are several downsides for conventional therapy. Intensive chemotherapy and radiotherapy can cause neutropenia and lymphopenia and significantly decline total numbers of immune cells. Furthermore, in some cases radiotherapy can even induce the recruitment of MDSCs into tumors (721).

It is becoming increasingly recognized that NK cells significantly contribute to the so-called ICD and the overall therapeutic outcome. In the context of chemotherapy-elicited NK cell responses, changes in the expression of death receptors as well as of NK cell-activating and inhibitory ligands following therapy play a major role. Classical cytotoxic drugs that are currently in clinical practice can upregulate the expression of the stimulatory ligands NKG2D and DNAM-1 through the DNA damage response pathway as well as the expression of the NKp30 ligand B7-H6 via an unknown mechanism (803). Alternatively, they decrease the expression of NK cell inhibitory ligands such as Clr-b (219, 255, 261, 651). Finally, chemotherapeutic drugs regulate NK cell activating ligands at the post-translational level. For instance, metalloproteinases (MMP) and ADAM enzymes on the surface of cancer cells can trigger the release of soluble NKG2D ligands in response to chemotherapy (802, 803). In contrast, treatment with gemcitabine was shown to inhibit shedding of the NKG2D ligand ULBP2 through ADAM10 in pancreatic cancer (414). In murine models, cisplatin induced the release of the chemokine chemerin, which enhanced NK recruitment and showed enhanced efficacy when it was combined with anti-angiogenic therapy targeting VEGF (354). Regarding NK cell responses to radiotherapy, it has been shown that irradiation of various cancer cell lines induced the upregulation of the NKG2D ligands MICA, MICB and ULBP1 (45, 661, 776), whereas the irradiation of human endothelial cells did not change the expression of NKG2D ligands (583). Thus, irradiation upregulates NKG2D ligands and, hence, potentially triggers anti-tumor NK cell responses. With respect to MHC-I

molecules it seems more likely that radiation therapy has a negative impact on NK cell-dependent cancer cell clearance. Yet, irradiation-induced upregulation of MHC-I molecules likely renders cancer cells more susceptible to clearance by cytotoxic T cells (599). Hence, a better understanding of dosage of conventional therapies in combination with immune therapies is direly needed to achieve long-term clinical benefit by reigniting anti-tumor immunity.

IV. Immunotherapy: a promising therapeutic option for cancer patients but with room for improvements

Despite improved treatment options, cancer remains the leading cause of morbidity and mortality worldwide and the number of newly diagnosed cases is expected to rise by 70% over the next two decades (World Cancer Report 2014), further emphasizing an urgent need for new therapeutic strategies. Traditional chemotherapy and targeted therapies have achieved limiting success, as resistance mechanisms and toxicity still represent major challenges for effective cancer treatment. In this scenario, cancer immunotherapy has emerged as a revolutionary and promising treatment approach. The relevance of the progress in this field was recently recognized by the Nobel Committee, leading to the assignment of the 2018 Nobel Prize in Physiology or Medicine to Dr. Allison and Dr. Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation". Human antibodies directed against immune checkpoint proteins such as cytotoxic T lymphocytes antigen-4 (CTLA4), programmed death-1 (PD-1), and programmed death-ligand 1 (PD-L1) have been employed to break the immune tolerance and stimulate T cell response (68, 268, 700). Adoptive T cell transfer (ACT), STING agonists and cancer vaccines harness the ability of the immune system to recognize and reject the tumor (663). In addition, multiple strategies have been envisaged to stimulate the function of anti-tumor effector cells or to dampen the pro-tumor functions of immunosuppressive cells (663).

Recent studies highlight the lack of correlation between T cell infiltration in solid tumors, response to immunotherapy (i.e., anti-PD-1) and density of immunogenic antigens (672), leading to the key questions of which antigen-independent factors limit anti-tumor responses. Growing evidence shows that, even in the presence of an immunotherapeutic intervention aiming to promote T cell expansion

and anti-tumor activity, the TME can compromise functions and fate of tumor-infiltrating immune cells to favor immunological tolerance and reduce anti-tumor effector functions. For instance, low pH, hypoxia, metabolic competition for limiting nutrients (e.g. glucose and glutamine), some metabolites (e.g. adenosine), macrophage-driven arginine depletion, nitric oxide (NO) production as well as tryptophan catabolism by indoleamine-pyrrole 2,3-dioxygenase (IDO) within the TME greatly impair T cell functions (47, 99, 116, 132, 249, 335, 557). The next challenge is therefore to anticipate the reasons why in certain patients and tumors immune intervention does not offer a durable response, or in the worst case, the tumor is completely refractory to this treatment. In this section, we offer an overview of the current state-of-the-art immunotherapies and the challenges that still need to be tackled in order to improve its efficacy.

IV.I Immune checkpoint blockade (ICB)

Immune checkpoints provide negative signals that restrict T cell immune responses and are critical for self-tolerance. However, cancer cells take the advantage of these co-inhibitory signals to limit T cells activity and further establish an immunosuppressive TME. In order to rejuvenate T cell anti-tumor responses, immune checkpoint blocking antibodies or recombinant forms of ligands have been developed. Currently, two classes of immune checkpoint blockade (ICB) have been approved by the FDA, the antagonistic antibodies of cytotoxic T cell lymphocyte-associated protein 4 (CTLA4) (i.e. ipilimumab, tremelimumab) and programmed death receptor 1 (PD-1) (i.e. nivolumab, pembrolizumab, pidilizumab) or its ligand (PD-L1) (i.e. atezolizumab, avelumab, durvalumab) (39). Clinical data have demonstrated that monoclonal antibodies that block CTLA4 and PD-1 signals can prevent the inhibition machinery on T cells and enhance T cell functions and lead to impressive therapeutic benefits in patients with different cancer types.

CTLA4 is a transmembrane glycoprotein constitutively expressed on T_{regs} and also expressed on other T cells following activation. CTLA4 can bind to its ligands CD80 (B7-1) and CD86 (B7-2) expressed on APCs. Since CTLA4 has a greater affinity to B7 proteins than the co-activating receptor CD28, CTLA4 is able to compete with CD28 for ligand binding and deliver an inhibitory signal to restrain T cell immune responses (39). Indeed, CTLA4 expression in T cells tunes down the amplitude of T cell receptor activation, resulting in reduced T cell proliferation and IL-2 production (369, 741). Similar to

CTLA4, PD-1 is also expressed on the surface of activated T cells and interacts with its own ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC), which are expressed on the surface of APCs, myeloid cells, and cancer cells. The interaction between PD-1 and its ligands provides a negative signal to inhibit cytokine production and T cell proliferation (216, 585). Interferes with the formation of immunological synapses and inhibits TCR-mediated effector functions. CTLA4-mediated inhibitory signaling usually takes place within the lymph nodes, where APCs interact with T cells, while PD-1-mediated inhibitory signaling is triggered mostly in the periphery, including the tumor. Mechanistically, both CTLA4 and PD-1 signals impede Akt activation, but they target different signaling molecules. CTLA4 signaling dampens T cell activation pathways by activating the serine/threonine phosphatase PP2A and SHP2, which directly dephosphorylates CD3 ζ (396, 446). In contrast, PD-1 signaling phosphorylates ITSM/ITIM motifs located in PD-1 cytoplasmic domain, which recruits tyrosine phosphatases SHP-1 and SHP-2. As a result of recruitment, SHP-1 and SHP-2 further inhibit TCR-induced activation of PI3K/Akt pathway (585, 788).

Immune checkpoint inhibitors have shown high response rates of prolonged duration in a subset of melanoma (312, 627, 713), renal cancer (21, 485) and lung cancer patients (63, 297, 577), raising the enthusiasm of setting-up new clinical trials for many other cancer types. It is clear that for several tumors such as colorectal cancer (CRC) (68, 389, 700), and pancreatic ductal adenocarcinoma (PDAC) (603), immunotherapy fails to show any clinical benefit. T cell infiltration and intratumoral localization, PD-L1 expression, tumor antigenicity and the fitness of tumor-infiltrating T cells are important factors that determine the success of ICB. Novel strategies aiming to modulate these features are attractive candidates to predict response to ICB as well as to restore sensitivity in those refractory cases. A list of the currently ongoing clinical trials with anti-PD-1, PD-L1 and CTLA4 antibodies can be found in (Table 1). More recently, co-inhibitory receptors have been described (namely Lag-3, Tim-3 and TIGIT) that are expressed by T cells, NK cells and some APCs and have more specialized and organ-specific functions. Targeting these receptors represents an alternative strategy with potentially more specificity and lower toxicity (12, 39, 663). More research is required to unravel which tumors are susceptible to these therapies and to design successful combinational therapies.

IV.II Adoptive T cell transfer (ACT)

Adoptive cell transfer (ACT) consists in collecting patients' own T cells, improve their performance *ex vivo* and re-transfer them back. There are three types of ACT: tumor infiltrating lymphocytes (TILs), chimeric antigen receptor (CAR) and T cell receptor (TCR) modified T cells. In TILs therapy, the TILs isolated from patients are expanded *in vitro* supplementing with IL-2 and anti-CD3. Prior to TILs re-transfer, patients have to be treated with lymphodepletion drugs to support the expansion and survival of infused TILs. In addition, treatments with high-dose of IL-2 are used to increase the survival of TILs (307, 597, 798). The therapeutic potential of TIL therapy is mainly hampered by the low frequency of TILs in tumor and the challenge to acquire sufficient cell numbers of tumor-reactive T lymphocytes during *in vitro* expansion phase. In contrast to TILs, CAR and TCR T cells use gene modification strategies to overcome the bottlenecks of TIL therapy and immune tolerance. Since most of tumor-associated antigens are derived from self-antigens, T cells recognizing tumor antigens are not naturally abundant. Thus, TCR therapy consists in overexpressing tumor-specific TCR on the surface of autologous T cells. In contrast, CAR T cell therapy consists in overexpressing chimeric antigen receptors, which are artificial fused membrane proteins, on autologous T cells (598). In this design, CARs directly recognize tumor antigens in an MHC-I-independent manner and could deliver TCR and co-stimulatory receptor signals into T cells upon recognition of tumor antigens. Importantly, CAR T cell therapy can be used in tumors downregulating antigen presentation and MHC-I expression.

Among all three treatments, CAR T cells therapy is the most advanced. In 2017, two CAR T cell therapies approved by FDA, Axicabtagene for refractory large B cells lymphoma and Tisagenlecleucel for B-cell precursor acute lymphoblastic leukemia (B-ALL) (502, 565). Although CAR T cell therapy has been a breakthrough success in hematopoietic malignancies, new clinical regimens are needed to make them effective against solid tumors. Moreover, T lymphocytes expressing CAR or TCR against tumor antigens retain their expression of endogenous TCR, which may recognize a variety of antigens. This may increase the risk of autoimmunity or other severe immune responses in patients receiving this therapy. Thus, enhancing therapeutic efficacy while keeping an adequate T cell response is a major challenge of ACT.

IV.III Cancer vaccines

The idea behind cancer vaccines is different from the vaccines that work against viruses. Instead of preventing diseases, cancer vaccines are designed to trigger and amplify anti-tumor immunity. Cancer vaccines aim to boost the quantity and activity of tumor antigen-specific CTLs as well as to create memory immune responses against tumors (79). Cancer vaccines can be made from tumor lysates, cancer cells with engineered cytokine production, tumor antigens or APC pulsed with tumor lysates.

Many therapeutic cancer vaccines are under development. Among them, Sipuleucel-T is approved by FDA on treating metastatic prostate cancer, which is made by *ex vivo* activated endogenous APCs pulsed with recombinant prostate antigen-prostatic acid phosphatase fused with GM-CSF (338). In this design, the growth factor signal promotes antigen presentation ability of the endogenous APCs to enhance CTL activation. The combination of conventional therapy or immunotherapy with cancer vaccine is the current strategy in many clinical trials. Moreover, the concept to develop personalized cancer vaccine is emerging, which contains predicted specific patient's neo-antigens, which is believed to provide more specific immune responses and better harness the existing anti-tumor immune responses in individual patient. In early phase of small cohort trial, melanoma patients treated with personalized cancer vaccine in combination with anti-PD-1 therapy showed striking clinical outcome (528, 611). Thus, cancer vaccine may provide safe, immunogenic and broad therapeutic options as a combinatory intervention to enhance tumor-specific immune responses.

IV.IV Stimulator of interferon gene (STING) pathway

STING, a transmembrane protein located on endoplasmic-reticulum (ER) membrane, acts as a sensor for cytosolic DNA to stimulate expression of interferon genes. Numerous cell types express the STING complex, such as endothelial, epithelial and hematopoietic cells (320). Mechanistically, cytosolic double strand DNA derived from pathogens or dying cells binds and activates cyclic GMP-AMP synthase (cGAS). Activated cGAS catalyzes the conversion of ATP and GTP into cyclic guanosine monophosphate-adenosine monophosphate (cGAMP), the ligand of STING. The accumulation of cGAMP stimulates STING-dependent phosphorylation of tank-binding kinase 1 (TBK1), which further phosphorylates the interferon regulatory factor 3 (IRF3). In addition, activated STING is reported to activate NF- κ B pathway. The activation of IRF3 and NF- κ B leads to

transcription of type I interferons (IFN) and pro-inflammatory cytokine (80, 320). In anti-tumor immunity, STING-mediated production of type I IFN in the TME activates CD103⁺ dendritic cells (cDC1), promotes T cell priming in lymph nodes and stimulates T cell recruitment into tumors (178, 236, 771). STING agonists are shown to enhance CTL-mediated anti-tumor immunity and induce tumor regression of distant tumors (142). Furthermore, STING agonists in combination with cancer vaccines could eradicate established PD-1 blockade-resistant tumors (234). Currently, several STING agonists are tested under phase 1/2 clinical trials, in which STING agonists are used in combination with immune checkpoint blockade.

IV.V Targeting regulatory T cells

T_{regs} are the most potent suppressor in the TME due to their multi-faceted suppressive activities to myeloid cells and lymphocytes. The increased frequency of T_{regs} in tumors has also been reported to associate with poor clinical outcomes in different cancer types (165, 645). Moreover, depleting tumor-infiltrating T_{regs} can reprogram the TME into immunosupportive and unleash anti-tumor responses (744). These findings pave the foundations for T_{regs}-targeting cancer treatments. CD25, known as the interleukin-2 high-affinity receptor alpha chain (IL-2R α), was the first surface marker of T_{regs} and CD25 expression is critical for T_{regs} survival (613). Interventions that block CD25 signaling and induce antibody-dependent cell death (ADCC) were developed, including daclizumab (an anti-human CD25 antibody), and denileukin diftitox (a recombinant fusion protein combining human IL-2 and diphtheria toxin fragment) (158, 324, 428, 576). However, those clinical data did not provide strong clinical benefit mainly because T_{regs} depletion is limited to the peripheral blood and lymph nodes but is not achieved within the tumor. A recent study demonstrated that optimizing Fc γ R binding affinity of anti-CD25 antibody can increase intratumoral T_{regs} depletion through ADCC and synergized PD-1 blockade (18). However, this type of T_{regs}-targeting approach remains difficult to be used because the systemic loss of T_{regs} will lead to severe inflammatory responses and autoimmunity. Hence, developing anti-CD25 antibody or other T_{regs}-depleting approaches to specifically target intratumoral T_{regs} without significant impact on other peripheral T_{regs} is an attractive strategy for cancer immunotherapy. Another way to inhibit T_{regs} functions in the TME is to block T_{regs} infiltration into tumors. CCR4/CCL22 and CCR4/CCL2 chemokine pathway have been revealed to control the

infiltration of T_{regs} into tumors (114, 153, 427). Anti-CCR4 mAb treatment can selectively decrease intratumoral T_{regs} number and induce host anti-tumor immunity (678). In line with these findings, anti-CCR4 mAb is under clinical trials, which display potent efficacy to augment immune responses (193, 525).

IV.VI Targeting NK cells

The engagement of NK cells represents an attractive immunotherapeutic strategy, due to their strong tumoricidal capacity. It has been demonstrated that activated NK cells can express PD-1 (7, 515) and CTLA4 (676). Accordingly, anti-PD-1 treatment in multiple myeloma was able to reengage NK cell anti-tumor responses (49). The direct impact of CTLA4 on NK cell function remains to be established (110, 382). CTLA4 is expressed on some cancer cells and NK cells express CD16 Fc receptor (138). Therefore, anti-CTLA4 antibodies might induce NK cell-dependent cancer cell killing via ADCC (386). Moreover, CTLA4 blockade and subsequent cytokine production by T cells is likely to trigger NK cell anti-tumor responses.

The use of agonistic antibodies represents a promising strategy to boost the effector functions of both, NK cells and T cells. Agonist antibodies for 4-1BB (CD137), which is expressed on cytotoxic NK cells and T cells, enhances anti-tumor immune activity in murine tumor models (37). Moreover, 4-1BB antibodies enhance trastuzumab- and rituximab-induced ADCC of mammary tumors and lymphomas, respectively (360, 361). However, early clinical trials revealed significant toxicity of high dose treatment with 4-1BB antibodies (22). Finally, NK cells express the co-stimulatory molecules glucocorticoid-induced TNFR-related protein (GITR, CD357) and CD27 (455), both of which are considered as targets for agonist antibodies in cancer therapy. Combining these agonistic antibodies with blockade of inhibitory receptors is a promising approach to unleash NK cell cytotoxicity.

Inhibitory KIRs dampen NK cell cytotoxicity upon interaction with self-MHC class I molecules on cancer cells. Moreover, inhibitory KIRs are also expressed by some effector CD4⁺ and CD8⁺ T cells. Hence, KIR-neutralizing immunotherapies have the potential to boost the cytotoxic activity of both T cells and NK cells. IPH2102 is a monoclonal antibody that interferes with KIR2DL1, KIR2DL2 and KIR2DL3 and enhances NK cell-mediated *in vitro* killing of cancer cells (595, 712). However, phase

1 and 2 clinical trials using anti-KIR as a monotherapy in acute myeloid leukemia (AML) or multiple myeloma have shown little clinical efficacy (50, 51, 727). Yet, KIR blockade might show synergy with CTLA4 or PD-1 checkpoint blockade which could further enhance NK cell function.

In addition to genetically engineered T cells, genetic modification of NK cells represents a promising immunotherapeutic strategy for cancer (256). The NK cell leukemia-derived NK-92 cell line has been successfully engineered to express activating chimeric antigen receptors (CARs) specific for tumor antigens (298), including CD19 (59) and CD20 (492) on B cell lymphomas, the glycolipid disialoganglioside G_{D2} , on neuroblastoma (204), HER2, on carcinomas (635, 708), epithelial cell adhesion molecule (EPCAM), on cancer stem cells (612), prostate stem cell antigen (PSCA) (701) and CD138, on multiple myeloma cells (331). However, NK-92 cells have some disadvantages that limit their clinical utility. NK-92 is a leukemia cell line that is positive for the Epstein–Barr virus (EBV) and lack the expression of certain NK cell-activating receptors, including NCRs and CD16. Thus, in order to prevent uncontrolled proliferation, NK-92 cells must be irradiated prior to adoptive transfer. Alternative approaches have used primary NK cells from peripheral blood or derived from pluripotent stem cells (197, 356).

In spite of these encouraging results, there are numerous obstacles to overcome in order to maximize the outcome of NK cell-based immunotherapies, including the systemic toxicity of cytokines such as IL-2, IL-12 and IL-15 (226, 273), poor NK cell infiltration of solid tumors as well as the elimination of factors that suppress NK cell function within the tumor (i.e. T_{regs} , MDSCs and immunosuppressive cytokines such as TGF- β). Therefore, strategies to address these issues with the ultimate goal to enhance NK cell infiltration and performance in solid tumors are desperately needed. For instance, a recent study showed that NK cells require HIF-1 α for the infiltration of hypoxic tumors and subsequent cancer cell lysis (373). Therefore, it is tempting to speculate whether tuning the HIF expression in NK cells prior to transfer, e.g. by genetic or pharmacological inhibition of prolyl hydroxylases, would be able to increase the infiltration and/or performance of NK cells in solid tumors.

IV.VII Targeting myeloid cells

In the last decade, immunotherapeutic options aiming to kill TAMs, to block their recruitment into the tumor or to re-educate their phenotype from a pro-tumor to a tumoricidal and immune stimulatory phenotype have been explored (517, 571).

The most advanced approach in clinical trials is probably the use of small molecule inhibitors of the tyrosine kinase activity of CSF1R (e.g., PLX3397) or blocking antibodies against the cognate ligand CSF1 (e.g., PD-0360324) or the receptor itself (e.g., emactuzumab, cabiralizumab). Besides the importance of CSF1 for survival and differentiation of macrophages in general, pro-tumor (M2-like) macrophages express most of the CSF1R and are more strictly dependent on this pathway (566). Targeting CSF1/CSF1R pathway can reduce TAM numbers and concomitantly increase the CD8⁺/CD4⁺ T cell ratio (584), polarize TAMs towards an anti-tumor phenotype (566) or result in a specific killing of the CD206^{high} M2-like TAM population and sensitization to anti-CTLA4 (800). Moreover, anti-PD-1 treatment may promote the secretion of CSF1 and the recruitment of TAMs. Thus, in this scenario combination of anti-PD-1 with anti-CSF1R be beneficial (503). Thus, the diversity of the targeting agent or, to a larger extent, the context specificity of the tumor type/model can underpin the different mechanism-of-action of CSF1(R) blockade alone or in combination with ICB.

Differently from CSF1, CCL2 (also known as MCP1) triggers CCR2-mediated release of monocytes from the bone marrow and their recruitment to the tumor (114, 567), where they can differentiate into TAMs or MDSCs, induce IL-4 mediated T_{H2} polarization (269) and CCR4-mediated T_{regs} recruitment (114, 427). CCL2 inhibition of metastasis-associated macrophages (MAMs) in breast cancer metastasis is efficient while the treatment is endorsed (60, 567). However, upon treatment withdrawal, a rebound of CCL2, together with a boost in IL-6 and VEGF, enhanced macrophage release from the bone marrow into the metastatic site with worsening of the metastatic disease outcome (60). This study warns some caution on possible therapeutic windows of such an approach. Antibodies or small molecule inhibitors of against CCR2 or CCL2 (i.e. PF-6309, Carlumab (CNT088)) have been tested in preclinical settings and in phase 1 or 2 clinical trials, alone or in combination (69, 801). Of note, Carlumab did not show prolonged inhibition of CCL2 (619).

Next to strategies aiming to block macrophage differentiation and recruitment, there are other strategies aiming to harness one or more macrophage functions. Agonist CD40 antibodies (e.g., ABBV-927 and APX005M) are tested in phase 1 and 2 clinical trials with promising results. CD40 agonists have demonstrated synergistic activity in combination with gemcitabine and resulted in complete tumor regression in preclinical models when paired with an anti-PD-1 and/or anti-CTLA4 (42, 43, 804). Mechanistically, CD40 agonists induce macrophage repolarization from an M2 to an M1 phenotype and their cytotoxic effect is T cell independent. However, CD40 activation in DCs is important for their maturation and efficient antigen presentation that leads ultimately to a boost in CTL infiltration and activation (42, 43). This aspect is important in the clinic when cold tumors such as pancreatic cancer need to be converted into a T cell inflamed tumor, prior administration of checkpoint inhibitors. Moreover, CD40 activation in innate immune cells converts PD-1^{high} T cells into PD-1^{low} T cells, reversing T cell exhaustion and reverting anti-PD-1 refractoriness (507). Despite the scarcity of late stage clinical studies, positive results from two trials (NCT03214250 and NCT02304393) combining CD40 activating antibodies with anti-PD-1/anti-PD-L1, could place CD40 agonists at the forefront in the immunoncology space.

Another key molecule involved in innate immunity and macrophage function is integrin-associated protein (IAP or CD47). CD47 is a receptor found to be overexpressed on cancer cells and acts as a “don’t eat me” signal to macrophages. CD47 binds the transmembrane signaling protein signal-regulatory protein α (SIRP α) expressed by TAMs (657). The interaction of CD47 with SIRP α inhibits macrophage phagocytosis, allowing cancer cells to escape immune surveillance (228). Moreover, the therapeutic effect of CD47 blockade may also rely on dendritic cell but not macrophage cross-priming of T cell responses (420). Hu5F9 and TTI-621 are CD47 antagonists currently undergoing clinical trials (228).

Tie2-expressing monocytes/macrophages (TEMs) are a highly pro-angiogenic subpopulation of myeloid cells in circulation and tumors, where they are closely aligned to tumor vessels expressing angiopoietin-2 (Ang2) (131, 133, 162, 451). Moreover, TEMs can express IL-10 and the T_{regs} chemoattractant CCL17 (133) and can suppress CTL proliferation and enhance T_{regs} expansion (131).

Of note, hypoxia can induce both Ang2 and Tie2 expression (279, 401). Thus, disrupting the Tie2/Ang2 signaling pathway is an attractive anti-tumor and anti-metastatic strategy (131, 133, 451).

In sum, as hypoxia and nutrient scarcity in the TME are major factors that polarize TAMs to a pro-tumor phenotype and that strongly impact on T and NK cell fitness, reduction of hypoxia or interventions targeting macrophage metabolism can be an alternative approach to induce anti-tumor immunity.

V. Direct and indirect effects of hypoxia on the immune landscape of the tumor

The family of hypoxia inducible factors (HIFs) are key orchestrators of the adaptive response to hypoxia and have a prominent role in the immune system (532, 640). HIF is a heterodimeric transcription factor composed of a constitutive β subunit (HIF-1 β) and of one of the highly regulated α subunits (HIF-1 α or HIF-2 α). HIF-1 α is ubiquitously expressed whereas HIF-2 α is expressed in a cell-specific manner and they activate overlapping but also a unique set of genes (532). Upon dimerization, HIF binds to hypoxia response elements (HRE) in the genome and drives the transcription of genes involved in angiogenesis, lymphangiogenesis, ECM remodeling, metabolic reprogramming, cell proliferation, invasion and immunomodulation.

HIF- α protein is tightly regulated at the post-translational level by the O₂/PHD/VHL axis. In normoxia, O₂-sensing prolyl hydroxylases (PHDs) hydroxylate proline residues of HIF- α , which can then be recognized and polyubiquitinated by the Von Hippel Lindau (VHL) E3 ligase and targeted for proteasomal degradation (321, 322, 789). In addition, hydroxylation of asparaginyl residues by O₂-sensing factor inhibiting HIF (FIH) prevents the interaction of HIF- α with coactivators and thus the formation of an effective transcriptional complex (381, 439). Of note, the role of FIH expression in immune cells is completely underexplored. In some cells, an hypoxia-independent mechanism of phosphorylation and dephosphorylation of PHD2 poses another layer of regulation of the HIF response (174, 175). In the immune system, the transcription of HIF- α can be triggered by several O₂-independent signaling pathways (i.e. TLR/NF- κ B, TCR/PI3K/mTOR and ERK pathways), a process

sometimes named pseudo-hypoxia. Importantly, HIF- α levels are also influenced by the metabolic status of the cell. PHDs and FIH require Fe^{2+} and α -ketoglutarate (α -KG) as cofactors and produce succinate as a byproduct of HIF hydroxylation (321, 322, 381, 789). The oncometabolite 2-hydroxyglutarate (2-HG) competes for the binding site of α -KG and acts as a competitive inhibitor of PHD/FIH (775). Reactive oxygen species (ROS) can also promote HIF-1 α stabilization via several mechanisms (487). Thus, the activation and metabolic status of the cell can govern HIF stabilization even in situations when oxygen is available by modulating PHD/FIH activity or by triggering O_2 -independent HIF stabilization.

Oxygen tension and metabolite fluctuations within the tumor establish distinct niches that profoundly shape immune cell localization and phenotype (98). Besides the shortage of oxygen, tumor hypoxic areas exhibit a range of other distinctive traits. Hypoxia directly modulates the expression of several cytokines and chemokines and induces the expression of CD39 and CD73, fostering the accumulation of the immunosuppressive metabolite adenosine. HIF-1 α contributes to the switch towards glycolysis, which subsequently results in glucose depletion, lactate accumulation and acidification of the TME. Poor vessel coverage and perfusion are exacerbated in hypoxic areas, directly affecting immune cell trafficking and aggravating the shortage of oxygen and nutrients and the accumulation of metabolic byproducts. Thus, the term “tumor hypoxia” can encompass not only oxygen shortage but also the effect of the other abovementioned hypoxia-related traits. Moreover, since HIF- α stabilization can be induced by other stimuli besides hypoxia, an integrative vision on both the effect of cell intrinsic HIF- α and the effect of the hypoxic environment is required to fully understand how tumor hypoxia influences tumor-infiltrating cells.

In sum, bearing in mind the intertwined relationship between oxygen and metabolism, a simplified, though more general conclusion might be that *i*) the normoxic niche is characterized by having higher oxygen and nutrient availability and by being rather immunostimulatory and *ii*) the hypoxic niche is characterized by having lower oxygen availability and low pH, and by being rich in lactate and adenosine, ultimately favoring immunosuppression. Accordingly, the definition of “metabolic immune niches”, taking into account both the relative positioning and skewing of specific immune cell subsets, is a potent tool to predict progression and therapy response. For example, more

macrophages in the hypoxic regions and perivascular areas of the tumor or more T cells at the edge of the tumor are a readout of bad prognosis, whereas abundance of TAMs in more normoxic areas or T cells within the tumor core are signs of good disease outcome (17, 99, 100, 242, 243, 402, 702, 761, 786, 794). A recent study revealed a unique gene signature in TAMs from breast cancer patients and identified a crosstalk between cancer cells and TAMs that enhances their pro-tumor functions and correlates with aggressiveness and short survival (104). It would be relevant to study whether this crosstalk takes place within a particular intratumoral niche. We have recently described a subset of podoplanin-expressing macrophages (PoEMs) located in the proximity of lymphatic vessels where they foster lymphangiogenesis and lymphoinvasion. From a metabolic point of view, this perilymphatic population of TAMs is characterized by high expression of genes related to glucose uptake and anaerobic glycolysis (54). In breast cancer patients, association of PoEMs with tumor lymphatic vessels correlates with lymph node and distant metastasis (54). Moreover, different T cell subsets also exhibit distinctive locations that may have opposite prognostic value (702). While T_{regs} are mainly concentrated in hypoxic areas, effector T cells are normally present around blood vessels and away from hypoxic areas (293, 379). The presence of Nrp1^+ T_{regs} correlates with poor prognosis in melanoma and head and neck squamous cell carcinoma patients (530). In this line, human clinical data indicated that higher intratumoral $T_{\text{H}2}$ cells infiltration reduced patient survival rate in pancreatic cancer patient as well as other tumor types, whereas these correlations are gone when looking at the total T cell population (159).

In this section we will focus on how tumor hypoxia dictates immune cell positioning, in particular within the normoxic and the hypoxic niches. Moreover, we will analyze the current knowledge on how the HIF pathway and tumor hypoxia regulate different aspects of immune cell function.

V.I Effect of hypoxia on innate immunity

V.I.I Effect of hypoxia on macrophages

Macrophages infiltrate solid tumors in large numbers and contribute to create a microenvironment that favors immune evasion, tumor angiogenesis and metastasis. Macrophages in hypoxic tumor regions express low levels of MHC-II (384, 489) and can interfere with the anti-tumor functions of

adaptive immunity (295). Tumor hypoxia promotes the recruitment of myeloid cell populations from the bone marrow via several mechanisms. Hypoxia-induced HIF-1 α stabilization drives the expression of chemokines such as CCL5 and CXCL12 (also known as SDF1a) by cancer cells (189, 413) as well as the expression of their cognate receptor CXCR4 on macrophages (632, 674). Likewise, hypoxia increases cancer cell expression of the myeloid cell chemoattractants VEGF-A and the endothelins (ET-1 and ET-2) in a HIF-1 α -dependent fashion (182, 265, 266, 398). The release of ATP and other DAMPs from hypoxic dying cells induces the recruitment and entrapment of TAMs to hypoxic and necrotic regions via the engagement of nucleotide receptors (P2XRs/P2YRs) and PRRs, respectively (120, 202). Finally, we have shown that hypoxia-driven expression of semaphorin3A (Sema3A) by cancer cells controls TAMs localization in hypoxic areas (99). Sema3A binds to Nrp-1 and PlexinA1/A4 on TAMs and attracts them to hypoxic tumors through VEGFR1 signaling. Hypoxia suppresses Nrp-1 expression on the TAMs surface and then Sema3A-PlexinA1/A4 mediate stop signals that ultimately lead to their entrapment in hypoxic areas. Accordingly, macrophage-specific deletion of Nrp-1 impaired TAMs recruitment into hypoxic tumors, angiogenesis and tumor growth and enhanced tumor immunity (99). The relevance of these findings has been underscored by two independent groups working in glioma. Genetic KO of Nrp1 in microglia and macrophages, systemic pharmacological inhibition of Nrp1 and treatment of patient-derived xenografts with anti-Sema3A had strong anti-tumor effect via impairing the recruitment of TAMs and reshaping of the inflammatory response (393, 476). The HIF-2 α isoform also plays an important role for the infiltration and migration of TAMs via the regulation of chemotactic receptor expression (CSF1R and CXCR4) (318). Macrophage-specific deletion of HIF-2 α reduced the tumor infiltration by TAMs and improved the outcome of hepatocellular carcinoma and colitis-associated colon carcinoma (318) (*Figure 2*).

The HIF pathway plays a central role in macrophage biology: from supporting the pro-inflammatory cytokine secretion, antigen presentation and glycolytic metabolism of M1-like macrophages during the early stages of tumorigenesis, to fueling the pro-tumor functions of M2-like macrophages in established solid tumors. M1 and M2 macrophages differentially express HIF-1 α and HIF-2 α , and HIF stabilization in macrophages can take place both under normoxia and under hypoxia. Hypoxia via

HIF-1 α enhances phagocytosis and antigen presentation in a mechanism involving p38 (11) and the production of IFN- γ and autocrine signaling (2). In M1 macrophages, HIF-1 α is essential to promote and sustain glycolysis and energy production (section VII.I.I) (148). Hypoxia strongly impacts the macrophage-mediated suppression of adaptive immunity for instance, via the HIF-1 α -mediated differentiation of immunosuppressive MDSCs into TAMs and their expression of PD-L1 ligand, ARG1 and NOS2 (145, 511) and via the induction of *Arg1* gene expression in macrophages (426). Besides hypoxia, T_H1 and T_H2 cytokines stabilize HIF-1 α and HIF-2 α in M1 and M2 macrophages, respectively, which oppositely regulate NO homeostasis (684). HIF-1 α induces the expression of NOS2 in M1 macrophages, which converts L-arginine into NO and citrulline, whereas HIF-2 α induces the expression of ARG1 in M2 macrophages, which breaks down L-arginine into L-ornithine and urea (684). NOS2-mediated NO production has dual effects on tumor growth depending on the stage and context: while it can promote cancer cell killing, it can also stimulate the secretion of ROS and RNS, which impair the anti-tumor adaptive immune response (720). L-arginine depletion due to macrophage ARG1 or NOS2 activity has strong inhibitory effects on T cell mediated anti-tumor responses (186, 588-591, 684). In this line, macrophage-specific deletion of HIF-1 α slowed down the growth of murine breast adenocarcinomas by improving T cell proliferation and function (186, 400). Moreover, hypoxic macrophages may contribute to the recruitment of neutrophils via the HIF-mediated upregulation of IL-8 (212).

One of the most well documented consequences of HIF-1 α stabilization in macrophages is the promotion of tumor angiogenesis. TAMs have been described to increase in number in premalignant lesions just before the angiogenic switch that precedes the transition to malignancy. Depletion of macrophages resulted in a reduction in vascular density, causing delayed tumor progression and metastasis. In turn, reintroduction of macrophages or VEGF-A led to a significant increase in vascular density and enhanced tumor progression (411, 412). In mice lacking VEGF-A specifically in myeloid cells the angiogenic switch does not occur, highlighting the role of myeloid-derived VEGF-A in fine-tuning tumor angiogenesis (675). Loss of VEGF-A expression in myeloid cells resulted in a marked increase in pericyte coverage and tumor oxygenation, indicating vascular normalization, which surprisingly resulted in a significantly higher tumor burden but it also rendered these tumors

vulnerable to chemotherapy (675). Hypoxic areas of tumors are also rich in lactate, which can drive VEGF-A expression by TAMs via the stabilization of HIF-1 α (135). HIF-1 α -dependent expression of the matrix metalloproteinase MMP9 by hypoxic TAMs contributes to tumor angiogenesis by releasing VEGF-A from the extracellular matrix and thus contributing to its bioavailability (189). Hypoxia fosters the pro-angiogenic function of TAMs via the hypoxia-driven upregulation of the mTOR inhibitor REDD1. In turn, REDD1 tunes down glucose uptake and glycolysis in hypoxic TAMs, thereby tilting the competition for glucose in favor of glycolytic endothelial cells, which thus acquire a motile and pro-angiogenic phenotype (87, 761). Contrary to HIF-1 α , HIF-2 α does not seem to contribute to VEGF-A expression in TAMs (3, 205), but it controls the expression soluble VEGF receptor 1 (sVEGFR1), which acts as a VEGF trap and, therefore, has an anti-angiogenic function (587). In addition to macrophages, Tie2-expressing monocytes (TEMs) represent another myeloid cell type that can contribute to tumor angiogenesis (162). Interestingly, hypoxia contributes to Tie2 expression, which is important for the recruitment and function of these cells (401).

In summary, therapeutic interventions aiming to block the hypoxic response in macrophages could potentially re-educate pro-tumor hypoxic TAMs and rewire them into anti-tumor macrophages. Importantly, HIF-1 α is an important regulator of metabolism in M1 macrophages and other anti-tumor immune cells (section VII), and this should raise caution on the use of HIF inhibitors and prompt the development of other more selective targets.

V.I.II Effect of hypoxia on neutrophils and MDSCs

Several studies reported that hypoxia induces cancer cell-derived production of neutrophil-attracting chemokines (i.e. IL-8, CXCL1, CXCL2 and CXCL5). IL-8 has been found around necrotic and presumably hypoxic areas in metastatic lesions from aggressive melanoma patients (377) as well as in implanted tumors of human pancreatic cell lines into nude mice (653). *In vitro* studies revealed that hypoxia, acidosis and the hypoxia/ROS/NF- κ B axis were responsible for the upregulation of IL-8 in IL-8-expressing cell lines (377, 477, 653). Interestingly, induction of IL-8 in HIF-1-deficient cancer cells was accompanied by a strong infiltration of neutrophils (477). Besides cancer cells, hypoxic macrophages may contribute to the IL-8-mediated recruitment of neutrophils, although the importance

of this contribution within the tumor remains unknown (212). At the time that these studies were carried out, neutrophils were regarded as mere bystanders of tumor progression due to their alleged short lifespan. Therefore, although the pro-angiogenic effects of IL-8 have been at least in part attributed to its CXCR1-mediated effect on endothelial cells (377, 477, 653), further studies are required to assess whether IL-8-recruited neutrophils actively contribute to the observed effects of IL-8. In addition to its role as a chemokine, tumor-derived IL-8 induces the exocytosis of ARG1 by neutrophils, thereby contributing to T cell suppression (600). In early stage PTEN-deficient uterine tumors, hypoxia-induced cancer cell expression of CXCL1, CXCL2 and CXCL5 promotes the recruitment of CXCR2⁺ anti-tumor neutrophils, resulting in a reduced tumor growth (56). Intriguingly, in PTEN-deficient murine prostate tumors the YAP-dependent expression of CXCL5 promoted the recruitment of CXCR⁺ MDSCs, which in this case favored tumor growth (742). These apparently conflicting studies highlight the fact that the pro- or anti-tumor role of neutrophils, as other immune cells, likely depends on several environmental factors and thus, on the tumor subtype and stage. In the context of tissue inflammation, hypoxia and HIF-1 α directly regulate neutrophil trafficking through the endothelium. On one hand, via the expression of integrin β 1 in neutrophils, thereby facilitating their adhesion to the endothelium (364) and, on the other hand, via the stimulation of Sema7A expression by endothelial cells, which facilitates neutrophil transmigration by engaging with PlexinC1 on neutrophils (482). Whether these mechanisms are also at stage in the context of tumor hypoxia needs further investigation (*Figure 2*).

Hypoxia influences many aspects of neutrophil biology including neutrophil lifespan, metabolism and phenotype (148). Neutrophil apoptosis is tightly controlled to avoid excessive pro-inflammatory immune reactions. Hypoxia-induced activation of HIF-1 α prolongs neutrophil half-life via the activation of NF- κ B and the secretion of CCL4/MIP-1 β (738, 739). Besides, HIF-1 α -mediated metabolic reprogramming towards glycolysis is essential for neutrophil survival (608). In line with this, loss of PHD2 in neutrophils promoted neutrophil survival, enhanced neutrophil chemotaxis and increased their functional capacity (608). In contrast, hypoxia-induced PHD3 expression in neutrophils is essential for hypoxic neutrophil survival, but not for other neutrophil functions, in a HIF-independent mechanism that involves the pro-apoptotic molecules Siva1 and Bcl-XL (737). A

recent study revealed that HIF-2 α is also responsible for the extended lifespan of inflammatory neutrophils, but is not required for chemotaxis, phagocytosis and respiratory burst (693). Thus, since neutrophils will likely encounter hypoxia in the TME, HIF-1 α and HIF-2 α together with other stimuli will likely elongate the half-life of tumor-associated neutrophils (TANs). Tumor hypoxia induces PD-L1 expression in MDSCs in a HIF-1 α but not HIF-2 α dependent manner (511). The seminal study by Fridlender et al. revealed that TGF- β blockade stimulated the recruitment and activation of “N1” anti-tumor neutrophils (233). Since TGF- β is produced by many hypoxic cells, it is logical to speculate that hypoxic TANs might be polarized towards an “N2” phenotype. Finally, neutrophils’ respiratory burst consumes important amounts of molecular oxygen, placing neutrophils as a potential contributor to perpetuate tumor hypoxia (85).

Of note, many of the abovementioned studies used models for inflammation-related diseases. Given that neutrophils encounter hypoxia in the TME, it would be of outmost importance to shed light into the role of hypoxia and the HIF pathway in neutrophils in the context of tumor biology. Furthermore, since most studies used the LysM promoter, which is more active in macrophages than in neutrophils (1), we recommend to use neutrophil-specific promoters such as MRP8 (544) or Ly-6G (292).

V.I.III Effect of hypoxia on dendritic cells (DCs)

The effect of hypoxia and HIFs on the activation, maturation and function of DCs has been addressed in several *in vitro* settings and murine models of inflammation. Yet, these studies have reached contradictory conclusions (767). Furthermore, there is still a significant gap of knowledge regarding its effects on DC recruitment, position and function in the context of the tumor.

Unlike the positive effect of hypoxia on macrophage phagocytosis, culture of human immature DCs under hypoxia represses their antigen uptake capacity, characteristic of immature DCs, in a mechanism that does not involve HIF-1 α (200, 524). Given the impact of antigen presentation by TIDCs to CTLs on the effectiveness of CTL-mediated tumor rejection, it would be relevant to unravel whether tumor hypoxia can affect this process. In addition, hypoxia fuels the migratory capacity of immature and mature DCs through the upregulation of chemokine receptors while it simultaneously represses cytokine expression (218, 359, 581). Several HIF-1 α -dependent and independent mechanisms have been proposed. In contrast, other authors reported that hypoxia can impair the

motility of monocyte-derived DCs by modulating the expression of metalloproteinases (796) and their inhibitors (570). A recent report demonstrated that stimulation of TLRs under normoxia induces glycolytic metabolism in DCs partially via the stabilization of HIF-1 α and NO production, which is essential for the oligomerization of CCR7 and the migration of DCs towards the lymph nodes (270). Moreover, inhibition of glycolysis by 2-DG injection *in vivo* impaired the migration of DCs to the lungs in a model of HDM-induced allergic asthma model (270). Several inflammatory signals alone or in synergy with hypoxia can stabilize HIF-1 α and induce the expression of costimulatory molecules (200, 328, 572, 581). In this line, hypoxia-differentiated DCs had an enhanced T cell stimulatory ability *in vitro* that required HIF-1 α and mTOR (572), supporting the idea that hypoxia rather favors the functions of mature DCs. However, other authors reported that hypoxia did not alter the T cell stimulatory capacity of DCs (200). Altogether, in the context of inflammatory hypoxia *in vitro*, HIF-1 α stabilization following hypoxia and/or TLR stimuli seems to trigger the first steps required for DC maturation: migration from the hypoxic site, usually rich in molecules that dampen the full maturation of DCs (i.e. VEGF) (238), to maturation-permissive environments such as the lymph nodes and expression of T cell stimulatory molecules. Importantly, *in vivo* studies using murine models of inflammatory diseases indicate that HIF-1 α in DCs limits CD8⁺ T cell expansion (281) as well as T_H1 inflammatory responses (280) and is essential for the induction of T_{regs} (227). Mechanistically, HIF-1 α in DCs impairs the production of IL-12, necessary for CD8⁺ T cell expansion and T_H1 responses (280, 281), while it promotes the production of IL-10 and TGF- β , potent inducers of T_{regs} (227). Finally, HIF-1 α negatively regulates the development of plasmacytoid DCs and genetic deletion of HIF-1 α in myeloid cells augmented infiltration of PyMT-MMTV tumors by pDCs (759). It still remains unclear whether this is a direct result of the lack of HIF-1 α in pDCs or an indirect result of the lack of HIF-1 α in other myeloid cells.

The discrepancy between the abovementioned studies highlights the importance of taking into account the whole complexity of the environment in which dendritic cells, in this case, carry out their functions. While hypoxia is a common trait of inflammatory sites and tumors, the cytokine and metabolic milieu are notably different. For instance, hypoxia in the TME is commonly accompanied

by glucose deprivation. Thus, further studies are required to shed light into the important question on how TIDCs are affected by the global composition of the TME.

V.I.IV Effect of hypoxia on innate lymphoid cells (ILCs)

The knowledge about the effect of hypoxia on innate lymphoid cell function tumors is still scarce and most of studies so far have focused on the NK cell subset. High numbers of NK cells within the tumor predict outcome in various types of cancers. It has been shown that the preoperative activity of NK cells predicts distant metastasis after tumor removal (363). The existing pre-clinical data suggests that NK cells primarily kill circulating cancer cells but show very low killing activity against established solid tumors (130, 272, 730). Nevertheless, more recent studies indicate that NK cells are capable of controlling solid tumor growth, particularly during early tumorigenesis (385). The cancer cell-killing efficiency of NK cells in solid tumors seems to depend rather on the activation state of NK cells, which can be modulated by the availability of oxygen. Hence, it is much more difficult to explain the link of NK cell density and outcome in solid tumors, given its dynamic oxygen gradients.

Hypoxia in hepatitis C-infected livers has been shown to compromise the anti-viral NK cell response (770). In the cancer setting, Sceneay et al. reported that myeloid immune suppressor cells indirectly inhibition NK cell function in the hypoxic primary TME and metastatic niches (626). Furthermore, several reports suggest a direct suppression of NK cell function by hypoxia via multiple mechanisms. For instance, hypoxia decreases the expression of NKG2D on the surface of NK cells. This is partially driven by the release TGF- β -containing tumor microvesicles in response to hypoxia (33, 512, 621). In a similar fashion, tumor microvesicles that deliver miR-210 to NK cells decrease the release of cytotoxic granules and the expression of the degranulation marker CD107a (512). From a therapeutic point of view, it will be key to reveal mechanisms that allow the reversal of hypoxia-induced NK cell inhibition. In this line, the study by Sarkar et al. suggests that hypoxic suppression of NK cell performance can be reversed by exogenous IL-2 treatment (621). In contrast, a transition of normoxic, pre-activated NK cells to an hypoxic environment leads to robust proliferation and enhanced effector function via stabilization of HIF-1 α . This observation could be of particular interest in the setting of adoptive NK cell transfer, where NK cells can be stimulated prior to transfer (349).

Recently, it has been shown that NK cells infiltrate into hypoxic areas in murine tumor models. NK cell-specific deletion of HIF-1 α reduced overall intratumoral NK cell densities and decreased overall NK cell cytotoxicity. Moreover, while HIF-1 α -proficient NK cells were predominantly found in hypoxic areas, loss of HIF-1 α induced the accumulation of NK cells in normoxic areas, inverting this situation (373). Curiously, specific deletion of HIF-1 α in NK cells impaired tumor growth independently of their cytotoxic activity, but because it resulted in non-functional angiogenesis likely resulting from the decrease in sVEGFR1-expressing NK cells especially in hypoxic areas. Intriguingly, HIF-1 α deficiency in NK cells gave rise to increased metastasis despite impaired growth of primary tumors. Whether hypoxia is the ultimate cause of HIF-1 α stabilization in NK cells demands further clarification. In this setting it is not understood yet to which extent the loss of HIF-1 α in NK cells compromises infiltration, survival or proliferation in hypoxic tumors. Nevertheless, this study strongly indicates that in addition to NK cell numbers, the positioning of NK cells within the oxygen gradient of tumor might be a prognostic factor. Noteworthy, boosting the hypoxic response in NK cells should have the opposite effect, increased cytotoxicity and vascular stabilization. Therefore, the HIF pathway could represent a promising target to enhance NK cell performance in the TME (*Figure 2*).

In addition to the impact of hypoxia on NK cell function, it is important to take into account the NK cell-extrinsic effects on a target cell, e.g. its susceptibility to lysis by NK cells. For instance, hypoxia leads to HIF-1 α -dependent downregulation of the activating NKG2D ligand MICA in cancer cells (778). Moreover, hypoxic cancer cells engage autophagy, which results in the degradation of cytolytic Granzyme B and impaired NK cell-mediated lysis (30). Moreover, hypoxia-induced autophagy blunts NK cell-dependent cancer cell killing via the degradation of the membrane connexin 43 in the cancer cell (698). There is also data showing that VHL-deficient clear cell renal cell carcinoma cells acquire resistance to NK cell-dependent killing, involving the accumulation of inositol 1,4,5-trisphosphate receptor type 1 (ITPR1), an intracellular channel that mediates calcium release and ER stress-induced apoptosis (461, 462). Therefore, targeting ITPR1 could reinstate cancer cell elimination by NK cells.

In summary, it becomes clear tumor hypoxia rather contributes to tumor escape from NK cell-mediated immunosurveillance. Therefore, dissecting the critically involved and hypoxia-associated pathways in the TME will likely yield attractive immunotherapeutic targets.

V.II Effect of hypoxia on adaptive immunity

V.II.I Effect of hypoxia on CD4⁺ T cells

Hypoxia modulates the expression of several T cell attracting chemokines by cancer cells and other immune cells. Hypoxic cancer cells, via HIF-1 α , secrete the chemokine CCL28 that recruits CXCR10⁺ T_{regs} into tumors (208). Cancer cell-derived VEGF-A has been shown to regulate T_{regs} chemotaxis by binding to Neuropilin-1 (Nrp1) on their surface. Consequently, a T cell-specific deletion of Nrp1 prevents T_{regs} infiltration into melanomas, breaking down an important mechanism for immune evasion, enhances the infiltration and activation of CD8⁺ T cells and limits tumor growth (285). Whether other Nrp1 ligands also mediate the recruitment of T_{regs} or other T cell subsets into the tumor or into hypoxic tumor niches remains unknown. Tumor-associated neutrophils (TANs), in particular N2 TANs, produce CCL17 and promote the recruitment of T_{regs} (471). Since N2 TANs arise in response to TGF- β (233), a cytokine highly abundant in hypoxic regions of the tumor, it would be interesting to unravel whether this chemotactic signal also affects intratumoral T_{regs} positioning. Although a direct link between hypoxia and CXCL9/10 expression has not been described, hypoxia could indirectly modulate the availability of these important T cell attracting chemokines through its effects on CXCL9/10-expressing cell types. Moreover, further investigations are required to assess whether hypoxia also impacts the trafficking of other CD4⁺ T cell subsets (*Figure 2*).

Given that the thymus and the secondary lymphoid organs tend to have lower oxygen tension (0,5-4,5%) than the bloodstream, we can conclude that activation of naïve T cells in secondary lymphoid organs takes place under hypoxia (83). After activation, CD4⁺ T cells undergo differentiation into various T effector or regulatory subsets. Hypoxia and HIF-1 α are involved in this process, although divergent roles have been described suggesting, again, that *i*) combined environmental conditions such as hypoxia and cytokine and metabolic milieu can fine-tune a different response than each

condition alone and that **ii**) hypoxia-induced HIF-1 α and normoxic HIF-1 α stabilization can have different effects (174).

HIF-1 α is involved in both T_H17 and T_{regs} differentiation and the presence of other cytokines, namely TGF- β and/or IL-6, are crucial to tilt the balance (*Figure 3*). A protocol mimicking the fluctuations in O₂ levels that accompany T cell activation *in vivo* supports this notion, which consists of priming of T cells in under mild hypoxia (5% O₂), as occurs in the lymph nodes, followed by reoxygenation mirroring T cells entry in the normoxic bloodstream (316). TGF- β instructs the differentiation of both T_H17 and T_{regs} since it induces the production of Foxp3 and ROR γ t in naïve T cells and (799). In the absence of other cytokines, TGF- β -driven Foxp3 inhibits the activity of ROR γ t and drives T_{regs} differentiation *in vitro*. The addition of the T_H17-polarizing cytokines IL-6, IL-21 and IL-23, in contrast, promotes ROR γ t expression and relieves its Foxp3-imposed suppression, therefore promoting T_H17 polarization (799). Moreover, hypoxia-driven HIF-1 α induces Foxp3 and the differentiation of T_{regs} in a mechanism mediated by TGF- β . Again, the concomitant presence of IL-6 and TGF- β abolished this effect and favored T_H17 polarization (128). In this line, Dang et al. unraveled that HIF-1 α stabilization under T_H17-polarizing conditions, both in hypoxia and in normoxia, enhances T_H17 and opposes T_{regs} differentiation through the induction of ROR γ t and IL-17 transcription and the proteasomal degradation of Foxp3 (156). Shi et al. described that T_H17-polarizing conditions induce an mTORC1-driven stabilization of HIF-1 α that acts as a metabolic checkpoint to induce glycolysis. This metabolic shift towards glycolysis is required to support of T_H17 metabolic demands while it blunts T_{regs} development (652). Noteworthy, the effect of HIF-1 α stabilization under hypoxia was not tested. Interfering with any of the steps of the mTORC1/HIF-1 α /glycolysis cascade during T_H17 polarization, including loss of HIF-1 α , impairs T_H17 differentiation and tilts the balance towards the formation of T_{regs}, which accordingly confers protection against T_H17-mediated neuroinflammation (156, 652). Supporting this, hypoxia via HIF-1 α enhances the glycolysis-driven migratory capacity of T_{regs} and their tumor infiltration, but it tunes down its OXPHOS-driven immunosuppressive capacity (473). In glioblastoma, T_{regs}-specific deletion of HIF-1 α leads to a decreased infiltration of T_{regs} and to an extended survival, thus indicating that the infiltration defect overrules the potential enhanced immunosuppressive activity (473). Activation

under hypoxia followed by reoxygenation potentiates T_H17 polarization, but not T_H1 and T_{regs}, in a hypoxia/mTORC1/HIF-1 α -driven mechanism (316). Interestingly, hypoxia/reoxygenation and TCR stimulation synergistically induce the expression of the HIF-1 α target gene miR-210 in T_H17 cells, which acts as a negative feedback loop to tune down HIF-1 α expression and T_H17 differentiation. In a T_H17-driven model of inflammatory colitis, T cell-specific deficiency of miR-210 fostered T_H17 formation as well as the conversion of T_H17 cells into T_H1-like cells, therefore worsening the disease severity (743). In conclusion, the differentiation of activated CD4⁺ T cells into T_H17 or T_{regs} in response to hypoxia and TGF- β depends on TGF- β concentrations and on the presence or the absence of T_H17-polarizing cytokines (128, 799) (*Figure 3*). HIF-1 α , either induced by hypoxia and/or by other stimuli such as TCR ligation, is at the crossroads of this fate decision via the regulation of key transcription factors, cytokines and cell metabolism (128, 156, 652, 799) (section VII.II).

The HIF pathway also regulates the balance between T_{regs} and T_H1 (*Figure 3*). VHL expression in T_{regs} is essential to maintain their identity after differentiation and their immunosuppressive functions (395). Genetic deletion of VHL specifically in differentiated T_{regs} and the subsequent HIF-1 α stabilization promotes their conversion to IFN- γ -producing T_H1-like effector cells by inducing a glycolytic metabolic program and by HIF-binding to the IFN- γ promoter, further amplifying the activation of T_H1 cells (395). *In vivo*, VHL loss in T_{regs} increases the numbers of T_H1 cells in almost all organs as well as the number of activated/memory CD4⁺ and CD8⁺ T cells in the spleen and lymph nodes, resulting in a severe lethal inflammation in young adult mice (395). In the TME, hypoxia via HIF-1 α promotes the production of IFN- γ by T_{regs}, which induced T_{regs} fragility and enhances the success of anti-PD-1 therapy (530). In the lung, PHD-mediated oxygen-sensing by CD4⁺ T cells and the subsequent HIF-1 α degradation is responsible for the maintenance of immune tolerance, which ultimately facilitates tumor colonization of the lung (129). PHD isoforms redundantly limit T_H1 differentiation and favor the induction of T_{regs}, partially due to the repression of the HIF-driven glycolytic metabolism and IFN- γ production (129). Pharmacological blockade of PHD in *ex vivo* cultured CD4⁺ T cells prior to adoptive T cell transfer improves the efficiency of this immunotherapy. These findings suggest that adding a PHD inhibitor to established clinical expansion protocols for human ACT could potentially improve the tumor regression rate (129).

Many of the studies addressing the role of hypoxia in T cell differentiation were carried out in the context of inflammatory hypoxia, in which antigen presentation is usually intact, a situation that is often impaired in the TME. Moreover, the cytokine and metabolic milieu of tumor hypoxia greatly differs from that of inflammatory hypoxia and tissue-specific environments. Although it is tempting to speculate that immunosuppressive signals in the TME will likely overrule the hypoxia-driven stimulation of anti-tumor T cell subsets (see next sections for further discussion), how the integration of the metabolic and cytokine signals in the TME shapes the function of specific CD4⁺ T cell subsets demands further clarification.

V.II.II Effect of hypoxia on CD8⁺ cytotoxic T cells (CTLs)

Until recently, little was known regarding how hypoxia/the HIF pathway regulates the pathways orchestrating the recruitment of CD8⁺ T cells in the tumor. Palazon et al. have now shown that tumor-infiltrating CTLs are an important source of the HIF-1 α target gene VEGF-A. In murine tumor models, CTL-derived VEGF-A contributes to the permeabilization of the endothelium and enables CTL recruitment. Accordingly, ablation of HIF-1 α or VEGF-A in T cells resulted in a specific defect in CTL transendothelial migration and homing to the tumor, vascular normalization and accelerated tumor growth (534) (*Figure 2*). Furthermore, T cell specific ablation of HIF-1 α , but not of VEGF-A, was accompanied by an increase in tumor-infiltrating T_{regs}, supporting the observations discussed above that HIF-1 α blunts T_{regs} development (156, 316, 652).

As mentioned above, CD8⁺ T cell activation in lymphoid organs takes place under hypoxia (83) and the HIF pathway is important for the maintenance of CTL effector functions. *In vitro* hypoxia-driven HIF-1 α stabilization in CTLs is required for their expression of effector molecules (i.e. IFN- γ , TNF- α and GzmB) (534), costimulatory receptors (i.e. OX40, GITR, and 4-1BB) (185, 532-534) and exhaustion-related markers (i.e. PD-1 and CTLA4) (185, 534), whereas HIF-2 α is dispensable (534). In this line, two studies highlighted the role of HIF negative regulators VHL and PHD in CTL function. Loss of VHL in CD8⁺ T cells promoted their effector capacity not only by an induction of glycolytic metabolism, but also by a HIF-dependent regulation of a set of effector molecules and activation-associated co-stimulatory and inhibitory receptors (185). Interestingly, enhanced HIF activity due to VHL loss prolonged the survival of effector CD8⁺ T cells by impairing their terminal

differentiation and freezing them into a previous state which retains their effector functions without being short-lived. Adoptive transfer of VHL-deficient OT-I CTLs exhibited an enhanced ability to control OVA-expressing B16 tumors compared to ACT of VHL-proficient OT-I CTLs, suggesting that enhanced activity of HIFs may be a potent strategy to sustain the effector function of CTLs in a context where prolonged antigen exposure induces CTL exhaustion (185). Similar to the positive effect on T_H1 differentiation (*Figure 3*), loss of all three PHD isoforms in CD8⁺ T cells unleashed IFN- γ production and protected mice from metastatic colonization in the lung, although the value of PHD inhibition prior to ACT of CTLs was not assessed (129). The nature of the signal that triggers HIF-1 α stabilization in tumor-infiltrating CTLs still remains unclear.

Tumor hypoxia can negatively impact the anti-tumor function of CTLs. Similar to NK cells, hypoxia drives cancer immune evasion by decreasing the susceptibility of cancer cells to immune cell-mediated killing in a HIF-1 α -dependent manner. Cancer cells undergo autophagy in response to hypoxia, which renders them resistant to lysis by cytotoxic T cells and NK cells (30, 510, 513). Hypoxia via HIF-1 α induces the expression of PD-L1 on cancer cells and on myeloid cells to favor immune escape (36, 511). VEGF-A expressed in the TME can induce the expression of PD-1 and other inhibitory checkpoints on tumor CTLs and induce T cell exhaustion (733). Moreover, hypoxia can promote the infiltration and suppressive function of T_{regs}. Thus, although hypoxia promotes CTL function *in vitro*, it is known that their anti-tumor function is highly impaired in the highly hypoxic TME and that CTLs are mostly found in well oxygenated areas (293). This suggests that hypoxia-related or tumor-related factors either prevent the stabilization of HIF-1 α or overrule its immunostimulatory effect.

VI. Tumor metabolism: beyond cancer cell metabolism

Due to high nutrient consumption and compromised tumor vascular supply, the tumor environment is frequently poor in nutrients and oxygen and cancer cells have to compete with neighbor cells for nutrients. Our understanding on the complexity of the metabolic networks (*Figure 4A*) and the different crosstalks between tumor compartments have represented a step-forward from the original

concept of “glucose-dependency of the cancer cells” introduced in the 20s by the German physiologist Otto Warburg (753). Warburg found that, even in the presence of oxygen, unlike the majority of normal cells, cancer cells prefer to metabolize glucose via glycolysis, a less efficient pathway for producing ATP when compared to OXPHOS (752), ascribing this phenomenon to an impairment of mitochondrial respiration. However, numerous studies have shown that mitochondrial respiration is intact in many tumors and that OXPHOS suppression by glycolysis stimulation is rather an adaptation to hypoxic conditions during tumor development. Supporting this idea, a metabolic zonation within glioblastoma tumors has very recently been reported, revealing progressive changes in the metabolic profile of cancer cells relative to their distance from the blood vessels that were associated with aggressiveness and therapy resistance (375). It is yet unknown whether and how metabolic zonation impacts on tumor stromal cells. Increased glucose consumption during tumorigenesis has been useful for clinical detection and monitoring by fluorodeoxyglucose positron emission tomography (FDG-PET) (5) but it is clear that this type of diagnostic outcome can also be inferred to the fact that extensive inflammation in general displays an augmented incorporation of radiolabeled glucose (677). The new evidence is that cancer cells can even live when starved from glucose and rely on additional means of energy supply, including the tricarboxylic acid cycle (TCA cycle, wherein carbon sources other than glucose can be channeled), fatty acid β -oxidation (FAO), or even opportunistic modes of nutrient acquisition, involving uptake of macromolecules or cells/cell remains, under metabolically unfavorable conditions (548).

The mechanistic target of rapamycin (mTOR) and the AMP-activated protein kinase (AMPK) are one of the most influent signaling pathways controlling both cancer and immune cells function and metabolism (415, 484, 625). mTOR is an evolutionarily conserved serine/threonine kinase composed by two complexes, mTORC1 and mTORC2, which are distinguished by the scaffolding proteins Raptor and Rictor, respectively (625). The PI3K/Akt pathway is a major trigger of mTOR activation. By inhibiting TSC1/2, Akt releases the activity of the small GTPase Rheb that, in turn, when in its GTP-bound state stimulates mTORC1 kinase activity (625). mTORC1 drives anabolic metabolism, including lipid, glutamine and glucose metabolism, while it inhibits catabolic processes, namely autophagy (625). Activation of mTOR drives glycolytic metabolism essentially through HIF-1 α and

c-Myc (81) as well as *de novo* fatty acid biosynthesis (FAS) via upregulating the transcription factors sterol regulatory element-binding proteins (SREBPs) (415). How mTOR orchestrates metabolic activities that shape immune effector responses depends on each cell type, nutrient availability in the microenvironment and on the specific tissue (415, 757). AMPK is a highly conserved serine/threonine protein kinase present in most cells that contains a catalytic α -subunit and two regulatory subunits (β and γ). The energy-sensing capability of AMPK can be attributed to its ability to detect and react to fluctuations in AMP:ATP ratio. High AMP concentrations promote the phosphorylation of AMPK in the α -subunit that leads to its activation. Active AMPK acts as a metabolic master switch that regulates several intracellular systems including the inhibition of glucose and anabolic metabolism (i.e. FAS, protein synthesis, amino acid uptake and *de novo* synthesis of amino acids) and the activation of catabolic metabolism (i.e. oxidative metabolism and mitochondria biogenesis) (287, 519). Moreover, AMPK activation suppresses mTOR and HIF-1 α signaling. In the next sections we will mention how mTORC1, mTORC2 and AMPK are differentially implicated in immune cell metabolism and function. However, for a more in-depth discussion of the implication of mTOR and AMPK signaling in cancer cell or in immune cell metabolism, we refer the reader to more extensive recent reviews (287, 415, 484, 519, 625).

Importantly for this review is the concept that the metabolic fingerprint in cancer cells will define the composition of the milieu to which stromal cells are exposed. In this way, changes in the metabolic state of cancer cells may induce phenotypic changes in other cells in their vicinity, including tumor-associated fibroblasts, endothelial cells and immune cells. Thus, stromal cells can be reprogrammed by cancer cells to acquire either pro-tumor or anti-tumor phenotypes. On the other hand, the opposite is also true: metabolism of stromal cells can also re-shape the metabolic behavior of cancer cells (481, 785). Finally, also stromal cells can enter in competition for the same metabolite so that their phenotype is tightly linked and a consequence of the “appetite” of neighboring cells.

Notably, while the technologies are quite advanced to calculate the percentage of oxygen in precise areas of the tumor (e.g., through paramagnetic resonance) (673), the technologies to detect and quantify metabolites in tumor sections or by *in vivo* imaging are blooming (181, 479). Remarkably, one of the major current caveats is the use of *in vitro* cultures is that the metabolite composition of

culture media and the oxygen tension of the incubators is far from physiological. The use of new medium formulations that aim to mimic physiological concentration in plasma (88) or in tumors (718) could greatly contribute to reproduce immune cell biology more faithfully. The future research should aim to design the metabolic topography of the tumor, with the detailed identification and localization of metabolites in the tumor milieu in order to increase our prediction on the function of the different immune cells in these niches (196).

VI.I Glucose, lactate and glutamine metabolism in cancer cells

Transformed cells reprogram their cellular metabolism to support cancer initiation, progression and aggressiveness (719). In 2011, Hanahan and Weinberg proposed this metabolic adaptation has one of an emergent hallmark of cancer (284). Since then, an explosion of studies in cancer cell metabolism have expanded our knowledge on how tumor-associated metabolic alterations have an impact at various stages of tumorigenesis (548).

Several oncogenic mutations drive alterations in cancer cell metabolism that allow them to survive in the harsh conditions of a malignant tumor and sustain their high proliferation needs. For example, in lung cancer, the copy number of mutant KRAS proportionally correlates with increase glucose uptake and the channeling of glucose carbons into the TCA cycle (347). In line with this, another study has found that paired colorectal cancer cell lines differing only for the mutational status of their KRAS or BRAF genes, displayed enhanced expression of glucose transporter-1 (GLUT1) and increased glycolysis when one of these two genes was mutated; it followed that glycolysis blockade hindered preferentially the growth of mutant colorectal cancer cells (790). Mirroring the pro-glycolytic effect of (proto)-oncogenes, loss of oncosuppressors such as PTEN in melanomas confers a glycolytic signature which results in increased glucose consumption, enhanced lactate production and reduced susceptibility to immunotherapeutic interventions as adoptive T cell transfer (102). As mentioned in the section above, hypoxia is a common trait of solid tumors and it drives the expression of PD-L1 on cancer cells (36). Importantly, PD-L1-mediated immune evasion is not only due to its binding to PD-1 on T cells, but PD-L1 in cancer cells also favors their glycolytic and glutaminolytic flux and therefore fosters metabolic competition in the TME (116). Although the yield of ATP production per molecule of glucose of aerobic glycolysis is much lower than that of OXPHOS, this metabolic switch meets the

energy requirements and underlies numerous advantages for cancer cells (40). The increased rate of glycolysis and branching metabolic pathways such as the pentose phosphate pathway (PPP) provide precursors for macromolecular biosynthesis (i.e., fatty acids and membranes, amino acids and proteins, etc.) and reducing equivalents in the form of NADPH required for rapid proliferation, together with nucleotide production (504). Importantly, the upregulation of glycolysis triggers the accumulation of extracellular lactate (299), which results in an acidic microenvironment that is harmless for cancer cells but fatal to normal cells (253). Although lactate was thought to be a mere waste product of glycolysis, developing evidences indicate that lactate could be used as a metabolic fuel for cancer cells. *In vivo* human experiments using isotope-labelled lactate have shown that in human lung tumors, lactate contributes more carbon to the TCA cycle than that of glucose (213, 313) (Figure 4B).

As for glucose uptake and glycolysis, oncogenic events have also been associated with a major boost in glutamine metabolism, such as MYC oncogene, the third most commonly amplified gene in human cancer (791), or mutations in the catalytic subunit of PI3K α (286), encoded by *PIK3CA*, mutated in a wide variety of human cancers including ~30% of colorectal cancers (CRCs) (617). These observations lead to the concept that cancer cells can rely on other sources to fuel carbons to the TCA cycle. Therapeutically speaking, the inhibition of these compensatory pathways may lead to synthetic lethality of cancer cells (719). Several studies have shown that glucose deprivation will foster glutamine uptake and entry into the TCA cycle in the form of α -ketoglutarate (α -KG), through a process known as glutamine anaplerosis (710, 781). Overall, glutamine can highly contribute to the core metabolic functions of cancer cells in different ways: energy formation, biomass assimilation and redox control (164). Glutamine contributes to ATP production by cancer cells through TCA cycle intermediates, NADH and FADH₂, which offer electrons for the mitochondrial electron transport chain. Also, although poor tumor vascularization induces hypoxia and inhibits OXPHOS, glutamine is redirected towards biosynthetic fates that do not require oxygen for the production of citrate, acetyl-CoA and lipids by reductive carboxylation (6). Glutamine transported into cells provides carbon and nitrogen required for the biosynthesis of glucosamine-6-phosphate, purine and pyrimidine nucleotides and non-essential amino acids, as aspartate and alanine (6). Interestingly, glutamine may be

exchanged to facilitate the uptake of a broad range of essential amino acids by LAT1/SLC7A5 (548) (*Figure 4B*).

VI.II Fatty acid metabolism and TCA cycle in cancer cells

Despite their voracity for glucose and glutamine, cancer cells have to deal *in vivo* with nutrient scarcity and with highly abnormal tumor vessels (548). To overcome these obstacles, cancer cells acquire alterations that will promote the use of alternative energetic pathways.

The TCA cycle is used as a source of numerous precursors to support proliferation. Furthermore, metabolites from the TCA cycle participate in the glycerol-phosphate and malate-aspartate shuttle systems responsible for moving reducing equivalents across the mitochondrial membranes that are required for biosynthesis. Glycerol-3-phosphate is a side product of glycolysis and is involved in lipid synthesis, while aspartate is used to synthesize proteins and nucleotides.

Although less studied, adaptations in lipid metabolism have also been pointed as one of the metabolic rewiring of transformed cells being important for cancer progression (140) (*Figure 4B*). Fatty acid metabolism constitutes another source of anabolic substrates and reducing equivalents for cancer cells. Fatty acid β -oxidation (FAO) is an important route for acetyl-CoA, NADH and FADH₂ and ATP production that will sustain cancer cell survival and proliferation. Metastasis formation and cell survival also rely on FAO (48). In human carcinomas, the fatty acid transporter CD36 identifies a unique subset of metastasis-initiating cells that respond to dietary lipids and CD36 expression correlates with poor prognosis (543). In mouse models, blockade of CD36-mediated fatty acid uptake restrains the appearance of metastasis or the shrinkage of already existing metastasis (543). In breast cancer, regulation of lipid metabolism by JAK/STAT3 pathway promotes cancer stem cell self-renewal and chemoresistance (749). On the other hand, *de novo* fatty acid synthesis (FAS), or lipogenesis, is also needed to produce new phospholipid bilayers (154). When tumors grow in areas with reduced blood vessel density the access to lipids in the circulatory system is reduced. Thus, by engaging FAS cancer cells are less dependent on the circulatory system around the tumor and can proliferate even in avascular conditions (575). Some cancer cells have the ability to store triacylglycerides in lipid droplets that can be used as an energy source (48). These lipid droplets

within cancer cells are now considered as hallmarks of cancer aggressiveness (48) and resistance to chemotherapy (569).

In conclusion, what Warburg and followers postulated at the beginning of the twentieth century, that enhanced glycolysis is due to mitochondrial dysfunction, has been now disproven by the experimental observation that most cancer cells maintain functional mitochondria (636). These organelles are essential for the production of cytoplasmic CoA, for citrate synthesis in TCA cycle, an important source of acetyl groups for protein acetylation and FAS (81), to restore the NAD^+ pool to support the high glycolytic flux (636) and, of course, mitochondria are key to sustain the electron transport chain, ending in ATP production.

VII. Immune cell metabolism

The emerging role of immunometabolism as an important regulator of immune system function has been widely investigated in the last decade. Immune cell activation leads to enormous alterations of several signaling pathways accompanied by a shift in energetic and metabolic demands to which immune cells need to respond and adapt. For instance, resting immune cells obtain most of their energy from FAO or the TCA cycle, linked to the generation of ATP via OXPHOS (55, 550), while after activation, interferon- γ (IFN- γ) or LPS-stimulated macrophages (M1-like) as well as T cells rapidly switch to aerobic glycolysis to face the increased demand for energy and biosynthetic precursors for proteins, lipids and nucleic acids (436, 505, 717). mTOR and AMPK play a central role in the orchestration of immune cell metabolism and highly contribute to the differentiation or polarization into specific immune cell subsets (415, 519). While mTOR is mostly required by anti-tumor effector immune cell subsets (i.e. M1-like macrophages, DCs, T_H1 and T_H17 CD4^+ T cells and effector CD8^+ T cells), AMPK supports pro-tumor immune cell subsets (i.e. T_{regs}) but also the formation of memory T cells. Overall, it is conceivable that different stimulus from the TME, namely scarce nutrient availability, low oxygen levels and the secretion of numerous cytokines and chemokines, may induce the activation of AMPK in immune cells, which in turns will lead to a metabolic switch to OXPHOS and consequently an induction of the immunosuppressive phenotype of

these cells. Therefore, the activation of AMPK in immune system usually correlates with increased tumor growth, aggressiveness and immune evasion (55).

Importantly, recent studies have brought to light an important caveat in the study of metabolism: the use of inhibitors and their potential unknown off-target effects. For instance, most of the studies on the FAO pathway relied on treatment with different doses of etomoxir to inhibit CPT1a, rate-limiting enzyme, and reached contradictory conclusions (715). Divakaruni et al. and Raud et al. have used genetic models to prove that the effects observed upon etomoxir treatment are not actually due to CPT1a inhibition, but rather due to off-target effects including suppression of OXPHOS and depletion of intracellular CoA levels (184, 573, 715). In the next section, we will dissect more in detail what is known and established regarding which metabolic pathways predominate in each immune cell subtype and how metabolism affects the balance between them. Nevertheless, it would be wise to keep in mind that new techniques in the metabolism field are blooming and therefore will likely challenge some of the current paradigms.

VII.I Metabolism and innate immunity

VII.I.I Macrophage metabolism

Macrophages are terminally differentiated innate immune cells that display high secretory, phagocytic and antigen-presenting abilities in response to tissue damage and infection. Given that macrophages provide first-line protection and possess critical functions to modulate tissue homeostasis and repair, they must maintain plasticity to adapt their functions to the biological need. Thus, it is reasonable to postulate that macrophages engage distinct metabolic programs during M1 and M2 activation to support their distinct functional specialties. In recent years, emerging evidence revealed that M1 macrophages enhance anabolic metabolism, including aerobic glycolysis, the PPP and FAS, while M2 macrophages engage catabolic metabolism, namely FAO and OXPHOS (452, 520, 521) (*Figure 5A,B*).

TLR signaling during M1 activation promotes aerobic glycolysis by boosting HIF-1 α and mTOR activity, which is central for the metabolic reprogramming of M1 macrophages. These signaling cascades drive a metabolic switch towards increased glycolysis, FAS and the PPP (232, 345, 593).

Inhibition of aerobic glycolysis or ablation of glucose transporter 1 (GLUT1) expression in macrophages blunts M1 polarization and the production of pro-inflammatory molecules while it promotes the secretion of anti-inflammatory cytokine IL-10 (469, 686). Evidences showed that alveolar macrophages with lack of Raptor have a reduction in glucose uptake, leading to a decrease in M1 polarization and pro-inflammatory responses (172), while macrophages deficient in TSC1 and TSC2 increase glycolysis, mitochondrial content, OXPHOS and FAS in an mTORC1-dependent manner, and consequently an increase in pro-inflammatory response and M1 polarization (172, 415). Furthermore, aberrant activation of AMPK during LPS stimulation could also impair macrophage M1 activation and stimulate production of anti-inflammatory cytokines (609). In addition to glycolysis and fatty acid metabolism, M1 and M2 macrophages display distinct activities on running TCA cycle. M1-like macrophages are proposed to have two recurrent and typical TCA cycle “break points” in which citrate and succinate accumulate (330) (*Figure 5A*). The first break point occurs at the level of isocitrate dehydrogenase (IDH), leading to the accumulation of citrate, whereas the second break point occurs at the level of succinate dehydrogenase (SDH), which allows for succinate buildup (141). The accumulation of succinate, either due to increased glutamine anaplerosis and oxidation in the TCA cycle or increased flux through the GABA shunt, can stabilize HIF-1 α and hence promote the transcription of pro-inflammatory and glycolytic genes, such as IL-1 β , NOS2, GLUT1 and PFKFB3 (294, 523, 686). It also follows that the increase in citrate efflux from the mitochondria sustains the NADPH levels necessary for FAS and ROS and NO production, through the actions of isocitrate dehydrogenase and malic enzyme (141, 319). Moreover, citrate can be used to fuel itaconate synthesis by mitochondrial aconitase 2 (ACO2) and cis-aconitate decarboxylase, also known as immune-responsive gene 1 (IRG1) (764). Itaconate is a signal metabolite with bactericidal activity (764) that increases following inflammatory stimuli. Itaconate is able to inhibit SDH activity and therefore to prevent the generation of ROS by the reverse electron transport (141, 380). During an inflammatory stimulus such as LPS, succinate accumulates so much in macrophages, that its SDH-mediated oxidation produces a large amount of coenzyme Q. Electrons are then forced back through complex I of OXPHOS, generating a large amount of ROS that activates the inflammasome and drives the production of pro-inflammatory signals such as IL-1 β , IL-6 and IL-18 (38, 469, 764). Therefore, the

production of itaconate provides a negative feedback mechanism to tune-down M1 activation by turning off SDH hyper-activity and enhancing NRF2-mediated anti-oxidant and anti-inflammatory responses (380, 470). Using murine models of peritoneal tumors, Weiss et al. showed that itaconate was highly abundant in peritoneal macrophages of tumor-bearing mice and that it promotes tumor growth (760). In addition to these findings, macrophage-specific deletion of glutamine synthetase (GS), the enzyme that generates glutamine from glutamate, has been shown to cause glutamate rerouting to the GABA shunt with accumulation of succinate at the TCA cycle (535). Most of the findings in the field of macrophage metabolism are either *in vitro* or in contexts other than cancer. The latter observation on GS deletion has actually been translated in mouse tumor models where we have shown that succinate accumulation following genetic deletion of glutamine synthetase directly and indirectly (through HIF-1) sustains a rewiring of TAMs into an M1-like phenotype, which leads to increased T cell recruitment and activation but also tumor blood vessel normalization, with increased perfusion, reduced permeability and prevented cancer cell dissemination (535). In addition to metabolic checkpoints controlled by the production of metabolites, the regulation of the electron transport chain (ETC) complex assembly also influences macrophage functions. Activating macrophages with living bacteria or bacterial products induce massive ROS production to stimulate pro-inflammatory activity by impairing the formation of the ETC supercomplex (245). In contrast, LPS-triggered NO production plays a negative feedback mechanism to resolve persistent M1 activation by blunting ETC function and OXPHOS activity (469, 714). A recent study demonstrated that macrophage-associated VSIG4, a B7-related protein identified as a negative regulator of T cell activation (732), could act as a M1 checkpoint inhibitor that reprograms pyruvate mitochondrial metabolism by reducing the conversion of pyruvate to acetyl-CoA, resulting in a reduction in ROS secretion and inhibits the pro-inflammatory responses of macrophages (404). In this line, LLC murine tumors were significantly smaller in VSIG4-deficient mice (410).

In contrast to M1 macrophages, M2 macrophages engage catabolic metabolism and possess low glucose flux but a high rate of FAO (*Figure 5B*). Expression of carbohydrate kinase like protein (CARKL) in M2 macrophages contributes to the reduced PPP flow (291). Moreover, M2 macrophages engage a PGC-1 α -dependent metabolic switch to sustain their OXPHOS activity and

FAO (722). Targeting FAO or PGC-1 β impairs M2 marker gene expression in macrophages stimulated with IL-4 (722). Moreover, CD36-mediated fatty acid uptake and subsequent liposomal lipolysis support both OXPHOS and M2 marker gene expression in IL-4-stimulated macrophages (308). Recent studies by Divakaruni et al. and Nomura et al. using a genetic deletion of CPT1a or CPT2 and pharmacologic models challenged this idea (184, 514). Divakaruni et al. suggest that high doses of etomoxir, considered a CPT1a inhibitor, impair the *in vitro* IL-4 mediated M2 polarization of macrophages due to the depletion of the intracellular free CoA pool but independently of expression of CPT1a or CPT2 (184). It still remains unknown how these mechanisms are at play in TAMs. Interestingly, several recent works reported that glycolysis plays a crucial role in M2 polarization even though IL-4-stimulated macrophages have only a slight increase of glucose metabolism compared to naïve macrophages (309). Activation of ATP citrate lyase (ACLY), an enzyme of FAS, and OXPHOS in M2 macrophages also stimulate production of acetyl-CoA, which directly impacts the expression of certain M2 marker genes via histone acetylation (147). Furthermore, impaired cholesterol efflux in macrophages leads to an elevated lipid content accompanying with M2-skewing phenotype (586, 643). However, uptake of modified low-density lipoprotein (LDL) in macrophages has also been reported to stimulate pro-inflammatory activity and M1 activation (301). Similar to LDL-modulated macrophage polarization, uptake of high density lipoprotein (HDL) has also been shown to promote both M1 and M2 phenotypes in macrophages (160, 620). Although it remains unclear why cholesterol metabolism could lead to distinct immune responses in macrophages, these studies uncover that the composition of lipid species and metabolic fate of those uptaken lipids may orchestrate macrophage polarization by modulating functions of nuclear receptors, such as PPAR and LXR (549). In contrast to the broken TCA cycle displayed by M1 macrophages, M2 macrophages have an intact TCA cycle and highly depend on glutaminolysis, which supports epigenetic reprogramming of M2 macrophages through the production of α -ketoglutarate (330, 417). M2 macrophages express high levels of PFKFB1 instead of PFKFB3 to reduce glucose influx (593) while TAMs may rather rely on PFKFB3 (761). A recent study in mouse tumor models has shown that accumulation of intracellular lactic acid could stimulate M2 activation by promoting HIF-1 α

stability, leading to VEGF production and tumor angiogenesis (135). Mirroring this, we have shown that an increase in glucose uptake and glycolysis directly in TAMs (by the genetic deletion of the mTOR inhibitor REDD1) does not change the polarization of macrophages (M1 and M2-like markers and functions) but rather subtracts glucose to the neighboring endothelium, breaking endothelial glycolysis and resulting in a more quiescent, less leaky tumor vasculature (87), which overall prevented cancer cell intravasation and metastasis (761). PFKFB3 knockout in REDD1-deficient macrophages completely abrogated this protective effect and restored a dysfunctional tumor angiogenesis and metastasis (761). Whether the reduced glucose uptake by REDD1-deficient macrophages alleviates the competition for glucose between TAMs and cancer cells or other stromal cells (i.e. pericytes and immune cells) and whether TAM-derived lactate following glycolysis can “signal” to other stromal cells or cancer cells remain to be elucidated (*Figure 5B*).

Together, these findings reveal that metabolic processes utilized by macrophages support metabolic demand and tailor immune responses by intervening signaling cascades and epigenetic programs. Furthermore, the emerging evidence suggest that targeting metabolism may be an attractive approach to fine-tune macrophage immune response in different diseases and further highlight the possibility that macrophages may control their surrounding neighbor cells through their metabolic processes (452, 535, 761).

VII.I.II Neutrophil and MDSC metabolism

Although mounting evidence shows the crucial role of TANs/MDSCs in the TME, the metabolic programming of these neutrophils is still not fully characterized (*Figure 6*). Neutrophils contain relatively few mitochondria and the energy required for neutrophil chemotaxis and activity is mostly derived from glycolysis (366, 592). Chacko and co-workers characterized the bioenergetic profile of human neutrophils and observed that these cells were unresponsive to mitochondrial respiratory inhibitors, indicating that they have a minimal requirement for OXPHOS and are primarily glycolytic (109). This observation has been underscored by Sadiku et al, who demonstrated that PHD2 inactivation and subsequent HIF-1 α stabilization increased glycolytic flux and glycogen stores and promoted aberrant neutrophilic responses (608). Moreover, it has been described that the PPP, namely glucose-6-phosphate dehydrogenase (G6PD) activity, is essential to sustain the NADPH

required by NADPH oxidase (NOX) to form ROS and fuel the respiratory burst (264). Glucose uptake and a shift toward PPP are essential for NETs formation (28, 336). Yet, a recent study has reported that glutamate and proline can maintain the ability of intratumor immature low-density neutrophils (but not in high-density neutrophils) to form NETs even under glucose deprivation, thereby supporting their pro-metastatic function (306).

MDSCs activate AMPK and rely on fatty acid uptake and FAO to support their immunosuppressive functions (282, 304). In this line, Rice et al. have recently described that tumor-elicited immature c-Kit⁺ neutrophils acquire an oxidative metabolic profile (i.e. high FAO and OXPHOS) that supports NOX2-mediated ROS production and T cell suppression (582). In tumor models and cancer patients, FATP2 is upregulated exclusively in PMN-MDSCs in response to GM-CSF/STAT5 signaling (723). Uptake of arachidonic acid by FATP2 is required for the synthesis of PGE₂ and for the immunosuppressive functions of PMN-MDSCs. Selective blockade of FATP2 by lipofermata reinvigorates anti-tumor adaptive immunity, delays tumor growth and promotes tumor regression in combination with immunotherapy (723). Interestingly, bone marrow neutrophils from mice with early stage tumors (termed PM-LCs after “PMN-MDSC-like cells”) displayed an increased spontaneous motility and lacked immunosuppressive activity, a trait that is lost as tumors progress. An increase in glycolysis and OXPHOS with a concomitant elevation in ATP production and the establishment of an autocrine ATP/ADP signaling through purinergic receptors account for the superior migratory features of these non-immunosuppressive PM-LCs (546) (see section IX.I for further details on purinergic signaling).

Very little is known regarding amino acid metabolism in neutrophils. High expression levels of ARG1 and NOS2 are a hallmark of MDSCs/N2 neutrophils and are crucial to deploy their immunomodulatory functions. For instance, IL-8 mediated exocytosis of neutrophil-derived ARG1 depletes arginine levels in the TME (600), impairing T cell proliferation, and production of NO by NOS2 drives CD8⁺ T cell suppression (132). Further studies are required to shed light into whether arginine metabolism controls neutrophil functions *per se*, in addition to the abovementioned effect on T cell suppression (*Figure 6*).

Taken together, these studies reveal that tumor progression and the acquisition of neutrophils/MDSCs' immunosuppressive features are concomitant with a dynamic evolution of their metabolism and nutrient usage, going from glucose-fueled glycolysis and OXPHOS to fatty acid-fueled FAO in the early and late stages, respectively. Moreover, this metabolic evolution might likely be dictated by the microenvironment of the organs where they are located, namely the bone marrow, blood or tumor. Further investigations dissecting how the environment modulates the metabolism of neutrophils and MDSCs and how these metabolic programs impact their function will help to develop immunotherapies targeting these cell types.

VII.I.III Dendritic cell metabolism

Dendritic cells (DCs) are professional antigen-presenting cells and express a variety of pattern recognition receptors (PRRs). Upon activation via PRR ligation, DCs undergo transcriptional and translational changes that allow them to process the antigen, migrate generate immunomodulatory molecules and mount specific immune responses. Noteworthy, *in vitro* differentiation of bone marrow-derived DCs (BMDCs) does not technically allow to generate pure DC subsets, and this limitation needs to be taken into account when drawing conclusions (recently revised in (254, 755)). More studies or technical advances are required to further detail subset-specific metabolic traits that reflect what occurs *in vivo*.

Activated DCs rely on glycolysis and the PPP to support their demands to produce energy, membranes and inflammatory mediators and their migratory capacity. In response to TLRs ligation, DCs immediately upregulate glucose uptake and lactic acid production, mediated by the PI3K/Akt pathway (367) and the TBK1/IKK ϵ pathway (206). Furthermore, the deletion of TSC1 and concomitant activation of mTORC1 in DCs increased glycolysis, mitochondrial respiration and lipid synthesis in part mediated by Myc, highlighting the importance of these master regulators for BMDC maturation (751). Glycolysis feeds the PPP to produce NADPH as well as the TCA cycle to produce mitochondrial citrate (206). Intriguingly, a recent study further revealed that TLR4 signaling stimulates glycogen metabolism to fuel citrate production and early glycolysis in DCs, thereby supporting early effector functions of TLR-activated DCs (695). Citrate is then exported to the cytoplasm where, together with NADPH, fuel FAS (206). Unlike in macrophages, where citrate is

used for the production of various mediators, in DCs the citrate flux into FAS is required for the expansion the endoplasmic reticulum (ER) and the Golgi apparatus (206) (*Figure 7A*). This uniqueness of citrate utilization in DCs has been suggested to be a critical event for supporting the maturation and specialized biological functions in activated DCs (206, 254, 755). In some NOS2-expressing DCs, mTORC1/HIF-1 α -driven NO production by NOS2 impairs electron transport chain (ETC) activity and thereby sustains aerobic glycolysis (207). This circuit seems to be sensitive glucose and likely to several amino acids (387). Importantly, most DCs are NOS2-deficient and rely on other mechanisms to sustain glycolysis, which may involve type I IFN, HIF-1 α , TBK1 and IKK ϵ , and may still partially maintain OXPHOS (206, 254, 270, 328, 387, 540, 755). Yet, exogenous NO could also promote HIF-1 α stabilization, raising the possibility that other NO-producing cells can shape DC metabolism (387). Guak et al. recently demonstrated that glycolytic metabolism is also essential for the oligomerization of CCR7 and the migration of DCs towards the lymph nodes, while mitochondrial metabolism is dispensable (270). The mechanism linking glycolysis to CCR7 oligomerization demands further investigation.

Although in general glucose metabolism and FAS enhance the pro-inflammatory features of DCs, several studies have suggested that inhibition of these pathways actually enhances DC-induced T cell activation (8, 387, 578). In a B16 melanoma model, mTOR inhibition prior to DC vaccine enhanced their anti-tumor efficiency (8). Lawless et al. propose a metabolic competition between interacting DCs and T cells in which both cell types engage contrasting metabolic states (glycolytic T cells and non-glycolytic DCs) to maximize the pro-inflammatory functions of both immune cells. Mechanistically, glucose limitation within the DC-T cell synapse inhibits the mTORC1/HIF-1 α /NOS2 circuitry in DCs, consequently tuning down glycolysis (387). Whether this favorable and synergic metabolic competition also takes place in the TME or in the tumor draining lymph nodes remains unknown.

In addition to glucose metabolism, type I interferon can enhance mitochondrial activity and FAO which support maturation of plasmacytoid DCs (pDCs) (773) (*Figure 7B*). In contrast to how fatty acid metabolism support pDC maturation, in tumor-bearing mice as well as in cancer patients a tumor-derived unknown factor induces lipid accumulation in cDCs and impairs their ability to process

tumor antigens and to effectively activate T cells. Both activation of FAS and lipid uptake via the upregulation of Msr1 expression contribute to the accumulation of lipids (296). Normalization of lipid abundance in DCs by pharmacological inhibition of FAS by TOFA, an ACC inhibitor, synergized with DC vaccination in murine tumor models (296). In this line, ROS-mediated activation of XBP1, an ER stress-induced transcription factor, elevated FAS and triggered the accumulation fatty acids and tolerogenic phenotype in tumor-infiltrating DCs (TIDCs) with markers of cDC2s (151). In a model of ovarian cancer, targeting XBP1 in TIDCs enhanced their anti-tumor function and enhanced the survival. However, it remains unclear whether TIDCs lose their ability to oxidize fatty acids and how accumulation of fatty acids could drive tolerogenic phenotypes. Moreover, DCs can also modulate their function and activity by sensing extracellular metabolites such as succinate (606), short chain fatty acid (660), adenosine/ATP (406) and lactic acid (501). It remains largely unexplored how amino acids can influence activation, maturation and functions in DCs (*Figure 7A,B*).

VII.I.IV Innate lymphoid cell (ILC) metabolism

In the bone marrow, NK cells develop and mature to fully differentiated naïve NK cells and this maturation process seems to be associated with distinct metabolic changes. In contrast to terminally differentiated cells, immature NK cells exhibit higher expression of certain nutrient receptors, such as the transferrin receptor CD71 and the amino acid transporter SLC3A2/CD98 as well as increased glucose uptake (445). It is likely that this metabolic profile is a prerequisite for the adequate proliferation and differentiation of immature NK cells.

Mature non-activated NK cells have a relatively low glucose uptake and show increased expression of genes that are involved in FAO and OXPHOS (346). Long-term cytokine stimulation increases glycolysis and OXPHOS (346, 445). mTORC1 plays a pivotal role in the development and differentiation of murine NK cells since it drives the increase in glycolysis during cytokine-induced NK cell activation (188, 445, 728). The increase in glucose metabolism is a prerequisite for the production of IFN- γ and granzyme B (GzmB) and, therefore, for the acquisition of effector functions (188). Moreover, mTOR-driven glycolysis is required to direct the lytic granules of activated NK cells towards the synapse with cancer cells (468). In ILC3s, unlike their counterpart T_H17, mTORC1/HIF-1 α -driven glycolysis is accompanied by an increase in mROS, which acts as a loop to sustain HIF-1 α

and ROR γ t (176). Although way less is known about the metabolism of human NK cells, the role for glucose metabolism and mTORC1 as master regulator of human NK cell effector function has been confirmed (344, 444, 445, 468). Despite its undisputed role as a key metabolic regulator, the precise mechanisms of mTORC1-mediated NK cell metabolism remain mostly unknown. In light of the studies highlighting the involvement of c-Myc, SREBPs and HIF-1 α on T cells metabolism and function (discussed below), it can be speculated that these transcription factors might also play a role in NK cell metabolism. It has been recently shown that SREBP transcription factors are required to induce a unique metabolic program in cytokine-triggered NK cells. Despite SREBPs are known for their crucial role in regulating lipid synthesis, in the context of NK cell activation SREBPs were essential to increase glycolysis and OXPHOS and to support NK cell effector function (23). SREBP1c induces the use of the citrate-malate shuttle (CMS) via the expression of *Slc25a1* and *Acly*. The CMS contributes to the formation of mitochondrial NADH donors for OXPHOS, of cytosolic NAD⁺, a cofactor of glycolysis, and cytosolic acetyl-CoA, which could potentially be used for acetylation reactions rather than for FAS (23). A recent study demonstrated that an NK cell-specific deletion HIF-1 α leads to impaired NK cell activation in response to NK cell receptor ligands under normoxic and hypoxic conditions (373). Therefore, it would be interesting to see whether HIF-1 α -dependent metabolic changes contribute to this phenotype (*Figure 8*).

Less is known regarding to which extent amino acids and fatty acids can fuel the metabolic demands of activated NK cells. Loftus et al. have recently reported that c-Myc accumulation, but not HIF-1 α , is crucial for the proper activation and IFN- γ and GzmB production of cytokine-stimulated NK cells (IL-2/IL-12). While mTORC1 promotes the translation of c-Myc minutes after IL-2/IL-12 stimulation, prolonged c-Myc levels are sustained by the SLC7A5-mediated import of long neutral amino acids (LNAAs) (i.e. methionine, phenylalanine, tyrosine, arginine and/or tryptophan) in exchange for intracellular glutamine (424). These data could at least partially explain the underperformance of NK cells in glutamine-deprived environments such as the TME. Although glutamine underwent glutaminolysis and glutamine anaplerosis in this setting, these pathways were not involved in the modulation of IFN- γ and GzmB levels. This suggests that the use of glutamine metabolism inhibitors could have therapeutic benefits by impairing cancer cell metabolism, promoting

macrophage M1 skewing as well as by increasing glutamine availability in the TME and thereby fueling NK cell anti-tumor functions (424, 535, 768). Further research is required to shed light on which LNAA is responsible for the regulation of c-Myc, how other activation queues modulate amino acid metabolism in NK cells and on the relevance of NK cell amino acid metabolism *in vivo* (Figure 8).

A recent study has demonstrated that obesity promotes the uptake of lipids, the accumulation of lipid droplets and lipid metabolism by NK cells both in mice and in human, which results NK cell paralysis and impaired their tumor killing capacity. The lipid-induced activation of the PPAR α/δ pathway and the concomitant inhibition of mTOR-mediated glycolysis and the activation of lipid oxidative metabolism in activated NK cells downregulates IFN- γ and GzmB and prevents the transport of the lytic granules to the tumor synapse (468). The presence of free fatty acids during the *in vitro* activation of NK cells prior to adoptive cell transfer or diet-induced obesity impaired the anti-tumor functions of NK cells in murine tumor models (468). This study supports the idea that reducing dietary fat intake may help to fuel NK cell mediated anti-tumor functions and raises caution towards the untargeted use rapamycin (Figure 8).

NK cells are part of the ILC family, yet, very little is known about metabolism of other ILC subsets and its functional impact. In analogy to naïve NK cells, quiescent ILC2 and ILC3 cells predominantly use OXPHOS rather than glycolysis prior to activation (763). A recently published study by Li et al. suggests that hypoxia and the HIF signaling pathway directly impacts on the late stage of maturation and function of ILC2 cells via the regulation of the IL-33-ST2 pathway (407). This very elegant study suggests that the VHL-HIF-1 α pathway plays very important role as a checkpoint for the terminal differentiation of ILC2 cells located in peripheral organs such as the intestine, lung or adipose tissue. VHL promotes maturation of ILC2s by restraining the HIF-1 α -driven glycolytic flux and by altering the epigenetic control of ST2 gene and downstream targets. This study highlights that the metabolic status of ILC precursors actively participates in the regulation of their maturation and is not just a “default” metabolic state during low energy-demanding states. In lung inflammation, activated ILC2 express high levels of arginase-1 (ARG1) and metabolize extracellular L-arginine. ARG1 expression in ILC2 is required to sustain proliferation and acts as a metabolic checkpoint as it fuels polyamine

biosynthesis and enhances aerobic glycolysis (480). Of note, ARG1-deficient ILCs did not reroute arginine towards other pathways, namely NOS2 (*Figure 8*). *Arg1* gene expression can be induced by hypoxia (426), however this raises the question of how ARG1 activity is regulated under hypoxia in ILC2 context, and how the HIFs participate in that regulation. Further research on ILC2 and ILC3 is desirable to extend our knowledge how their function and metabolism are modulated by hypoxia and the HIF signaling pathway.

In summary, the metabolism NK cells as well as other ILC subsets remain largely unexplored but holds great promise for therapeutic exploitation of in a variety of diseases including cancer.

VII.II Metabolism and adaptive immunity

T cells engage distinct metabolic programs during activation, proliferation and differentiation. In the quiescent state, naïve T cells mainly rely on FAO and OXPHOS to support their low metabolic demands (*Figure 9A*). Upon TCR and co-stimulatory receptor engagement, activated T cells rewire their metabolism in order to meet the energetic and anabolic requirements to support their rapid proliferation and effector function (520). Activated T cells increase glucose and glutamine uptake, aerobic glycolysis, the PPP, OXPHOS, glutaminolysis and FAS while they suppress FAO. Moreover, the TCA cycle is also used as a source of intermediates for nucleotide, protein and lipid synthesis (*Figure 9B*).

CD28 co-stimulatory receptor engages signaling cascades to activate the PI3K/AKT pathway and increase the glycolytic flux that, in turn, activates mTOR activity (231, 564). Raptor-mTORC1 signaling couples glycolysis, OXPHOS, FAS and cholesterol synthesis to the TCR-induced exit from quiescence (784). TSC2 deficiency increases glycolysis, decreases FAO and stimulates effector T cells (561). Accordingly, TSC1 deficiency in T cells leads to reduced mitochondrial membrane integrity and increases ROS. mTOR activation also increases HIF-1 α and Myc expression. HIF-1 α upregulates the transcription of the glucose transporter GLUT1 and the glycolytic enzyme lactate dehydrogenase A (LDHA) and boosts the activity of pyruvate dehydrogenase kinase 1 (PDK1), thereby augmenting glycolytic and glutaminolytic metabolism (350). The tremendously increased glycolytic flux becomes an important source of ATP and fuels the PPP and serine biosynthesis pathway that provide intermediates for nucleotide and fatty acid synthesis (747). It has been shown

that glycolysis is specifically required for effector cytokine production and expansion rather than supporting survival and development of memory T cells (300, 679). Production of phosphoenolpyruvate (PEP), a metabolic intermediate of glycolysis, inhibits SERCA and maintains a Ca^{2+} cytoplasmic pool necessary to sustain NFAT signaling upon T cell activation (300). Overexpression of phosphoenolpyruvate carboxykinase 1 (PCK1), the enzyme that converts TCA-derived oxaloacetate into PEP, prior to adoptive cell transfer of CD4^+ or CD8^+ T cells circumvented the requirement for glucose and boosted their $\text{IFN-}\gamma$ production in the TME, which suppressed tumor growth and prolonged survival in a murine model of melanoma (300). Moreover, several works report that when the glycolytic flux is low, glycolytic enzymes acquire other roles and can regulate cytokine production, indicating that the switch to aerobic glycolysis also modulates T cell effector functions (115, 457, 552). These mechanisms may partially underlie the dysfunction of effector T cells in the glucose-deprived TME. Noteworthy, OXPHOS is still required not only as a source of ATP, but also to maintain low levels of mitochondrial ROS that sustain NFAT signaling and T cell expansion upon activation (642) (*Figure 9B*).

Apart from changes in glucose metabolism, T cell activation is also coupled with increased amino acid metabolism. Myc stimulates glutaminolysis to fuel polyamine biosynthesis, which is essential for the activation-induced metabolic reprogramming of T cells (747). While low levels of mitochondrial ROS are required for proper T cell activation, high levels are detrimental (641, 642). Upon activation, glutathione (GSH), generated in part from glutamate by glutamate cysteine ligase (GCLC), buffers ROS levels and allows low ROS-dependent NFAT activation and mTORC1 to drive c-Myc expression and the shift towards glycolysis and glutaminolysis (440). In certain circumstances such as hypoxia, glutamine anaplerosis feeds the reductive carboxylation of α -ketoglutarate (α -KG) into citrate, which is subsequently exported to the cytoplasm and fueled into FAS (463). The parallel increase in FAS and in the PPP coordinately sustain nucleotide and lipid synthesis while maintaining the redox balance (463, 747). Moreover, glutamine anaplerosis also contributes to the formation of the TCA intermediate oxaloacetate. In proliferating cancer cells, oxaloacetate is a precursor for aspartate generation and supports protein and nucleotide synthesis (163). Whether a similar mechanism is also used by activated T cells to sustain their proliferation rate remains to be clarified. Other amino acids

are also important for the proper activation of T cells. The system L transporter, SLC7A5, which controls the uptake of leucine and other long neutral amino acids (LNAAs), is coupled to mTOR activation, sustained c-Myc expression, amino acid transporter expression, T cell activation and clonal differentiation. SLC7A5-null T cells are unable to activate mTORC1 and c-Myc and therefore fail to reprogram their metabolism upon TCR stimulation (659). Moreover, T cell proliferation requires the uptake of extracellular L-arginine to sustain the expression of certain TCR components (591) and cell cycle progression (589). In consequence, depletion of this amino acid by the high ARG1 and NOS2 activity in myeloid cells, as is often observed in the TME, leads to T cell anergy (186, 588, 590, 684). So far, little is known regarding the metabolic fates of arginine in T cells. However, a few studies point towards specific roles of arginine and arginine-related enzymes in T cell differentiation (782), death (729) and memory acquisition (249, 729), which will be further discussed in the next sections (*Figure 9B*).

In addition to the general metabolic regulation and reprogramming upon activation, different subsets of effector and regulatory T cells engage unique metabolic pathways in order to support their specialized functions (*Figures 10,11*) and the acquisition of T cell memory is also associated to a wave of metabolic reprogramming that differs from activation (*Figure 9C* and section VII.II.III). In the next sections, we will describe how metabolism controls CD4⁺ T cell differentiation and effector function, CD8⁺ T cell function and T cell memory acquisition.

VII.III CD4⁺ T cell metabolism

The differentiation of activated CD4⁺ T cells into effector T_H1, T_H2 and T_H17 cells or into T_{regs} cells engages different molecular mechanisms and is linked to a metabolic rewiring to adapt to their distinct usage of glucose, amino acid and lipid metabolism. In general, effector T helper cells predominantly engage aerobic glycolysis and FAS while T_{regs} mostly rely on FAO and OXPHOS (251, 652) (*Figures 10,11*).

T_H1, T_H2 and T_H17 differentiation requires an increase in glucose uptake and aerobic glycolysis, while T_{regs} preferentially use FAO (435, 467). T_H1 cells require enhanced glucose metabolism to fuel their effector function through the posttranscriptional and epigenetic regulation of IFN- γ by glycolytic enzymes and metabolites (115, 300, 552). Chang et al. unraveled a new function of glyceraldehyde-3-

phosphate dehydrogenase (GAPDH) as a metabolic checkpoint: GAPDH sequesters IFN- γ mRNA by binding its 3'-UTR region and inhibits its translation. Since aerobic glycolysis engages GAPDH enzymatic function, upon CD4⁺ T cell activation IFN- γ mRNA is freed from GAPDH inhibition and promptly translated (115). Moreover, the expression of lactic acid dehydrogenase A (LDHA) relieves the burden of mitochondria as an energy house to burn acetyl-CoA for ATP production. Hence, citrate can be exported to maintain high concentrations of cytosolic acetyl-CoA, which is used to acetylate histones of the promoter of IFN- γ gene, fueling IFN- γ transcription and maintaining T_H1 immune response (552). Notably, T_H2 cells have a higher OXPHOS rate than other T helper subsets, suggesting that glycolysis-derived pyruvate is rather directed to feed the TCA cycle than used to produce lactate (783). T_H17 cells, oppositely to T_H1 and T_{regs}, express high levels of pyruvate dehydrogenase kinase 1 (PDHK1 or PDK1). PDHK1 activity halts the entry of pyruvate in the TCA cycle and diminishes the formation of mitochondrial ROS, which is crucial to support T_H17 differentiation (250). Knockdown or inhibition of PDHK1 selectively suppresses T_H17 cells while sparing T_H1 and increasing T_{regs}, through a mechanism at least partially involving ROS-mediated inhibition of IL-17 production (250).

Different transcription factors support these changes in glycolytic activity. T_{regs} exhibit better peripheral tolerance through metabolic adaptation. In low glucose and high lactate conditions, Foxp3 suppresses c-Myc expression to turn glycolysis off. Concurrently, Foxp3 induces OXPHOS and increases the NAD⁺/NADH ratio to resist lactate-mediated suppression of T cell function and proliferation (16). IRF4 controls T_H1 metabolism and effector function (438). HIF-1 α is the well-studied transcription factor controlling the balance between T_H17 cells and T_{regs} (652) (section V.II.I). T_H17 differentiation requires HIF-1 α to engage glycolytic activity and to promote IL-17 expression via the formation of a complex with ROR γ t and p300 (652). Moreover, HIF-1 α attenuates T_{regs} development through binding Foxp3 and targeting it for proteasomal degradation (156) as well as through the inhibition of pyruvate entry in the mitochondria and OXPHOS-driven immunosuppressive capacities (473). Foxo1-mediated transcription also skews CD4⁺ T cell metabolic process into reduced glycolytic but enhanced OXPHOS (506, 529). Foxo1 is a pivotal regulator of T_{regs} cell function and T_{regs}-specific deletion of Foxo1 induces the development of a fatal

inflammatory disorder (529). Unexpectedly, tumor-infiltrating T_{regs} downregulated Foxo1 target genes and forced expression of Foxo1 selectively in T_{regs} was sufficient to deplete them, thereby activating effector CD8⁺ T cells and inhibiting tumor growth (429) (Figures 10,11).

The catalytic subunit mTOR is required for effector T cell differentiation and its deficiency leads to the differentiation of T_{regs} (166). While mTORC1 signaling participates in T_{H1}, T_{H2} and T_{H17} differentiation, mTORC2 is exclusively involved in T_{H2} differentiation (167, 378, 783, 784). PI3K/Akt pathway and Rheb/mTORC1 signaling is required for the differentiation of T_{H1} and T_{H17} cells *in vitro* through the induction of the transcription of T-bet and ROR γ t, respectively (167), and the translocation of ROR γ t to the nucleus (378). Deletion of Rheb in CD4⁺ T cells impairs the development of experimental autoimmune encephalitis (167). In contrast, Rictor/mTORC2 signaling is involved in GATA3 transcription and T_{H2} cell development both *in vivo* and *in vitro* (167). Furthermore, *in vitro* as well as in a model of T_{H2}-mediated asthma, Rheb-independent Raptor/mTORC1-driven or RhoA/mTORC2-driven glycolytic program positively regulates GATA3, IL-2Ra, IL-4Ra and IL-4 and is therefore crucial for T_{H2} differentiation, but not for T_{H1} and T_{H17} (783, 784). It still remains unknown how these mechanisms may dictate the differentiation of T cells towards a specific subset within the TME.

FAS is strongly required for effector CD4⁺ T cells but dispensable for T_{regs} differentiation. Deletion of acetyl-CoA carboxylase 1 (ACC1) in CD4⁺ T cells blocked FAS and interfered with the metabolic flux of glucose-derived carbon via glycolysis and the TCA cycle, which strongly impaired the differentiation of effector CD4⁺ T cells *in vitro*, in particular T_{H17}, and induced the differentiation of T_{regs} (53). In the EAE model, T cell specific ACC1-deficient mice had lower CD4⁺ T cell infiltration in the spinal cord, lower percentage of T_{H1} and T_{H17} cells and higher percentage of T_{regs} and were protected against EAE (53). Moreover, ACC1 controls the DNA binding ability of ROR γ t and therefore, the transcription of ROR γ t downstream genes (203). In humans, obesity upregulates ACC1 and thereby promote T_{H17} differentiation (203). Instead, T_{regs} rely on the uptake of exogenous fatty acids, that enter in the mitochondria via CPT1a to sustain their high rate of FAO (53, 250, 467). In a recent study, Raud et al. proved that CPT1a is dispensable for T cell homeostasis and for the differentiation and suppressive function of T_{regs}. The inhibiting effect of high doses of etomoxir on

T_{regs} differentiation are due to CPT1a-independent off-target effects that reduce the levels of TCA cycle intermediates and OXPHOS (573). Surprisingly, Pacella et al. revealed that expansion of activated T_{regs} in the context of the tumor is not only sustained by FAO of extracellular lipids, but also by a strong increase in glycolysis that concomitantly fuels FAS (531). This way, T_{regs} may impose a competition for glucose as a mechanism to exert their immunosuppressive functions in the TME. This finding has recently been reinforced by the work of Liu et al. that identifies the establishment of a metabolic competition for glucose during the crosstalk between human effector T cells and T_{regs} , which causes DNA damage and the senescence of effector T cells (419). A recent study in a mouse model of glioblastoma has suggested that activation of different metabolic routes may serve distinct purposes in T_{regs} function, and that HIF-1 α is involved in this switch (473). While hypoxia and HIF-1 α -driven glycolysis is important for tumor-infiltrating T_{regs} migration, FAO and mitochondrial metabolism are essential to sustain their immunosuppressive ability. Inhibition of T_{regs} migration via genetic deletion of HIF-1 α or inhibition of FAO by etomoxir increases the lifespan of glioblastoma-bearing mice in a mechanism that seems to involve reactivation of anti-tumor CTLs (473). In addition to FAS, fatty acid uptake is required for the proliferation of CD4⁺ T cells after antigen stimulation. Mechanistically, TCR-activated mTORC1 signaling in CD4⁺ T cells controls fatty acid biosynthesis through SREBP1 activation and fatty acid uptake through PPAR- γ activation (15). Lipids are necessary to generate membranes and also important for posttranscriptional modifications (423). Thus, it would be attractive to study whether lipid synthesis could also influence the function of transcription factors involved in T cell differentiation (*Figures 10,11*).

The amino acid transporter SLC1A5/ASCT2 facilitates glutamine uptake, which is required for TCR-stimulated mTORC1 activation and T cell effector function. Glutamine deprivation or the deficiency of SLC1A5/ASCT2 limits T_H1 and T_H17 differentiation (333, 500) and drives the formation of T_{regs} (355, 465). The glutamine-dependent accumulation of the TCA intermediate α -ketoglutarate (α -KG) is required for T-bet expression and the activation mTORC1 signaling to support T_H1 differentiation, and to further inhibit T_{regs} generation (355). The predominance of T_{regs} upon glutamine restriction can be mimicked by targeting the glutamine-dependent nucleotide synthesis pathways and abrogated by inhibiting glutamine synthetase (GS), suggesting that T_{regs} have a superior capacity to produce

endogenous glutamine in conditions of low extracellular glutamine (465). However, it still remains unclear which enzyme is responsible for the conversion of glutamate into α -KG to support T-bet and T_H1 differentiation. T_H17 differentiation under T_H17 polarizing conditions requires the silencing of the *Foxp3* promoter, which is achieved through the GOT1-mediated transamination of glutamate into α -KG and subsequently into *R*-2-hydroxyglutarate (*R*-2-HG) by IDH1/2. In turn, *R*-2-HG maintains the hypermethylation and silencing of the *Foxp3* promoter by antagonizing the TET1/2 demethylases (774). In line with the observation that glutamine metabolism is preferentially increased in T_H17 cells (250), Johnson et al. have recently shown that glutaminase (GLS) activity sustains T_H17 and restrains T_H1 and CTL development and effector function. Mechanistically, GLS is required to neutralize ROS by glutamate-derived glutathione as well as to inhibit IL-2/mTORC1 signaling via α -KG-mediated changes in chromatin accessibility (333). Interestingly, while chronic or complete GLS deficiency impairs overall effector T cell function *in vivo*, transient GLS inhibition prior to adoptive cell transfer of CAR-T cells improved their effector function against B cell leukemia cells, indicating that transient GLS inhibition has the potential to enhance anti-tumor T_H1 responses *in vivo* (333). Intriguingly, these studies indicate that glutamine-derived α -KG controls on one hand the T_H1/T_{regs} balance in favor of T_H1 , and on the other hand the T_H1/T_H17 balance in favor of T_H17 . Therefore, it is logic to speculate that other factors, likely cytokines or the enzymes and pathways that convert glutamate into α -KG, are crucial to determine whether glutamine-derived α -KG induces or inhibits T_H1 polarization. Other amino acids are also essential for $CD4^+$ T cell differentiation. Leucine uptake via SLC7A5 is required to support the global metabolic rewiring during T_H1 and T_H17 differentiation but dispensable for the formation of T_{regs} , and its involvement in T_H2 differentiation was not tested (659). Isoleucine uptake via SLC3A2, a branched-chain amino acid transporter, is involved in the *in vivo* maintenance of T_{regs} through their metabolic reprogramming (315). It would be interesting to assess whether tumor-infiltrating T_{regs} use this mechanism to maintain their tumor-promoting functions. NOS2 expression is induced after *in vitro* T cell activation and mediates the nitration of tyrosine residues of ROR γ t, which impairs ROR γ t-mediated IL-17 transcription (782). The severity of autoimmune encephalitis was increased in NOS2-deficient mice and correlated with an increased number of T_H17 and T_H1 cells,

although the involvement of other NOS2-expressing cells was not further investigated (782) (*Figures 10,11*).

Interestingly, immune modulators and defense mechanisms can also affect T cell metabolic rewiring and phenotypic rewiring upon TCR activation. Complement binding to the complement regulatory receptor CD46 on T cells stimulates their proliferation and differentiation, and it does so partly by promoting GLUT1 and SLC7A5/LAT1 expression that respectively enhance glucose and amino acid uptake during T_{H1} responses (362).

In conclusion, the metabolic profile of effector T cells resembles that of cancer cells in several aspects, anticipating the harsh metabolic competition observed between them in the TME. Moreover, T_{regs} have a unique ability to adapt harsh metabolic environment and the preference to oxidize fatty acids may provide advantage for them to survive and function in inflammatory microenvironments, such as infectious loci and tumors, where the nutrient availability is scarce. Most of the advances regarding how metabolism is involved in T cell differentiation and effector function were carried out in the context of *in vivo* inflammation or *in vitro* conditions of polarization, that consist in the extrapolation of single or few cytokines' effects on a certain, isolated cell type – a condition that is never found *in vivo* where cells are connected and exposed to multiple stimuli. Therefore, given that the unique composition of the TME likely differs from the environment of the currently studied models, it is of outmost importance to further investigate how the metabolic and immunomodulatory signals in the TME integrate and regulate T cell function.

VII.II.II CD8⁺ cytotoxic T cells (CTL) metabolism

Like CD4⁺ T cells, naïve CD8⁺ T cells maintain low metabolic rate and mostly rely on OXPHOS for ATP generation and fuel nutrients for cell survival and homeostasis (*Figure 9A*). Upon TCR stimulation, CD8⁺ T cells undergo a metabolic switch from OXPHOS to glycolysis. Similar to CD4⁺ effector T cells, CTLs increase GLUT1 expression to promote inflammatory phenotype and expansion (637). Moreover, TCR signal triggers the activation of mTORC1 and the expression of HIF-1 α to sustain glucose uptake and glycolysis (221). TCR signaling promotes pyruvate dehydrogenase kinase 1 (PDHK1 or PDK1) rapid activation, inhibiting pyruvate import into mitochondria and facilitating lactic acid production (457). Similar to the glycolysis-independent

function of GAPDH in CD4⁺ T cells (115), in CTLs with low glycolytic flux lactate dehydrogenase (LDH) binds to and represses the translation of IFN- γ , TNF- α and IL-2 mRNA. Consequently, engagement of LDH in aerobic glycolysis upon PDHK1 activation enhances cytokine production without affecting the cytotoxic function of effector CTLs (457) (*Figure 12*).

Glutamine metabolism is also critical for T cell survival and effector function upon activation. Mitochondria can generate biosynthetic intermediates through glutamine metabolism (94). Glutaminolysis promotes CD8⁺ T cell differentiation and effector function by modulating histone and DNA methylation through S-2-HG synthesis (706). Treatment of CD8⁺ T cells with S-2-HG prior to adoptive cell transfer results in an improved anti-tumor effect (706). GLS-deficient stimulated CTLs expressed more effector proteins but were more prone to exhaustion, while transient GLS inhibition prior to adoptive cell transfer of anti-viral CD8⁺ T cells improved their effector function vaccinia virus (333). Given its effect on T_H1 and CTLs, it would be relevant to assess the potential of transient GLS inhibition to enhance anti-tumor T_H1 and CTL responses *in vivo*. In addition to glutamine, activated T cells also increase the uptake of other amino acids, including leucine and phenylalanine. CTLs upregulate the System L transporter, SLC7A5, which mediates uptake of large neutral amino acids. The deficiency of SLC7A5 impairs leucine uptake, which results in inability to engage metabolic reprogramming and declined effector function upon antigen stimulation (659). Furthermore, serine is also an essential amino acid supporting T cell proliferation. Mice fed with a serine-restricted diet show impaired antigen-specific CD8⁺ T cell expansion and pathogen clearance (432). Moreover, increasing L-arginine concentrations or enforcing mitochondrial fusion in CTLs promotes OXPHOS and IFN- γ production to enhance T cell survival, persistence and anti-tumor ability *in vivo* (249).

Activation of CD8⁺ T cells induces FAS via the mTOR/SREBP pathway, which is required to meet the heightened lipid requirements of proliferation and effector function (348). Moreover, CTLs readily uptake extracellular fatty acids (522) and also rely on FAS for their expansion (394). In metabolically challenging environments such as the TME, concurrent hypoglycemia and hypoxia trigger the PPAR- α -mediated FAO to preserve CTL effector function (795). Further promoting FAO by fenofibrate improves CTL anti-tumor immunity (795). Inhibiting cholesterol esterification in T

cells can increase cholesterol level, which enhances T cell receptor clustering and the formation of the immunological synapse (787). Remarkably, CTLs derived from the draining lymph nodes of murine models of PD-1 blockade therapy show concomitant expression of mTOR and AMPK, as well as their downstream transcription factors PGC-1 α and T-bet (112). An activation of the mitochondria and an increased generation of mitochondrial ROS in hypoxia underlies this unique co-expression of mTOR and AMPK (112). Of note, the dynamic of mitochondria also affects CD8⁺ T cells differentiation. CD28 signal induces mitochondrial engagement and cristae remodeling to the metabolic capacity by the expression of CPT1a and transient FAO activation, which is essential for T cell effector functions and memory T cell differentiation (353) (*Figure 12*).

VII.II.III Memory T cell metabolism

The generation of memory CD8⁺ and CD4⁺ T cells also requires metabolic reprogramming. Different from effector T cells, memory CD8⁺ T cells rely on fatty acid-fueled OXPHOS during quiescent status, and they are prone to rapidly switch their metabolism to glycolysis upon re-encountering antigens (271) (35). Upon antigen activation, CD8⁺ T cells undergo asymmetric division and hence asymmetric segregation of c-Myc that will predict whether they remain as short-lived effector cells or develop into long-lived memory cells. The daughter cell proximal to the APC contains high c-Myc levels, more amino acid transporters and increased mTORC1 activity; whereas the distal daughter cell displays less mTORC1 and more AMPK. This asymmetric distribution of mTOR/AMPK activities leads to higher glycolytic activity in proximal cells, which supports effector functions. On the other hand, the distal cells increase OXPHOS to persist as long-lived memory cells (562, 726). As a consequence, decreasing glucose metabolism by the hexokinase inhibitor 2-deoxyglucose (2-DG) during *in vitro* priming enhances the formation of long-term memory T cells (679). In mouse melanoma models, T cells primed *in vitro* in the presence of 2-DG prior to ACT accumulate at higher numbers in the tumor and show an increased fitness, resulting in a more potent and long-term anti-tumor activity (679) (*Figure 9C*). In addition to metabolic regulations orchestrating differentiation of memory CD8⁺ T cells, the uptake of acetate in memory CD8⁺ T cells can drive GAPDH acetylation for catalyzing the rapid recall immune response upon acute infection (32).

Memory T cells have an enhanced mitochondrial biogenesis and fuel OXPHOS via an increased flux of FAO (716). Interestingly, memory T cells use extracellular glucose to synthesize the fatty acids and rely on their expression of the lysosomal acid lipase (LAL) to conduct lipolysis to fuel FAO and OXPHOS, engaging in what has been termed “fatty acid futile cycle” (522). A similar skewing towards memory T cells can also be produced by Akt inhibition that leads to an increase in FAO in activated T cells (150). Pharmacological inhibition of Akt in human TILs is able to induce a memory phenotype in both CD4⁺ and CD8⁺ T cells (150), indicating that this pathway is used by both CD4⁺ and CD8⁺ T cells subsets, and not only in CTL. Of note, the previous studies drawn their conclusions thanks to the use of the CPT1a inhibitor etomoxir. In contrast, Raud et al. have combined genetic and pharmacological models as well as human samples from patients with inherited deficiencies in FAO to report that ACC2/CPT1a are dispensable for T cell memory formation, and that the previously described effects of high doses of etomoxir were due to the off-target effects affecting other mitochondrial processes that still require further validation (573). IL-7 induces expression of the glycerol channel aquaporin 9 (AQP9) in memory CD8⁺ T cells can support fatty acid esterification and triglyceride (TAG) synthesis and storage, which serves as a central component of IL-7-mediated memory CD8⁺ T cells survival (152). Memory T cells upregulate the cytosolic phosphoenolpyruvate carboxykinase (PCK1) to increase the conversion of oxaloacetate (OAA) into phosphoenolpyruvate (PEP). Interestingly, the OAA used as substrate by PCK1 derives from citrate produced both from glucose and from glutamine. PEP is used to synthesize glycogen that subsequently undergoes glycogenolysis to generate glucose-6-phosphate, ensuring a high PPP flux and high levels of PPP-derived reduced glutathione to maintain survival of memory T cells (433). It is tempting to speculate that the channeling of the OAA produced in the first step of FAS into gluconeogenesis may represent a way to economize resources and to ensure a slow release of glycogen-derived antioxidants to sustain their own survival. CD8⁺ tissue resident memory T cells (T_{RM}) have also been reported to elevate their fatty acid metabolism and OXPHOS. A recent study revealed that T_{RM} increase lipid uptake through high expression level of fatty acid binding proteins 4 and 5 (FABP4 and FABP5) and the deficiency of FABP4/5 impairs long-term maintenance of T_{RM} cells (538). A recent study highlighted a characteristic metabolic feature of effector memory T cells (T_{EM}) consisting in their inability to

upregulate fatty acid metabolism in low glucose environments, which confers them the unique ability to sustain IFN- γ production in nutrient-poor environments such as the TME (195). In activated T cells, NOS2-derived NO forms peroxynitrite adducts and shortens T cell survival. Therefore, deletion of NOS2 or inhibitors of the NOS2-peroxynitrite pathway enhance memory responses and block post-activation death in mouse and human T cells at least in part via the upregulation of anti-apoptotic molecules (729). It would be interesting to elucidate whether NO, either autocrine or from other cell types, can impair memory T cell formation in the TME (*Figure 9C*).

VIII. Targeting hypoxia and metabolism to tackle immune evasion and enhance immunotherapy

Immunotherapy with immune checkpoint inhibitors (ICIs) has shown dramatic and long-lasting responses in subsets of cancer patients and in some cancer types (699). Yet, the overall response rate remains about 30% (699). The efficacy of immunotherapy is compromised by cancer cell-intrinsic pathways that make them invisible to the cytotoxic immune cells, mechanisms impairing the access of immune cells to the tumor or to certain regions within the tumor and the establishment of an immune-restrictive TME. As explained in the previous parts of this review, hypoxia and metabolism strongly modulate immune cells and, therefore, can also strongly impact on the clinical outcome of immunotherapy. We propose four main metabolism/hypoxia-based therapeutic approaches aiming at reinvigorating the anti-tumor immune response via **i**) altering the recruitment (*i.e.*, turning “cold” tumors into “hot” tumors) and the location of specific immune cell subsets within different tumor niches to foster anti-tumor immune phenotypes, **ii**) promoting cancer cell immune-recognition, **iii**) rewiring immune cell fitness so to improve their function in a restrictive TME, and **iv**) rewiring the TME into an immune permissive milieu that favors anti-tumor immune responses (*Figure 13*).

VIII.I Altering immune cell recruitment and positioning

As the tumor vasculature is morphologically abnormal and dysfunctional, some anti-angiogenic agents, at specific dosages (260), can “normalize” instead of pruning blood vessels in the tumor, and thus reduce tumor hypoxia. In doing so, recruitment of immune cells in response to hypoxia-driven

chemokines is affected. As normalized vessels are more perfused and are more permissive to T cell rolling (260), T cell recruitment will be further affected (260). Finally, if hypoxic areas are reoxygenated, immune cells located in those areas might be re-educated. In hypoxic areas lactate accumulation usually takes place and increases the recruitment of MDSCs to the tumor (314).

Some targeted therapies directed against the chemokines responsible for the recruitment of pro-tumor immune cells have been proposed. For instance, cancer cell-derived Sema3A binds to neuropilin-1 (Nrp-1) and PlexinA1/A4 on tumor associated macrophages (TAMs), attracting TAMs to hypoxic tumors through VEGFR1 signaling, and hypoxia-induced downregulation of Nrp-1 is responsible for their entrapment in hypoxia. In gliomas, genetic KO of Nrp1 in microglia and macrophages, systemic pharmacological inhibition of Nrp1 and treatment of patient-derived xenografts with anti-Sema3A had strong anti-tumor effect via impairing the recruitment of TAMs and reshaping of the inflammatory response (99, 393, 476). Moreover, Nrp1 expression by tumor-infiltrating T_{regs} regulates their chemotaxis and stability within the tumor via VEGF-A and Sema4A signaling, respectively (168, 285). Loss of Nrp1 as well as hypoxia-driven HIF-1 α induce IFN- γ expression by T_{regs} and thus T_{regs} fragility, which is required for the success of PD-1 blockade (530). Whether loss of HIF-1 α would revert T_{regs} fragility was not tested, but another study showed that HIF-1 α -deficient T_{regs} are more capable of suppressing CTLs *in vitro* (473). Yet, loss of HIF-1 α impaired T_{regs} migratory capacity and tumor infiltration in glioblastoma-bearing animals, prolonging their survival. Thus, it would be promising to explore which combinational therapies targeting these pathways that could synergistically induce tumor regression. While HIF inhibitors could also impair the anti-tumor function of other cells, anti-Nrp1 therapy could potentially impair the suppressive functions of T_{regs} and macrophages and its combination with anti-VEGF-A and immunotherapy could inhibit T_{regs} infiltration and angiogenesis and further reinvigorate CTLs.

Among the numerous obstacles to overcome in order to maximize the outcome of NK cell-based immunotherapies is the poor infiltration of solid tumors by NK cells. Hence, strategies to address this challenge with the ultimate goal to enhance NK cell infiltration in solid tumors are a promising therapeutic avenue. Recently, it has been shown that NK cells infiltrate into hypoxic areas in murine

tumor models and NK cell-specific deletion of HIF-1 α reduced overall intratumoral NK cell densities and particularly the number of NK cells in hypoxic areas (373). Consequently, tuning the HIF expression in NK cells prior to transfer, e.g. by genetic or pharmacological inhibition of PHDs, should foster the infiltration of NK cells in solid tumors.

VIII.II Promoting cancer cell immune-recognition

In addition to mediating resistance to conventional chemotherapy and radiotherapy, it is becoming clear that tumor hypoxia counteracts the success of modern immunotherapies.

One crucial mechanism of immunosuppression is the expression of PD-L1 on cancer cells, macrophages, MDSCs and dendritic cells, which is strongly induced by hypoxia in a HIF-1 α -dependent manner (36, 511, 536). Beyond inducing T cell dysfunction upon binding to PD-1 on T cells, PD-L1 on cancer cells sustains their glycolytic metabolism via activation of Akt/mTOR signaling and fosters the establishment of an immunosuppressive TME (116). Consequently, blocking PD-L1 under hypoxic conditions enhances the activation of T cells (511). Mechanistically, the upregulation of PD-L1 in hypoxia is achieved by cooperative binding of HIF-1 α and pyruvate kinase M2 (PKM2) to the PD-L1 promoter. Therefore, the inhibition of PKM2 in macrophages, MDSCs and cancer cells results in a decrease of PD-L1 expression (536). Moreover, in neuroendocrine pheochromocytomas and paragangliomas, the expression of PD-L2 shows a strong association with HIF-1 α (558). In summary, it becomes conceivable that hypoxia gives rise to an immunosuppressive microenvironment which can overcome the effect of checkpoint blockade by increasing PD-L1/ PD-L2 expression on stromal cells and cancer cells. Thus, the combination of PD-L1/PD-L2 blockade and HIF-1 α inhibition may represent a novel approach to improve the outcome of checkpoint immunotherapy. Yet, since HIF-1 α underlies the metabolism of several anti-tumor immune cells, is important to assess whether the effect on these cells would balance out the anti-tumor effects of HIF inhibition.

Another emerging checkpoint that blunts both innate and adaptive immune responses is CD47 (418). This membrane protein is able to negatively modulate T cell activation and cytokine production by interacting with the signal regulatory protein-alpha (SIRP α), expressed by TAMs or DCs. Binding of

CD47 to SIRP α will also deliver an anti-phagocytic signal (325, 418, 420, 526). High levels of CD47 have been detected in various tumor types and its expression shows correlation with HIF target gene expression as well as patient survival (118, 211, 325, 442, 793). Furthermore, it was demonstrated that CD47 expression in triple-negative primary breast cancer cells is induced by hypoxia in a HIF-1 α -dependent manner. Besides being involved in the ‘don’t-eat-me’ signal, CD47 contributed to maintain a cancer stem cell phenotype (793). Hence, CD47 has become a target for cancer immunotherapy and the benefit of CD47 blockade is currently tested in several clinical trials (418). CD47 blockade in the context of adaptive immunity yields increased cancer cell lysis and IFN- γ release by CD8⁺ T cells (420, 668, 703). In tumors that are resistant to CD47 blockade, CpG treatment could be beneficial to overcome the “don’t-eat-me” signal of CD47 via metabolic rewiring of macrophages and to promote macrophage-mediated phagocytosis of CD47-expressing cancer cells, altogether leading to tumor shrinkage and prolonged survival (416). A very recent study hints towards another potential mechanism of resistance to CD47 blockade. In the context of chronic infection, where T cell exhaustion is considerable, a new subset CD8⁺ T cells that express SIRP α has been discovered, in which the expression of inhibitory receptors is counterbalanced by the expression of co-stimulatory receptors (498). Hence, SIRP α ⁺ CD8⁺ T cells retain their proliferative capacity, IFN- γ expression and cytolytic function. Accordingly, CD47-expressing cells are more susceptible to CD8⁺ T cell-killing *in vivo* (498). It still remains unknown whether this subset of SIRP α ⁺ CD8⁺ T cells also exists in tumors and if so, it would raise caution towards the use of CD47 blockade since it could negatively affect CTL-mediated anti-tumor immunity.

Expression of HLA-G, the non-classic major histocompatibility complex (MHC) class I molecule, is important for the maintenance of immune homeostasis and tolerance in healthy adult tissues. However, there is increasing evidence that HLA-G contributes to tumor immune escape and, hence represents an immunotherapeutic target (93, 601). HLA-G exerts its immunosuppressive effect by direct binding to inhibitory receptors CD85j on monocytic cells, B cells, T cells, and NK cells; to CD85d on dendritic cells, monocytes, and macrophages; and to CD158d on NK cells (9, 92). Elevated expression of HLA-G has been reported in various malignancies with a high a high tumor grade where it leads to immune escape (368, 408, 707, 779). Consequently, the expression of HLA-G on

cancer cells is associated with a poor prognosis (13, 274, 486). Interestingly, the HLA-G promoter and non-promoter regions contain several hypoxia responsive elements (HREs) and, in HLA-G-negative cancer cells, hypoxia leads to an upregulation of HLA-G mRNA and protein in HIF-1 α -dependent fashion (215, 247, 777). Given the immunosuppressive function of HLA-G on cytotoxic T cells and NK cells, HLA-G expression in hypoxic cancer cells may drive immune evasion and, hence, represents a novel immune checkpoint molecule. Noteworthy, glucose deprivation in combination with hypoxic stress leads to increased surface expression of HLA-E cancer cells (623). Therefore, it will be interesting to investigate the impact of hypoxia on other MHC-I molecules in a cancer cell context.

VIII.III Rewiring immune cell fitness and function

VIII.III.I Repolarization of TAMs

Several strategies have been proposed to re-educate TAMs into anti-tumor M1-like macrophages. Targeting glutamine metabolism is an attractive strategy due to its potential anti-tumor effects on cancer cells, macrophages, CD4⁺ T cells and NK cells (333, 417, 424, 535, 768), although it can interfere with CD8⁺ T cell differentiation, proliferation and cytokine production (94, 706). Glutamine synthetase (GS) deletion in macrophages prevents metastasis dissemination in a murine tumor model via a metabolic rewiring of TAMs into an M1-like phenotype, resulting in increased T cell recruitment and activation and tumor blood vessel normalization (535). Since glutaminolysis-derived α -KG is important for M2 polarization, glutaminase (GLS) could be a potential target to repolarize TAMs into M1, although this approach still needs to be tested in the context of cancer (417). A subset of podoplanin-expressing perilymphatic TAMs (PoEMs) stimulate lymphangiogenesis, lymphoinvasion and metastatic dissemination (54). Given that PoEMs express higher levels of glucose uptake and glycolysis-related genes compared to non-PoEMs, it would be interesting to explore whether this population could be targeted with metabolic reprogramming therapies (54). Macrophage-associated VSIG4 has been proposed as a M1 metabolic checkpoint inhibitor. Targeting VSIG4 could a potential strategy to re-polarize TAMs into anti-tumor M1 macrophages via the alteration of their metabolism (404). CpG treatment of macrophages activates FAS, FAO and

cholesterol biosynthesis to increase membrane fluidity and to overcome the “don’t-eat-me” signal of CD47 (416). Treatment of murine model of pancreatic cancer resistant to CD47 blockade with CpG allows the engulfment of CD47-expressing cancer cells and induces a macrophage phenotype switch, overall resulting in a relevant anti-tumor response and thus improving the overall survival (416).

VIII.III.II Enhancing DC function

Abnormal lipid accumulation is arising as a characteristic trait of tumor-associated DCs (TIDCs) and impairs their ability to process tumor antigens (151, 296). This accumulation is triggered by a tumor-derived factor that still remains unknown. Strategies aiming at normalizing lipid abundance in TIDCs have proved to be beneficial in murine tumor models. For instance, pharmacological inhibition of FAS by TOFA, an ACC inhibitor, reverted this effect and synergized with DC vaccination (296). Furthermore, silencing of XBP1, an ER stress-induced transcription factor, tuned down FAS and lipid accumulation, leading to a suppression of the tolerogenic phenotype of TIDCs and dampening tumor progression (151).

VIII.III.I Enhancing NK cell cytotoxicity

mTORC1 is a critical player in NK cell metabolism. In addition to its involvement in the development and differentiation of murine NK cells, mTORC1 is a crucial driver of glycolysis during NK cell activation (188, 445, 728). Moreover, SREBP transcription factors are required for metabolic reprogramming of NK cells during activation by increasing the citrate malate shuttle, glycolysis and OXPHOS (23). Therefore, boosting these pathways in should enhance the tumoricidal function of NK cells. Yet, SREBP activators for clinical use are currently not available and current mTOR-based therapeutic strategies aim at mTOR inhibition in cancer cells (see above) and, therefore, are likely to interfere with NK cell activation in the TME.

NK cells require the uptake of glutamine to sustain the import of other essential long neutral amino acids (LNAA) through SLC7A5 and to ensure the c-Myc-driven production of IFN- γ and GzmB. Targeting glutamine metabolism in cancer cells in order to increase glutamine availability in the TME might unleash NK cell anti-tumor functions in tumors where NK cell activation can take place (424). While transient inhibition of glutaminase (GLS) prior to ACT of CD4⁺ T cells favors T_H1 and CTL

responses (333), and could induce macrophage to M1 phenotype (417), it can also impair CTL function (94, 706). Thus, the overall effect of these therapies should be carefully evaluated and might strongly be influenced by the immune cell composition and the degree of T cell or NK cell-mediated responses in each tumor type. Another interesting observation is that obesity promotes uptake and accumulation of lipids by NK cells, resulting in NK cell paralysis. Therefore, reducing dietary fat intake has been proposed to foster NK cell-mediated anti-tumor responses (468).

Noteworthy, HIF-1 α is a critical regulator of glycolysis and glutamine metabolism and as recently demonstrated, NK cell-specific deletion HIF-1 α results in impaired NK cell activation and cancer cell killing. Moreover, it was shown that HIF-1 α in NK cells contributes to vessel maturation (373). Although, HIF1 α -dependent metabolic changes in NK cells have not been fully elucidated yet, it is tempting to speculate that boosting HIF activity could enhance infiltration and cytotoxicity of NK cells as well as tumor vessel normalization.

VIII.III.I Enhancing T cell effector and memory function

Several strategies have been envisaged to rewire T cell metabolism in order to cope with the metabolic restrictions imposed in the TME. First, promoting effector function may have beneficial effects but a major caveat of this approach is that effector T cells are typically short-lived, which can translate in a failure to control tumor growth and metastasis in the long term. Therefore, a growing interest towards inducing T cell memory has arisen, which could potentially entice cancer cell killing in the short-term while creating a reservoir of long-lived memory T cells ensuring a protective long-term effect.

Overexpression of phosphoenolpyruvate carboxykinase 1 (PCK1) in tumor-specific T cells or prior to ACT has been shown to sustain T cell anti-tumor responses in a glucose-deprived TME (300). In addition, PD-1 alters T cell metabolic reprogramming by inhibiting glycolysis, required by effector CD4⁺ and CD8⁺ T cells, and promoting lipolysis and FAO, required for T_{regs} (116, 547). Therefore, PD-1 blockade can improve the metabolic fitness of tumor-infiltrating T cells and may be one of the underlying mechanisms that contributes to the therapeutic benefits of PD-1 blockade. Combined targeting of TIGIT and PD-1 further enhances CD8⁺ T cell activation and function to improve survival rate (547). Additionally, targeting costimulatory receptors can also alter T cell metabolism.

For example, agonistic anti-4-1BB antibody treatment activates glucose and FAO to support CTL proliferation and a memory-like state (125). 4-1BB activation also promotes PGC-1 α -dependent mitochondrial function, which further provides metabolic support to improve the response of anti-PD-1 and ACT (458). Similarly, glucocorticoid-induced TNFR-related protein (GITR) agonism upregulates nutrient uptake, lipid stores and glycolysis in CTLs to support their proliferation, and further increases IFN- γ production in combination with PD-1 blockade treatment (607).

In contrast to sustaining metabolic fitness of effector T cells *in vivo*, modulating metabolism of T cells during *in vitro* expansion for ACT therapy can also improve therapeutic benefits. Treating T cells with the glycolysis inhibitor 2-deoxyglucose or with an Akt inhibitor during *in vitro* TIL expansion has been shown to promote memory T cell formation and to elicit stronger anti-tumor responses (150, 679). Since ACT-refractory melanoma patients exhibit higher glycolytic activity in cancer cells (102), combining glycolysis inhibition by an LDHA inhibitor with ACT elicit superior therapeutic potential. Hypoxia and low glucose TME causes a metabolic switch in CTLs through enhancing PPAR- α signaling and FAO that have been suggested to preserve CTL effector functions. In murine melanoma models, applying the PPAR- α agonist fenofibrate to reprogram CTL metabolism can increase the therapeutic effect of PD-1 blockade (795). Modulating the signaling domain CAR T cells also represents a promising strategy to enhance their persistence and metabolic fitness. The inclusion of 4-1BB domain in CAR T cells enhances FAO and mitochondrial biogenesis, promoting the outgrowth of T cells with memory phenotype. In contrast, CAR T cells with CD28 domains increase glycolysis and form short-lived effector T cells (343). Of note, modulating cholesterol metabolism in T cells through inhibition of ACAT1, a cholesterol esterification enzyme, can improve the formation of the immunological synapse efficiently to increase their effector function. The ACAT1 inhibitor avasimibe, already in clinical trials for the treatment of atherosclerosis, exhibits anti-tumor effect and shows better efficacy in combination with anti-PD-1 therapy (787).

CTLs lose their mitochondrial fitness due to impaired mitochondrial biogenesis, which weakens T cell anti-tumor responses. Overexpression of PGC-1 α in tumor-specific T cells boosts mitochondrial activity and biogenesis and improves T cell anti-tumor activity (116, 628). *In vivo* treatment with the

PGC-1 α agonist bezafibrate can increase OXPHOS and FAO and synergize with PD-1 blockade for tumor suppression (112, 127). Mitochondrial dynamics also regulate metabolic reprogramming in T cells through controlling mitochondrial fusion and fission. Preventing mitochondrial fission by treating *in vitro* expanded tumor-specific T cells with a mitochondria fission inhibitor, Mdivi-1, could enhance T cell anti-tumor responses by skewing expanded T cells to acquire memory phenotype (73). Interestingly, it has also been reported that tumor-specific T cells with lower mitochondrial membrane potential, a subset with decreased oxidative stress, can elicit superior anti-tumor responses (680).

Two studies have proposed therapeutic approaches intervening T cell glutamine metabolism, which would synergize with their effects on macrophages, NK cells and cancer cells (333, 417, 424, 535, 768). Transient glutaminase (GLS) inhibition, but not chronic inhibition, unleashes T_H1 and CTL development and effector function *in vivo* by the activation of IL-2/mTORC1 signaling. Transient GLS inhibition prior to adoptive cell transfer of CAR-T cells improved their effector function against B cell leukemia cells (333). Moreover, glutaminolysis drives the synthesis of the epigenetic regulator S-2-HG and thereby promotes CD8⁺ T cell differentiation and effector function (706). Treatment of CD8⁺ T cells with S-2-HG prior to ACT results in an improved anti-tumor effect (706).

Tumor-infiltrating T cells often commit to T cell exhaustion due to chronic antigen persistence, a dysfunctional state in which they express lower amounts of effector molecules and higher levels of co-inhibitory receptors and reduce their proliferative capacity (762). It would be interesting to explore the link between the metabolic stress in the TME and the commitment to T cell exhaustion, anergy or senescence. The findings of this question would be vital for preventing the engagement of T cells into these distinct dysfunctional programs and for developing more effective interventions to reinvigorate dysfunctional T cells in the TME.

VIII.IV Rewiring the TME: metabolic competition and immunomodulatory metabolites

In the tumor context, the high energy demand of malignant cells as well as active stromal cells, a poor vascular flow and defective lymphatic drainage will result in a shortage of key metabolites and in the abundance of waste products. This makes the TME a harsh metabolic environment and installs a tight competition for vital nutrients. Not only this, but also the by-products (that have high chances to be stagnant inside the tumor) have a negative impact on neighboring cells such as immune cells (750).

An example is how the high demand of cancer cells for glucose creates a competition with T cells that ultimately are hampered in their activation. It follows that melanomas from patients with higher glycolytic activity, respond less to ACT (102). Also, endogenous T cell tumor infiltration is reduced in melanoma and NSCLC patients with a high expression of glycolysis-related genes. It is not only the glucose competition itself that will reduce glucose availability to T cells but also because high glycolysis by cancer results in the decrease of immunostimulatory signals (e.g. IRF1, CXCL10) and in the increase of immunosuppressive metabolites (e.g. lactate) (102). Therefore, either glycolysis inhibition or LDHA blockade can, for a short period, precondition the TME and increase the effectiveness of the ACT (102). If on one hand, metabolism rewiring modulates the success of immunotherapy, on the other hand anti-PD-L1 blocking antibodies themselves can bind to cancer cells and decrease their glycolytic flux, thus harnessing glucose competition and further increasing T cell cytotoxicity (116). Other types of competition rather than glucose have been suggested also for other metabolites e.g., glutamine in the context of cancer cell-cancer-associated fibroblast crosstalk (785). Moreover, low glutamine levels favor the differentiation of naïve T cells into T_{regs} (355, 465), which could at least partially underlie the thrive of the immunosuppressive T_{regs} at the expense of other anti-tumor CD4⁺ subsets.

Glycolysis-driven acidification and lactate accumulation are one of the hallmarks of tumors (311, 596). Lactate is not only a waste product of glycolysis but has been considered a metabolic fuel (221, 322), a signaling molecule in angiogenesis (135, 605, 724) and an immunosuppressive metabolite that impairs immunosurveillance by CTLs (214, 225) and NK cells (314, 431). Acidic conditions lower the T cell secretion of IL-2, TNF and IFN- γ and upregulate CTLA4 expression, thereby decreasing the cytotoxic potential of CTLs (64, 82). Likewise, IL-2-dependent activation and cytotoxicity of NK cells are diminished under acidic conditions (222, 223, 491, 644). Moreover, extracellular sodium lactate and lactic acid can selectively regulate CD4⁺ and CD8⁺ T cells migration (276). Lactate was also reported to inactivate cytokine release (i.e. IL-12) from DCs and to inhibit the differentiation and activation of monocyte-derived dendritic cells (262, 288). Recently, Colegio and co-workers showed that cancer cell-derived lactate sustains the pro-tumor M2-like phenotype of TAMs by inducing macrophage expression of VEGF-A and ARG1 in a HIF-1 α -dependent manner (135). In melanomas,

an acidic tumor milieu due to the high glycolytic rate of melanoma cells fosters TAM skewing towards an M2-like phenotype and consequently anti-tumor T cell evasion (58).

Cancer cells cope with lactate accumulation by increasing the transfer of lactate and protons (H^+) across the plasma membrane into the extracellular space. The major enzymes involved in this process are the monocarboxylate transporter MCT1 and MCT4, which are both upregulated hypoxia, though MCT4 is considered the most hypoxia-induced lactate transporter (277, 351, 542). Furthermore, enhanced CO_2 production by cancer cells is a major contributor to the acidification of the TME. The molecules of CO_2 coming out of the PPP and the TCA cycle are converted into bicarbonate (HCO_3^-) and H^+ by carbonic anhydrases (CA) and the extracellular H^+ drastically lowers the microenvironmental pH (453, 639, 683). Noteworthy, the major enzyme for pH regulation under hypoxic conditions is carbonic anhydrase IX (CAIX), a HIF-1 α -regulated gene (453, 545). Hence, major contributors to tumor acidification, MCTs and CAIX, are upregulated in response to hypoxia and thus they are attractive targets to trigger an anti-tumor immune response, particularly in hypoxic tumors. Interestingly, a recently developed CAIX-targeting antibody against its enzymatic activity reduces acidification and induces antibody-dependent cell-mediated cytotoxicity in renal cell carcinoma via NK cells, macrophages and the complement system (117). Yet, a phase 3 clinical trial with girentuximab, a chimeric monoclonal antibody against CAIX, had no clinical benefits in patients with clear cell renal cell carcinoma (111). However, the impact of girentuximab on immunosuppression is not clear. It is possible that the simultaneous blockade of CAIX and immune checkpoint inhibitors might yield superior therapeutic outcome.

The acidic microenvironment is responsible for the selection of acidic-resistant phenotype, a powerful proliferative advantage. Initially thought as a metabolic waste, lactate the end product of glycolysis can be a paracrine signaling molecule (311, 596). Acidosis often precedes angiogenesis, since lactate increases the production of the VEGF and its receptor VEGFR2 by cancer cells and endothelial cells, respectively (605). Moreover, lactate can stabilize HIF in endothelial cells independently of hypoxia via the pyruvate-mediated inhibition of PHD activity and consequently promote angiogenesis (666). The impact of lactate on angiogenesis could be also explained by induction of IL-8 production by endothelial cells, through NF- κ B stimulation (724). Lee et al. showed that under hypoxic conditions,

the stabilization of N-Myc downstream-regulated gene 3 (NDRG3) protein expression by lactate binding promotes angiogenesis and cell growth apparently via the ERK1/2 signaling pathway (392). Low extracellular pH together with hypoxia results in cell death escape through activation of intracellular pathways for instance the extracellular-signal-related kinase (ERK1/2) (157). The activation of ERK1/2, acidification and hypoxia also lead to the increased release and activation of acidic proteases such as cathepsin B (604), MMP2 and MMP9 (157, 341) which are responsible for the degradation of the extracellular matrix of the tumor, facilitating invasion and metastasis (89, 90). Other hypoxia-driven immunosuppressive metabolites that abundantly occur in tumors are adenosine and kynurenine. Adenosine is produced by the action of CD39/CD73 and can bind to several receptors expressed in different levels across the different immune cell types. Noteworthy, there is preclinical evidence that suggest that targeting the adenosine receptor A2AR enhances immunotherapy (434) and clinical trials that with drugs that target A2AR or CD73 are currently on the way (409). Hence, it seems conceivable that such compounds are able to boost the outcome of immunotherapies in hypoxic tumors. Tryptophan metabolism has gained new attention in tumors since it influences immune evasion. Indoleamine 2,3-dioxygenase (IDO) catabolizes the essential amino acid tryptophan into the immunosuppressive metabolite kynurenine (602). While in one hand the expression of IDO in APCs is related with tumor progression and poor responses to immunotherapies, on the other hand the generation of kynurenine, a ligand for endogenous aryl hydrocarbon receptor (AhR), induces T_{regs} differentiation and suppress DCs immunogenicity (466, 508). How purinergic signaling and tryptophan metabolism impact immune cell function and the strategies envisaged to revert it are revised in detail in sections IX.I and IX.II, respectively.

In sum, the metabolic competition and crosstalk inherent in the TME between cancer cells and immune cells is crucial and determinant for metabolic alteration that will determine the pro- or anti-inflammatory function of immune cells. Thus, future studies pinpointing metabolic targets common to both tumor and immune cells will lead to a multi-pronged attack to successfully open new strategies to eradicate cancer. Thus, it is important to define metabolic signatures (that can be strictly dependent or not to the activation status of oncogenes and oncosuppressors, as aforementioned) in order to predict or improve the response to immunotherapies.

IX. Two examples of metabolic and hypoxia-based immunotherapies

IX.I Nucleotide metabolism

Nucleotides are not only building blocks for nucleic acids and crucial components of cellular metabolism, but also potent signaling molecules when released into the extracellular milieu. Nucleotides are released from stressed or dying cells either passively, due to cell lysis, or actively, through membrane channels, by exocytosis of vesicles or as part of the content of exosomes. ATP, UTP and its derivatives act as immunomodulators via P1 and P2 purinergic excitatory receptors expressed on several immune cells. Extracellular ATP is degraded through the action of membrane-bound ectonucleotidases, which dephosphorylate ATP into adenosine (177). There are two main ectonucleotidases responsible for ATP degradation in the TME: the ectonucleoside triphosphate diphosphohydrolases (ENTPDases) including CD39 (also known as NTPDase 1), which sequentially dephosphorylates ATP into ADP and AMP, and CD73 (also known as 5-NT), which dephosphorylates AMP into adenosine. Adenosine signaling is terminated when it is removed from the extracellular space by the activity of adenosine deaminase, which converts it to inosine, by cellular uptake through nucleoside transporters or by phosphorylation and conversion to AMP due to intracellular adenosine kinases (177). Notably, the metabolic master regulator AMPK is sensitive to changes in the AMP:ATP ratio, linking the action of CD39/CD73 with intracellular metabolic reprogramming.

Phosphorylated nucleotides and adenosine elicit opposing responses on immune cells. ATP, UTP, UDP and UDP-glucose signal through ionotropic P2X receptors or metabotropic P2Y receptors, inducing chemotactic and excitatory effects on immune cells. Inversely, adenosine binds to four P1 G-protein-coupled receptors, namely A1R, A2AR, A2BR and A3R. These receptors differ between them for their tissue distribution, affinity for adenosine, the type of G protein they are coupled with, and the downstream pathway (61, 62, 122, 155). A2A and A2B receptors are mainly involved in the control of immunity and inflammation; they are coupled to G_s proteins and trigger cAMP formation (61, 122, 155). In contrast, A1 and A3 receptors are coupled to G_{i/o} proteins and their activation reduces the

intracellular levels of cAMP; they can elicit pro-inflammatory responses depending on the context (61, 62, 122, 155). Reduced ATP signaling and increased activation of A2A and A2B adenosine receptors serves to limit the extent and duration of inflammation (106). Thus, ATP dephosphorylation into adenosine via the action of CD39 and CD73 dictates which kind of immune response is deployed. ATP and UTP act as “find me” signals that promote the recruitment of monocytes, dendritic cells and neutrophils (120, 124, 202). Through binding to P2X₇R on dendritic cells, ATP induces the activation of the inflammasome and the maturation of pro-inflammatory cytokines such as IL-1 β and IL-18, which are required for the polarization of IFN γ -producing CTLs (27). T cells express several ATP receptors, including P2X₁R, P2X₄R and P2Y₁₂R (746). In effector T cells, TCR ligation induces the Ca²⁺-mediated activation of the transcription factor NFAT and the translocation of ATP receptors P2X₁R, P2X₄R to the membrane (769). Besides driving IL-2 secretion and T cell proliferation, NFAT promotes the translocation of pannexin-1 at the immune synapse, contributing to a controlled release of ATP (769). Signaling of autocrine ATP together with ATP from other sources through P2X₁R, P2X₄R and P2Y₁₂R is required to sustain NFAT activation and IL-2 secretion, thereby enhancing effector T cell activation and proliferation and preventing anergy (630, 769). Similarly, activation-induced ATP release by $\gamma\delta$ T cells and autocrine ATP signaling through P2X₄R is required for the secretion of effector cytokines such as TNF- α and IFN- γ (443). IL-6 induces ATP synthesis and ATP release by T_{regs} (629). Autocrine stimulation of the P2X₇R by ATP in T_{reg} impairs their immunosuppressive functions and results in T_{reg} conversion to T_H17 cells (629) or in T_{regs} apoptosis (24). In contrast with the general anti-tumor immune responses elicited by ATP, signaling of ATP through P2YRs and P2X₇Rs in cancer cells has been associated with cancer cell proliferation and dissemination but also, in some instances, with inhibition of proliferation and induction of apoptosis (reviewed in (177)). Thus, treatment regimens aiming at promoting ATP signaling must be evaluated with care.

Hypoxia is one of the most important inducers of CD39, CD73, A2AR and A2BR expression and, thus, plays a decisive role in the outcome of purinergic signaling. As mentioned in the previous sections, HIF-1 α may have an immunostimulatory effect on T cells and macrophages (156, 535).

However, many of these effects can be ascribed to the hypoxia-independent activation of HIF-1 α in the context of inflammatory diseases, where the antigen load is high (156). In the TME, oppositely, the detrimental effect of hypoxia on the anti-tumor T cell response is likely due to the hypoxia-driven accumulation of adenosine. Thus, in most cases the adenosine-mediated immunosuppressive effect overrules the cell autonomous/direct immunostimulatory effect of HIF-1/hypoxia in T cells (156, 267) or in M1-like macrophages (535). An exception is represented by endometrial cancer, wherein CD73 deletion accelerates tumor progression, suggesting that in this case adenosine has an anti-tumor effect by promoting epithelial integrity and limiting invasiveness (67). Mechanistically, adenosine usually antagonizes the molecular pathways triggered by ATP. Macrophages express A2A and A2B receptors. Adenosine binding to A2ARs promotes macrophage polarization into M2-like phenotype and the expression of anti-inflammatory IL-10 by macrophages, dendritic cells and neutrophils (105). Deletion of A2ARs in myeloid cells reduced tumor growth and metastasis due to the activation of CTLs and NK cells (105). Activation of A2BRs in macrophages and DCs induces the production and secretion of VEGF-A and IL-6 and thereby promotes angiogenesis, T_H17 polarization and fibrosis (667, 765). Moreover, A2BR signaling in DCs impairs their maturation and their capacity to present antigen and activate T cells (766). Adenosine inhibits neutrophil chemotaxis directly by binding to A3Rs or indirectly by impairing the secretion of neutrophil chemoattractants (106). Furthermore, it inhibits their oxidative capacity (682) and their transendothelial migration (681). Given the dual role of neutrophils in cancer progression, the consequences of impaired neutrophil infiltration and function on tumor growth and metastasis formation remain unclear and should be further investigated. Adenosine signaling through A2ARs in effector T cells mainly impairs T cell activation and proliferation by constraining NFAT activation and IL-2 secretion (78). The cytotoxic functions of CTLs and NK cells is also impaired by activation of A2ARs (44, 475). On the other hand, adenosine signaling through A2ARs in T_{regs} induces the expression of CTLA4, PD-1, Foxp3 and CD39/CD73, which helps to maintain their identity and their immunosuppressive functions (106).

Given the immunosuppressive effects of the adenosine signaling, the effects of A2AR blockade in tumor immunotherapy have been investigated. Several A2AR antagonists tested for safety and tolerability firstly in patients with Parkinson disease are currently studied in cancer, alone or in

combination with PD-1 or PD-L1 inhibitors, such as PBF-509, NIR178, MK-3814 (399). CPI-444 has been evaluated in a phase 1a/1b study in combination with the anti-PD-L1 antibody Atezolizumab in patients with advanced solid tumors. Clinical activity was observed in all tumor types both as a single agent and in combination with Atezolizumab and the disease control rate was 45% in the overall patient population (229). Clinical trials are also ongoing for an A2BR antagonist (PBF-1129) and for two monoclonal antibodies against CD73, namely MEDI9447 and BMS-986179 (399). MEDI9447 has been evaluated in a phase 1/2a trial in combination with anti-PD-L1 therapy in patients with advanced solid tumors and in a phase 2 study in combination with antibodies against PD-L1, CTLA4 and OX40 in relapsed ovarian cancer patients. Agents targeting CD39 are under development in preclinical studies. Overall, in the next coming year, we will understand which combination and which tumor type are suited for this type of approach and if adenosine signaling can be targeted in those patients that have shown resistance to checkpoint inhibitors.

IX.II Tryptophan metabolism and indoleamine 2,3-dioxygenase (IDO)

Indoleamine (2,3)-dioxygenase (IDO) is an enzyme that catabolizes tryptophan to kynurenine and is highly expressed in cancer cells, myeloid cells and endothelial cells. Tryptophan is essential for supporting T cell proliferation. Tryptophan-deprived T cells will be halted at a mid-G1 arrest point and lose their effector functions as a result of the activation of the serine/threonine-protein kinase GCN2 and the inhibition of mTOR activity (464, 495, 689). In addition, kynurenine can promote T_{regs} differentiation by activating aryl hydrocarbon receptor (AhR) signaling cascades (466, 508). In physiology, kynurenine can accumulate in the placenta and induce T_{regs} cells that may help to prevent rejection of the semiallogenic fetus. In cancer, IDO-induced tryptophan depletion and kynurenine accumulation may facilitate the establishment of an immunosuppressive microenvironment and promote immune evasion of cancer cells. In support of this notion, it has been reported that active IDO is widely expressed in the TME of different cancer types (709). Expression of IDO by immunogenic mouse cancer cells transfected with a construct containing the mouse cDNA of *Indo* (the gene encoding IDO) prevents their rejection when these cells were implanted in pre-immunized mice (*i.e.*, mice that received a cell vaccine for this tumor) while systemic administration of an IDO inhibitor could prevent this rejection (709). Among all the cells, it has been recently reported that IDO

production in DCs is induced by hypoxia and this increase was dependent on adenosine A3 receptor (A3R) activation, but not on A2AR or A2BR (see section IX.I). Consistently, A3R blockade in hypoxia inhibited IDO induction in DCs (664). IDO activity in a subset of pDC in tumor draining lymph nodes is responsible for the activation of T_{regs} and the hindrance of T_H17 presumably through the inhibition of IL-6 expression. In a murine tumor model, the combination of an IDO inhibitor with an anti-tumor vaccine unleashed the conversion of T_{regs} into T_H17 cells that enhanced $CD8^+$ T cell activation and anti-tumor function (648). IDO is not only expressed and active in many antigen-presenting cells, whereby it promotes peripheral tolerance to tumor-associated antigens, but it is also expressed by cancer cells themselves. IDO enzymes and IDO-related enzymes such as the tryptophan 2,3-dioxygenase (TDO) are active in many tumors, providing a direct defense against T cell attack and facilitating survival, growth, invasion, and metastasis of malignant cells (559). In many studies, high IDO expression in tumor or in tumor-draining lymph nodes associates with a poor disease outcome (259).

To reverse IDO-mediated immune evasion, different IDO inhibitors are under clinical trial, alone or in combination with immune checkpoint inhibitors (711). While the recent results of a phase 3 clinical trial have shown that the selective oral IDO inhibitor Epacadostat failed to improve the efficacy of the PD-1 checkpoint inhibitor Keytruda when the two drugs were used together to treat patients with newly diagnosed melanoma, other proof-of-concept trials are ongoing in patients with unresectable or metastatic melanoma, non-small-cell lung cancer, kidney cancer, bladder cancer and squamous cell carcinoma of the head and neck. In these studies, Epacadostat combined with the CTLA4 inhibitor Ipilimumab, or the PD-1 inhibitors Keytruda or Opdivo, improved response rates compared to the checkpoint inhibitors alone. Thus, IDO blockade may alleviate the immunosuppressive features of the TME and further reinforce therapy efficacy of other cancer immunotherapies. It results that IDO activity has been also tested as a putative predictive biomarker for resistance to immunotherapy (66). In a cohort of twenty-six NSCLC patients, of which 14 of them (54%) presented early progression (< 3 months) to Nivolumab, the high kynurenine to tryptophan ratio before treatment significantly correlated with resistance to anti-PD-1 treatment. Vice versa, taken as a therapeutic target, IDO-based strategies will need a better patient stratification. For example, the initial mouse work with IDO

inhibitors takes advantage of cancer cells with “induced” IDO expression (709). Thus, it is important to understand if the metabolic target itself, namely IDO, is present and/or which agent can be administered in combination in order to promote a higher dependency of the tumor on IDO as an immune suppressive cue. As hypoxia induces *Indo* transcription, it is possible for example that a combination with agents that modulate the level of oxygen in the tumor by their effect on the tumor vasculature (namely anti-angiogenic therapy; see (97, 224)) might induce IDO expression and render the tumor immune evasion more dependent on this pathway. Another recent study has shown that activated CTLs promotes IDO expression and the tryptophan transporter SLC1A5 in stem cell-like immune evasive melanoma cells (421). It follows that higher tryptophan uptake and IDO activity end up in increased release of kynurenine in the extracellular milieu. In turn, kynurenine is transported inside the T cells where it binds to the cytoplasmic transcription factor aryl hydrocarbon receptor (AhR) that induces the transcription of PD-1. Consistently, kynurenine plasma levels were strongly correlating with PD-1 expression in breast and colon cancer patients, but not in healthy individuals. Therapeutically, inhibiting IDO in cancer cells or the AhR in CTLs can reduce immune evasion and lead to novel combinatorial regimens (421).

X. Preclinical evidence for response, resistance and refractoriness to immune checkpoint inhibitors

X.I Clinical response to immune checkpoint blockade

Immunotherapy by immune checkpoint inhibitors (ICIs) constitutes an important breakthrough in cancer therapy. In recent years, the number of clinical approvals has been increasing at an extraordinary rate, due to the demonstrated efficacy across different solid and hematologic malignancies. Several ICIs entered the FDA accelerated approval program, making these new drugs available to the patient earlier, which was justified by the efficacy and safety of ICIs in phase 1 trials (329). However, in parallel, there are also reports of negative results, evidencing the limitations of this therapeutic approach.

X.I.I Biomarkers of response

Unfortunately, there is still a long way before we can accurately predict response to the approved ICIs. Regarding anti-CTLA-4 antibodies, even though some biomarkers of response have been identified, none of them has yet been included in the clinical routine. Regarding blockage of the PD-1/PD-L1 axis, only PD-1 expression has been identified as a relevant predicted biomarker. However, it is believed that the full picture is much more complex, with many more players involved (690). Another biomarker used to predict response to the approved ICIs, is the “mutational load” of the tumors. However, there is still no cut-off value defined to apply in the clinics. In a recent study, a comprehensive immunogenomic analysis of TCGA data was compiled for more than 10,000 tumors across different cancer types, which may become a valuable resource for future studies (694). Another related biomarker is the presence of microsatellite instability (MSI), which was found to predict response to ICIs in colorectal cancer. Hence, PD-L1 expression together with MSI analysis is currently being used in gastrointestinal cancers.

Tumor size is a common parameter analyzed to evaluate cancer therapeutic response, although in this type of immunological treatment, initially some patients could even present an increase in tumor size, due to infiltration of inflammatory cells (pseudoprogression). Thus, this parameter cannot be used in the same way to predict response, as with other types of treatment.

X.I.II Overcoming resistance

Many patients still do not benefit from ICIs treatment and other approaches are being attempted, such as combinations of drugs which will lead to maximal therapeutic benefit, but with minimum adverse events (4). One of the approaches is the combination of different T cell ICIs in one treatment. The rationale for this combination comes from the fact that blockade of one of these T cell immune checkpoints alone might induce the expression of other co-inhibitory receptors, rendering cancers resistant to therapy (4). Other immunostimulatory approaches include therapeutic vaccines, cytokines, oncolytic virus therapy and adoptive T cell transfer (see section IV for a further explanation on these therapies). Combinations of ICIs and chemotherapy or radiotherapy have also shown therapeutic benefits, since chemotherapy and radiotherapy in some cases are able to stimulate the function of different immune cells besides exposing cancer cell antigens upon cancer cell killing (240, 758).

Another approach is the combination with targeted therapies, in which case its success depends on each combination.

X.I.III Adverse effects

ICI therapy has been described to induce immune-related adverse events, which is a consequence of overstimulation of the immune function. The side effects associated with either CTLA4 or PD-1/PD-L1 antibodies, can go from cutaneous (rash and pruritus) and gastrointestinal (diarrhea), to more difficult to handle auto-immune conditions, including Crohn's disease, Hashimoto's thyroiditis, autoimmune hepatitis, uveitis and hypophysitis (4). Thus, this is another issue that has to be taken into consideration when using ICI therapy.

X.II Preclinical studies

Many pre-clinical studies have been set up on the use of ICIs, before and after the approval of the ICI Ipilimumab (anti-CTLA4) for human metastatic melanoma treatment in 2011. As mentioned above, despite the great success of ICIs in different cancer types, there are still many patients who do not benefit from this therapeutic strategy. Our knowledge is still very limited regarding the markers of response and refractoriness to ICIs, which justifies further investment in pre-clinical studies.

As one would expect from the clinical studies, by far, the great majority of preclinical studies available were conducted in melanoma models (Table 2). Nevertheless, there is a considerable amount of studies in other models, including the ones with clinical approval of ICIs, such as head and neck (Table 3), lung (Table 4), hematological (Table 5), renal and urothelial (Table 6), but also in other "less immunogenic" cancers such as breast (Table 7), central nervous system (Table 8) and digestive system cancers (Table 9).

In general, most preclinical studies show that single agent ICI therapy has limited effectiveness in melanoma models (Table 2). Thus, several combinations have been explored, including combinations with adoptive T cell transfer, cancer vaccines, oncolytic virus, regulatory T cell targeting, HDAC inhibitors, heparanase KO, IDO inhibitors, STING activator, targeted therapy, chemotherapy, radiotherapy and surgery. In general, the different combinations led to improvement of the anti-tumor

effects compared to either drug alone. These studies are aligned with the results of clinical studies in which ICIs were found to be more effective than control interventions, in terms of tumor progression and survival (340). Peculiarly, head and neck cancer and especially the squamous cancer cell subtype (HNSCC) is an excellent model for immunotherapeutic interventions due to its high mutation load, high T cell infiltration, PD-L1 overexpression and, importantly, in human papillomavirus (HPV) positive cases, there is potential to use targeted therapy against HPV viral proteins which serve as tumor antigens (805) (Table 3). In lung tumors, PD-L1 blockade showed some efficacy in preclinical models, but there are unsuccessful cases reported (Table 4). This is reinforced by clinical evidence, where important clinical response with ICIs has been seen in some patients with non-small cell lung cancer (NSCLC). Nevertheless, further efforts should be put on improving the selection of patients and optimize patient response (290). Particularly in hematological tumors, the oncogenic role of PD-1/PD-L1 axis in Hodgkin lymphoma and initial clinical trials showed very good response rates and a durable response. As a result, many clinical trials are testing PD-1 blockade either alone or in combination with other therapeutic approaches, with promising results (460) (Table 5). In renal cancer, several trials are ongoing with ICIs combination with anti-angiogenic therapies (VEGF pathway inhibitors) which are showing encouraging results (25) (Table 6). Even though breast cancer is considered as “immunologically silent” and thus not so promising in terms of response to immunotherapy interventions, many pre-clinical studies have been set up using ICIs alone or in combinations (Table 7). In clinical studies, PD-1/PD-L1 blockade showed variable percentage of response in triple negative breast cancer (TNBC) but a subset of patients experienced durable responses. Also, there is early evidence for positive results for combination with chemotherapy and many clinical trials are ongoing with different combinations (560). An interesting number of preclinical studies also exist in central nervous system tumors, especially in glioma models (Table 8). In a recent meta-analysis, the authors concluded that there are significant anti-tumor effects with anti-PD-1 antibody, while either IDO or CTLA4 blockade have little efficacy (246). Many studies also exist in digestive cancers, mainly in colon models, followed by liver, gastric, pancreas, GIST (gastro-intestinal stromal tumors) and esophageal cancer. Even though there is evidence for anti-tumor effects with ICIs alone, as for the other tumors, the different combinations also enhanced ICI efficacy (Table

9). Regarding gynecological cancers, most studies are in ovarian cancer, followed by cervical cancer, in which ICI combinations also showed effectiveness (Table 10). A similar scenario was also observed for prostate cancer.

As stated above, the metabolic crosstalk between cancer cells and immune cells plays a crucial role in the regulation of the immune response. Although we have been able to stimulate the activity of immune cells by targeting the inhibitory immune checkpoint proteins, immune cells will not be able to thrive and enter inside a tumor without a favorable metabolic environment. Thus, it would make sense to explore combinatory strategies to target both features. However, only a few metabolic targets have been explored so far, and this could partly explain cases of treatment resistance. Future studies should envisage to investigate this issue, aiming to improve the response to immunotherapy.

XI. Conclusive remarks

Cancer cells are equipped with different immunosuppressive mechanisms to oppose anti-tumor immune responses. They may mock tumor-associated antigens in several ways and reduce tumor immunogenicity to avoid T cell recognition. Further, cancer cells upregulate PD-L1/L2 expression to provide a co-inhibitory signal to suppress T cells anti-tumor functions. The combined use of checkpoint inhibitors against PD-1 and CTLA4 (or other immunotherapeutic regimens) shows great clinical promise in patients with advanced cancer. However, single compound treatment often remains unresponsive and therapeutic success by combining checkpoint inhibitors with other anti-cancer drugs is only achieved in a fraction of patients (and needs to be closely monitored to an increased toxicity of the combination regimen). This implies that other mechanisms of T cell suppression are still at play that can overrule checkpoint inhibition, or that other targets may play an important role in preconditioning the tumor to (better) respond to conventional immunotherapies. Along this line, it has become evident that tumors may differ in the composition, phenotype and intratumoral localization of immune cells, and this diversity strongly influences the success of immunotherapy.

In the last decade, immunometabolism has emerged as a key player in the tumor-associated immune response. Metabolism can influence antigen presentation, immune cell function and trafficking and

the expression of immune checkpoints. Moreover, metabolism greatly contributes to the harsh conditions of the TME that ultimately suppresses immune cell functions and T cell fitness. Recent studies have shown that cancer cells can also metabolically exhaust tumor-infiltrating T cells, since they are competing for the same nutrients. Oncogenic mutations enable cancer cells to drastically alter their metabolism in order to sustain their uncontrolled growth in hypoxic and/or nutrient-deprived environments. From a historical perspective, aerobic glycolysis was considered as the main metabolic pathway used for cancer cell energetics and building blocks, but recent reports made clear that functional mitochondria are also required for cancer cell growth. Therefore, recently developed therapies target the aberrant metabolism of cancer cells in order to block their energetic or anabolic supply. On the other hand, different immune cell subsets and phenotypes require distinct metabolic features enabling their functional activity. For example, the rule of thumb establishes that memory T cells and T_{regs} rely on FAO and OXPHOS, while CTLs and other effector anti-tumor immune cells prefer aerobic glycolysis and glutaminolysis. Yet, we need to move beyond this dogmatic view and expand our knowledge on *i)* how immunometabolism is regulated at the tumor site, where the complexity of the TME will likely tailor unique “tumor niche-associated” metabolic programs for particular immune cell subtypes displaying particular phenotypes, *ii)* how and if the immune system displays different metabolic vulnerabilities according to the primary tumor tissue of origin or the genetic marks of the primary tumor types and *iii)* whether different metastatic sites may be characterized by specific immunometabolic checkpoints. Importantly, metabolism-based therapeutic strategies may hamper the lifespan of cancer cells yet produce a detrimental effect on the anti-tumor immune system and thus, create a situation of non-cell autonomous drug resistance. Thus, it will be relevant to investigate which therapeutic targets would either be directed at a unique vulnerability or at a shared vulnerability with similar anti-tumor effects in different cell types. Alternatively, research on new drug delivery methods could provide the means to selective modify the metabolism of a specific immune cell subset or phenotype. One could also speculate that the metabolic signatures of tumors responding or refractory to checkpoint inhibition might differ, and thus also the relative availability of glucose, glutamine, fatty acids, oxygen levels or other nutrients. Therefore, future research should aim to determine the differential metabolism in tumors resistant versus refractory to

checkpoint inhibitors, in order to identify the targetable metabolic pathways in cancer cells that could have an additive effect to checkpoint inhibition.

In the last 30 years, several efforts were made to target cancer cell metabolism. The current principle of immune metabolism moves far beyond the original concept springing 90 years ago from the ideas of Otto Warburg to study metabolism to specifically tackle cancer cells. Immunometabolism keeps into account that cancer cells are embedded in a context of immune cells and other cells. However, the *in vitro* to *in vivo* disconnect had limited the success of preclinical and clinical translation with only a handful of targets that have made to the clinic. Technical advances, such as the use of new medium formulations more faithfully resembling physiological concentrations will be extremely useful to reduce this disconnection. A step beyond will be to design a metabolic topography of the tumor, with the detailed identification and localization of metabolites in the tumor milieu in order to increase our prediction on the function of the different immune cells in these niches.

Looking at metabolic dynamics and interplay within the tumor to trigger the immune system and integrating human and mouse datasets, current research in immunoncology will be able to re-purpose the armamentarium of metabolic drugs currently used in preclinical and clinical settings for the treatment of diseases other than cancer, or that so far have been conceived to target cancer cell metabolism. This new branch of research will thus hold the opportunity to disclose certainly novel biology. It will also allow efficient target identification and lead compounds with an immunotherapeutic effect when used alone or that synergize with or sensitize the tumor to currently available drugs such as immune checkpoint inhibitors. Hopefully, the intertwined, *in vivo* embedded, study of immunometabolism will pave the way to a new era of successful preclinical phases and clinical translation.

In conclusion, it is becoming clear that targeting the immune landscape and metabolic pathways can achieve positive endpoint only when the tumor is considered as a heterogeneous entity: how do oncogenic mutations modify metabolism? How is the molecular target regulated within the tumor? How is the general immune landscape of the tumor? Which are the metabolic alterations that define the composition of an immunosuppressive TME? Which of the cancer cell compartments and their crosstalk drives these metabolic alterations? Can we “normalize” the TME to sustain T cell fitness

and effector functions? Are the different metabolic features of the metastasis (vs. the primary tumor) impacting on a diverse immune response? These and other questions will lead to a more thorough cohort selection and ultimately to precision medicine where each cancer patient can be treated with a specific cocktail of drugs.

XII. Figure legends

Figure 1. The immune system in cancer

Immune cells are dynamic by nature and therefore may adopt an anti- or pro-tumor phenotype in response of the environment they encounter. Here we offer a classification of the main tumor-infiltrating immune cell lineages (in rows) based on their most usual anti- or pro-tumor effect (green left and red right columns, respectively). When their role is still unclear they are grouped in the middle column (orange). Within each cell, the main transcription factors are indicated in white, upstream cytokines to each cell type/phenotype are indicated by a blue arrow and downstream cytokines are indicated by a blue arrow (for T_H17 , the brackets indicate that only in certain cases). The mostly used markers for the identification of each cell are indicated underneath, with the icon of a mouse or a human for murine and human markers, respectively. Shared markers are indicated with both icons. In some instances, the specific antibody clone is specified in brackets. Abbreviations: M1 or M2 macrophage (M1 or M2); conventional dendritic cells 1 or 2 (cDC1 or cDC2); plasmacytoid dendritic cells (pDC); N1 or N2 neutrophils (N1 or N2); myeloid-derived suppressive cells (MDSCs); NK cells (NK); innate lymphoid cells type 1, 2 and 3 (ILC1/2/3); $CD4^+$ T helper cells type 1, 2 and 17 ($T_H1/2/17$); $CD8^+$ T cells (CD8 T); and $CD4^+$ regulatory T cells (T_{reg}).

Figure 2. Hypoxic instruction of immune cell positioning

Hypoxic cells secrete several cytokines and chemokines and establish a gradient that shapes the recruitment or the exclusion of several immune cell subsets in hypoxic areas. When the involvement of hypoxia-inducible factor 1 alpha (HIF-1 α) or HIF-2 α has been described, it is indicated within each cell. Dendritic cells are not included in this figure due to the fact that the impact of hypoxia on the positioning of dendritic cells has not been described.

Abbreviations: C-X-C chemokine receptor type 1, 2 or 4 (CXCR1/2/4); C-X-C chemokine ligand type 1, 2, 5, 12 (CXCL1/2/5/12), C-C receptor 10 (CCR10), C-C ligand 5/28 (CCL5/28), pattern recognition receptor (PRR), (P2XR), (P2YR), vascular endothelial growth factor A (VEGF-A), (soluble) vascular endothelial growth factor receptor 1 (sVEGFR1 or VEGFR1), neuropilin-1 (Nrp1),

semaphoring 3/7A (Sema3/7A), interleukin-8 (IL-8), damage-associated molecular pattern (DAMP), tumor growth factor beta (TGF- β), endothelin 1/2 (ET-1/2), granzyme B (GzmB), interferon gamma (IFN- γ), TNF receptor apoptosis-inducing ligand (TRAIL).

Figure 3. Hypoxia, HIF and cytokine-mediated control of CD4⁺ T cell subset plasticity

Hypoxia, HIFs and cytokines (i.e. TGF- β and IL-6) control T_H17/T_{reg} and T_H1/T_{reg} balance through several mechanisms. HIF-1 α , induced either by hypoxia or by other stimuli, is a central orchestrator of these balances. Hypoxia and TGF- β can potentially induce both T_H17 and T_{reg} development and is the presence or absence of IL-6 what skews the balance towards T_H17 or T_{reg}, respectively. The modulation of glycolysis, ROR γ t, IL-17 and Foxp3 underlie these events. Furthermore, VHL and PHDs are necessary to maintain T_{reg} identity and in their absence, HIF-1 α promotes T_H1 differentiation via induction of glycolysis and IFN- γ .

Abbreviations: interleukin-6/17/22/23 (IL-6/17/22/23), tumor growth factor beta (TGF- β), interferon gamma (IFN- γ), Von Hippel-Lindau (VHL), prolyl hydroxylases (PHDs), mammalian target of rapamycin complex 1 (mTORC1), ROR-related orphan receptor gamma t (ROR γ t).

Figure 4. General metabolic pathways and metabolic pathways in cancer cells

(A) Glycolysis consists in the conversion of glucose to pyruvate. G6P, an intermediate of glycolysis, can be rerouted to the PPP pathway to generate ribose-5-P and NADPH, which are required for nucleotide synthesis, maintenance of the redox balance and for FAS. Pyruvate can be either converted to lactate and secreted or enter in the mitochondria and feed the TCA cycle. Fatty acids and glutamine can also undergo anaplerotic reactions and feed the TCA cycle by engaging in FAO and glutaminolysis, respectively. The TCA cycle generates reducing equivalents (NADH, FADH₂) that can enter the ETC and contribute to the synthesis of ATP and mROS. Moreover, the TCA cycle also serves as a source of metabolic intermediates such as citrate, that is shuttled from the mitochondria to the cytoplasm to fuel FAS. FAS is essential to generate membranes as well as lipid mediators. Glutamine metabolism serves other purposes besides

glutamine anaplerosis, such as for instance the synthesis of glutathione, ornithine or α -KG and epigenetic regulators. Finally, arginine can be converted into ornithine or to NO by the action of ARG1 and NOS2, respectively, which is crucial for several immune responses.

(B) Cancer cell increase glycolysis, lactate uptake and conversion to pyruvate, PPP, FAO, FAS, glutaminolysis, glutamine anaplerosis and arginine metabolism. Moreover, cancer cells maintain intermediate levels of the TCA cycle and OXPHOS.

Increased fluxes are indicated by a wider color band and/or thicker arrows, while reduced fluxes are indicated by a thinner color band and/or a dotted arrow. A transparent color band and a question mark next to the name of the pathway indicate that the contribution is still unclear. Abbreviations: pentose phosphate pathway (PPP), fatty acid oxidation (FAO), fatty acid synthesis (FAS), tricarboxylic acid cycle (TCA cycle), oxidative phosphorylation (OXPHOS), glucose transporter 1 (GLUT1), glucose-6-phosphate (G6P), phosphoenolpyruvate (PEP), glyceraldehyde 3-phosphate dehydrogenase (GAPDH), lactate dehydrogenase A (LDHA), monocarboxylate transporter (MCT), nicotinamide adenine dinucleotide phosphate (NADPH), coenzyme A (CoA), α -ketoglutarate (α -KG), oxaloacetate (OAA), flavin adenine dinucleotide (FADH₂), nicotinamide adenine dinucleotide (NADH), electron transport chain (ETC), mitochondrial reactive oxygen species (mROS), acetyl-CoA carboxylase (ACC), ATP citrate lyase (ACLY), adenine triphosphate (ATP), solute carrier family 1 member 5 (SLC1A5), glutaminase (GLS), glutamine synthetase (GS), glutamic-oxaloacetic transaminase 1/2 (GOT1/2), glutamate dehydrogenase 1 (GLUD1), glutathione (GSH), arginase-1 (ARG1), nitric oxide synthase 2 (NOS2), nitric oxide (NO).

Figure 5. Metabolic pathways in M1 and M2 macrophages

(A) M1 macrophages increase glycolysis, PPP to support the production of ROS, citrate efflux from the mitochondria, FAS, glutaminolysis and glutamine anaplerosis and arginine conversion to NO. On the other hand, M1 macrophages have a minimal requirement for FAO and do not divert arginine towards ornithine and polyamine synthesis. Moreover, M1 macrophages present two characteristic “brake points” of the TCA cycle, which are indicated with red crosses. These break

points occur at the level of isocitrate dehydrogenase (IDH) and of succinate dehydrogenase (SDH), leading to the accumulation of citrate and succinate, respectively, and maintain intermediate levels of OXPHOS.

(B) M2 macrophages increase FAO, glutamine anaplerosis (GLS) and cataplerosis (GS), the TCA cycle, OXPHOS and arginine conversion to ornithine. Compared to M1, M2 macrophages maintain intermediate levels of glycolysis and FAS. Conversion of arginine to NO is reduced and the PPP is inhibited by CARKL.

Increased fluxes are indicated by a wider color band and/or thicker arrows, while reduced fluxes are indicated by a thinner color band and/or a dotted arrow. A transparent color band and a question mark next to the name of the pathway indicate that the contribution is still unclear. Abbreviations: pentose phosphate pathway (PPP), fatty acid oxidation (FAO), fatty acid synthesis (FAS), tricarboxylic acid cycle (TCA cycle), oxidative phosphorylation (OXPHOS), glucose transporter 1 (GLUT1), glucose-6-phosphate (G6P), phosphoenolpyruvate (PEP), glyceraldehyde 3-phosphate dehydrogenase (GAPDH), lactate dehydrogenase A (LDHA), monocarboxylate transporter (MCT), nicotinamide adenine dinucleotide phosphate (NADPH), reactive oxygen species (ROS), coenzyme A (CoA), α -ketoglutarate (α -KG), oxaloacetate (OAA), flavin adenine dinucleotide (FADH₂), nicotinamide adenine dinucleotide (NADH), electron transport chain (ETC), mitochondrial reactive oxygen species (mROS), acetyl-CoA carboxylase (ACC), ATP citrate lyase (ACLY), adenine triphosphate (ATP), solute carrier family 1 member 5 (SLC1A5), glutaminase (GLS), glutamine synthetase (GS), glutamic-oxaloacetic transaminase 1/2 (GOT1/2), glutamate dehydrogenase 1 (GLUD1), glutathione (GSH), arginase-1 (ARG1), nitric oxide synthase 2 (NOS2), nitric oxide (NO), carbohydrate kinase-like protein (CARKL).

Figure 6. Metabolic pathways in neutrophils and myeloid-derived suppressive cells (MDSCs)

The metabolism of neutrophils is poorly characterized in the context of the tumor and the metabolism of neutrophil-specific subsets (i.e. N1 or N2) is completely underexplored. In the context of inflammation, neutrophils require an increased flux of glycolysis and PPP to sustain nucleotide synthesis, the respiratory burst and NET formation and have a minimal requirement for the TCA

cycle, OXPHOS and FAS. In contrast, MDSCs display an enhanced FAO, exclusively express fatty acid transport protein 2 (FATP2) to import arachidonic acid required for the synthesis of PGE₂, and express high levels of ARG-1 and NOS, which altogether sustain their immunosuppressive function. Glutamine metabolism in neutrophils or MDSCs is unknown.

Increased fluxes are indicated by a wider color band and/or thicker arrows, while reduced fluxes are indicated by a thinner color band and/or a dotted arrow. A transparent color band and a question mark next to the name of the pathway indicate that the contribution is still unclear. Abbreviations: pentose phosphate pathway (PPP), fatty acid oxidation (FAO), fatty acid synthesis (FAS), tricarboxylic acid cycle (TCA cycle), oxidative phosphorylation (OXPHOS), glucose transporter 1 (GLUT1), glucose-6-phosphate (G6P), phosphoenolpyruvate (PEP), glyceraldehyde 3-phosphate dehydrogenase (GAPDH), lactate dehydrogenase A (LDHA), monocarboxylate transporter (MCT), nicotinamide adenine dinucleotide phosphate (NADPH), coenzyme A (CoA), α -ketoglutarate (α -KG), oxaloacetate (OAA), flavin adenine dinucleotide (FADH₂), nicotinamide adenine dinucleotide (NADH), electron transport chain (ETC), mitochondrial reactive oxygen species (mROS), acetyl-CoA carboxylase (ACC), ATP citrate lyase (ACLY), prostaglandin E2 (PGE₂), solute carrier family 1 member 5 (SLC1A5), glutaminase (GLS), glutamine synthetase (GS), glutamic-oxaloacetic transaminase 1/2 (GOT1/2), glutamate dehydrogenase 1 (GLUD1), glutathione (GSH), arginase-1 (ARG1), nitric oxide synthase 2 (NOS2), nitric oxide (NO), myeloid-derived suppressive cells (MDSCs).

Figure 7. Metabolic pathways in conventional DCs (cDCs) and plasmacytoid DCs (pDCs)

Very little is known about DC metabolism, and in particular about tumor-associated DC metabolism.

(A) Upon activation, conventional DCs (cDCs) increase glycolysis and PPP, but they decrease OXPHOS, while maintaining intermediate levels of the TCA cycle. This is thought to contribute to the efflux of citrate from the mitochondria to the cytosol. The channeling of citrate towards FAS supports organelle function, but lipid accumulation is associated with a tolerogenic phenotype. In NOS2-expressing DCs, NO production inhibits the ETC and further sustains the decrease of OXPHOS. The contribution of fatty acid and amino acid metabolism to cDC function is still subject to controversy.

(B) Plasmacytoid DCs (pDCs) increase FAO to support their maturation and decrease glycolysis and PPP. The contribution of FAS, OXPHOS and amino acid metabolism still remains unclear.

Increased fluxes are indicated by a wider color band and/or thicker arrows, while reduced fluxes are indicated by a thinner color band and/or a dotted arrow. A transparent color band and a question mark next to the name of the pathway indicate that the contribution is still unclear. Abbreviations: pentose phosphate pathway (PPP), fatty acid oxidation (FAO), fatty acid synthesis (FAS), tricarboxylic acid cycle (TCA cycle), oxidative phosphorylation (OXPHOS), glucose transporter 1 (GLUT1), glucose-6-phosphate (G6P), phosphoenolpyruvate (PEP), glyceraldehyde 3-phosphate dehydrogenase (GAPDH), lactate dehydrogenase A (LDHA), monocarboxylate transporter (MCT), nicotinamide adenine dinucleotide phosphate (NADPH), coenzyme A (CoA), α -ketoglutarate (α -KG), oxaloacetate (OAA), flavin adenine dinucleotide (FADH_2), nicotinamide adenine dinucleotide (NADH), electron transport chain (ETC), mitochondrial reactive oxygen species (mROS), acetyl-CoA carboxylase (ACC), ATP citrate lyase (ACLY), solute carrier family 1 member 5 (SLC1A5), glutaminase (GLS), glutamine synthetase (GS), glutamic-oxaloacetic transaminase 1/2 (GOT1/2), glutamate dehydrogenase 1 (GLUD1), glutathione (GSH), arginase-1 (ARG1), nitric oxide synthase 2 (NOS2), nitric oxide (NO).

Figure 8. Metabolic pathways in ILCs

Upon activation, NK cells increase glycolysis, which feeds the TCA cycle and OXPHOS and supports NK cell effector function. SREBP1c-induced export of mitochondrial citrate via the citrate malate shuttle is essential to support the metabolism of effector NK cells. Cytosolic acetyl-CoA could potentially be used for acetylation reactions rather than as fuel for FAS. ILC3 identity relies on the production of mROS, important to sustain ROR γ t expression. An increase of glutamine uptake in activated NK cells facilitates the uptake of long neutral amino acids, which are essential to sustain c-Myc levels and thereby to fuel NK cell effector functions. Glutamine anaplerosis also takes place, but its contribution to NK cell function is unknown. The exact contribution of lipid metabolism has not been fully elucidated, but lipid accumulation in NK cells drives NK cell paralysis. In particular for the

ILC2 subset, ARG-1 activity is increased and fuels polyamine synthesis. Further studies are required to study ILC subset-specific metabolism.

Increased fluxes are indicated by a wider color band and/or thicker arrows, while reduced fluxes are indicated by a thinner color band and/or a dotted arrow. A transparent color band and a question mark next to the name of the pathway indicate that the contribution is still unclear. Abbreviations: pentose phosphate pathway (PPP), fatty acid oxidation (FAO), fatty acid synthesis (FAS), tricarboxylic acid cycle (TCA cycle), oxidative phosphorylation (OXPHOS), glucose transporter 1 (GLUT1), glucose-6-phosphate (G6P), phosphoenolpyruvate (PEP), glyceraldehyde 3-phosphate dehydrogenase (GAPDH), lactate dehydrogenase A (LDHA), monocarboxylate transporter (MCT), nicotinamide adenine dinucleotide phosphate (NADPH), coenzyme A (CoA), α -ketoglutarate (α -KG), oxaloacetate (OAA), flavin adenine dinucleotide (FADH₂), nicotinamide adenine dinucleotide (NADH), electron transport chain (ETC), mitochondrial reactive oxygen species (mROS), acetyl-CoA carboxylase (ACC), ATP citrate lyase (ACLY), solute carrier family 1 member 5 (SLC1A5), glutaminase (GLS), glutamine synthetase (GS), glutamic-oxaloacetic transaminase 1/2 (GOT1/2), glutamate dehydrogenase 1 (GLUD1), glutathione (GSH), arginase-1 (ARG1), nitric oxide synthase 2 (NOS2), nitric oxide (NO).

Figure 9. Metabolic pathways in naïve, activated and memory T cells

T cell metabolism is strongly rewired upon activation and again in the acquisition of memory.

(A) Naïve T cells mostly rely on FAO, TCA cycle and OXPHOS and maintain intermediate levels of glutaminolysis and glutamine anaplerosis to support their metabolic needs. Accordingly, naïve T cells have a reduced flux of glycolysis, PPP and FAS.

(B) Upon activation, T cells increase glucose and glutamine uptake, glycolysis, PPP, FAS, glutaminolysis, glutamine anaplerosis and arginine uptake and reduce FAO. Glutamate is also diverted towards polyamine synthesis and glutathione synthesis. Activated T cells maintain intermediate levels of the TCA cycle and OXPHOS. TCA cycle and reductive carboxylation are also used as a source of metabolic intermediates. Moreover, uptake of leucine is required to sustain T cell activation.

(C) Memory T cells decrease glycolysis and increase both FAS and FAO and engage what has been termed “fatty acid futile cycle” to fuel the increased flux of the TCA cycle and OXPHOS. Moreover, the OAA produced in the first step of FAS is used for glycogen synthesis and subsequently undergoes glycogenolysis and fuels PPP and glutathione synthesis. Arginine is essential to promote mitochondrial fusion.

Increased fluxes are indicated by a wider color band and/or thicker arrows, while reduced fluxes are indicated by a thinner color band and/or a dotted arrow. A transparent color band and a question mark next to the name of the pathway indicate that the contribution is still unclear. Abbreviations: pentose phosphate pathway (PPP), fatty acid oxidation (FAO), fatty acid synthesis (FAS), tricarboxylic acid cycle (TCA cycle), oxidative phosphorylation (OXPHOS), glucose transporter 1 (GLUT1), glucose-6-phosphate (G6P), phosphoenolpyruvate (PEP), glyceraldehyde 3-phosphate dehydrogenase (GAPDH), lactate dehydrogenase A (LDHA), monocarboxylate transporter (MCT), nicotinamide adenine dinucleotide phosphate (NADPH), coenzyme A (CoA), α -ketoglutarate (α -KG), oxaloacetate (OAA), flavin adenine dinucleotide (FADH₂), nicotinamide adenine dinucleotide (NADH), electron transport chain (ETC), mitochondrial reactive oxygen species (mROS), acetyl-CoA carboxylase (ACC), ATP citrate lyase (ACLY), solute carrier family 1 member 5 (SLC1A5), solute carrier family 7 member 5 (SLC7A5), glutaminase (GLS), glutamine synthetase (GS), glutamic-oxaloacetic transaminase 1/2 (GOT1/2), glutamate dehydrogenase 1 (GLUD1), glutathione (GSH), arginase-1 (ARG1), nitric oxide synthase 2 (NOS2), nitric oxide (NO).

Figure 10. Metabolic pathways in CD4⁺ T cells

Metabolism strongly underlies and influences the differentiation of CD4⁺ T cells into T helper subsets and T_{regs} as well as their function and ability to adapt in certain metabolic environments.

(A) T_H1 increase glycolysis, PPP, FAS, glutamine anaplerosis, glutathione synthesis, uptake of leucine and arginine and conversion of arginine into NO. T_H1 cells maintain intermediate levels of the uptake of exogenous fatty acids and glutamine, glutaminolysis, TCA cycle and OXPHOS and suppress FAO. Engagement of GAPDH and LDHA in glycolysis promotes the expression of

IFN- γ through epigenetic mechanisms. Rheb/mTORC1 and HIF-1 α signaling are key for T_{H1} metabolism and differentiation.

(B) T_{H2} increase glycolysis until the formation of pyruvate, which is imported to the mitochondria to feed the increased flux of the TCA cycle and OXPHOS, while the conversion of pyruvate to lactate is inhibited. Moreover, T_{H2} cells increase the uptake of arginine and the conversion of arginine into ornithine. T_{H2} cells maintain intermediate levels of FAS and suppress PPP, FAO, glutaminolysis, glutamine anaplerosis and the conversion of arginine into NO. Rheb-independent Raptor/mTORC1 and RhoA/Rictor/mTORC2 signaling are key for T_{H2} metabolism and differentiation.

(C) T_{H17} increase glycolysis, but the entry of pyruvate to the mitochondria is blocked by the expression of PHDK1. They also increase PPP, FAS, glutamine uptake, glutaminolysis (GLS activity) and leucine and arginine uptake. Glutamate is diverted into several pathways necessary to maintain T_{H17} identity: it fuels glutathione synthesis thereby neutralizing ROS and allowing IL-17 synthesis and it is converted into α -KG and subsequently to R-2-HG, which is required to epigenetically silence Foxp3. T_{H1} cells maintain intermediate levels of the uptake of exogenous fatty acids, TCA cycle and OXPHOS and suppress FAO and conversion of arginine into NO, although the fate of arginine is still unclear. Rheb/mTORC1 and HIF-1 α signaling are key for T_{H17} metabolism and differentiation.

(D) T_{regs} increase FAO, the TCA cycle, OXPHOS and the uptake of isoleucine. T_{regs} maintain intermediate levels of PPP and glycolysis until the formation of pyruvate, which is imported to the mitochondria to feed the increased flux of the TCA cycle and OXPHOS, while the conversion of pyruvate to lactate is inhibited. T_{regs} suppress FAS and glutamine metabolism. The contribution of arginine metabolism is underexplored. AMPK signaling is key for T_{regs} metabolism and differentiation.

Increased fluxes are indicated by a wider color band and/or thicker arrows, while reduced fluxes are indicated by a thinner color band and/or a dotted arrow. A transparent color band and a question mark next to the name of the pathway indicate that the contribution is still unclear. Abbreviations: pentose

phosphate pathway (PPP), fatty acid oxidation (FAO), fatty acid synthesis (FAS), tricarboxylic acid cycle (TCA cycle), oxidative phosphorylation (OXPHOS), glucose transporter 1 (GLUT1), glucose-6-phosphate (G6P), phosphoenolpyruvate (PEP), glyceraldehyde 3-phosphate dehydrogenase (GAPDH), lactate dehydrogenase A (LDHA), monocarboxylate transporter (MCT), pyruvate dehydrogenase kinase isozyme 1 (PDHK1), nicotinamide adenine dinucleotide phosphate (NADPH), coenzyme A (CoA), α -ketoglutarate (α -KG), oxaloacetate (OAA), flavin adenine dinucleotide (FADH₂), nicotinamide adenine dinucleotide (NADH), electron transport chain (ETC), mitochondrial reactive oxygen species (mROS), acetyl-CoA carboxylase (ACC), ATP citrate lyase (ACLY), solute carrier family 1 member 5 (SLC1A5), solute carrier family 7 member 5 (SLC7A5), solute carrier family 3 member 2 (SLC3A2), glutaminase (GLS), glutamine synthetase (GS), glutamic-oxaloacetic transaminase 1/2 (GOT1/2), glutamate dehydrogenase 1 (GLUD1), glutathione (GSH), arginase-1 (ARG1), nitric oxide synthase 2 (NOS2), nitric oxide (NO), IL-17 (interleukin-17), interferon gamma (IFN- γ), AMP-activated protein kinase (AMPK), mammalian target of rapamycin complex 1/2 (mTORC1/2), hypoxia-inducible factor 1 alpha (HIF-1 α).

Figure 11. Metabolic control of CD4⁺ T cell subset plasticity

Metabolic reprogramming is at the core of the balance between T_H1, T_H17 and T_{regs}. In the boxes, the top darker part indicates the main metabolic pathways, the middle intermediate part indicates the master signaling pathways and the bottom lighter indicates specific enzymes or proteins that sustain a particular subset. The metabolites, cytokines or target processes to tilt the balance in favor of one or another subset are indicated next to each arrow.

Abbreviations: pentose phosphate pathway (PPP), fatty acid oxidation (FAO), fatty acid synthesis (FAS), oxidative phosphorylation (OXPHOS), glyceraldehyde 3-phosphate dehydrogenase (GAPDH), lactate dehydrogenase A (LDHA), pyruvate dehydrogenase kinase isozyme 1 (PDHK1), α -ketoglutarate (α -KG), acetyl-CoA carboxylase (ACC), ATP citrate lyase (ACLY), solute carrier family 1 member 5 (SLC1A5), solute carrier family 7 member 5 (SLC7A5), solute carrier family 3 member 2 (SLC3A2), glutaminase (GLS), glutamic-oxaloacetic transaminase 1/2 (GOT1/2),

glutathione (GSH), Von Hippel-Lindau (VHL), prolyl hydroxylases (PHDs), ROR-related orphan receptor gamma t (ROR γ t), adenosine A2A receptor (A2AR), P2X purinoceptor 7 (P2X₇R), interferon gamma (IFN- γ), AMP-activated protein kinase (AMPK), mammalian target of rapamycin complex 1 (mTORC1), hypoxia-inducible factor 1 alpha (HIF-1 α).

Figure 12. Metabolic pathways in effector CD8⁺ cytotoxic T cells (CTLs)

CTLs increase glycolysis, fatty acid uptake, FAS, glutamine uptake, glutaminolysis, glutamine anaplerosis, glutathione synthesis and uptake of leucine, serine and arginine. Engagement of GAPDH in glycolysis and the blockade of the pyruvate entry to the TCA cycle by PDHK1 promotes the expression of IFN- γ through epigenetic mechanisms. Glutamate is diverted into several pathways necessary for their effector function: it fuels glutathione synthesis and it is converted into α -KG and subsequently to S-2-HG to mediate epigenetic regulation. Arginine is essential to promote mitochondrial fusion. mTORC1 and HIF-1 α signaling are key for CTL metabolism and function.

Increased fluxes are indicated by a wider color band and/or thicker arrows, while reduced fluxes are indicated by a thinner color band and/or a dotted arrow. A transparent color band and a question mark next to the name of the pathway indicate that the contribution is still unclear. Abbreviations: pentose phosphate pathway (PPP), fatty acid oxidation (FAO), fatty acid synthesis (FAS), tricarboxylic acid cycle (TCA cycle), oxidative phosphorylation (OXPHOS), glucose transporter 1 (GLUT1), glucose-6-phosphate (G6P), phosphoenolpyruvate (PEP), glyceraldehyde 3-phosphate dehydrogenase (GAPDH), lactate dehydrogenase A (LDHA), monocarboxylate transporter (MCT), pyruvate dehydrogenase kinase isozyme 1 (PDHK1), nicotinamide adenine dinucleotide phosphate (NADPH), coenzyme A (CoA), α -ketoglutarate (α -KG), oxaloacetate (OAA), flavin adenine dinucleotide (FADH₂), nicotinamide adenine dinucleotide (NADH), electron transport chain (ETC), mitochondrial reactive oxygen species (mROS), acetyl-CoA carboxylase (ACC), ATP citrate lyase (ACLY), solute carrier family 1 member 5 (SLC1A5), solute carrier family 7 member 5 (SLC7A5), glutaminase (GLS), glutamine synthetase (GS), glutamic-oxaloacetic transaminase 1/2 (GOT1/2), glutamate dehydrogenase 1 (GLUD1), glutathione (GSH), arginase-1 (ARG1), nitric oxide synthase 2 (NOS2), nitric oxide (NO), interferon gamma (IFN- γ), mammalian target of rapamycin complex 1 (mTORC1).

Figure 13. General hypoxia and metabolism-based strategies to enhance immunotherapy

We propose four main metabolism/hypoxia-based therapeutic strategies that aim at reinvigorating the anti-tumor immune response via **i)** altering the recruitment (*i.e.*, turning “cold” tumors into “hot” tumors) and the location of tumor-infiltrating immune cells within different tumor niches to promote anti-tumor immune phenotypes, **ii)** promoting cancer cell immune-recognition by inducing antigenicity or limiting immune evasion mechanisms, **iii)** rewiring immune cell fitness in order to improve their function in a restrictive TME, and **iv)** rewiring the TME into an immune permissive milieu that favors anti-tumor immune responses.

Abbreviations: tumor microenvironment (TME), tumor-associated macrophage (TAM), dendritic cell (DC), natural killer cell (NK cell).

XIII. References

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