Cell Cycle 10:3, 374-379; February 1, 2011; © 2011 Landes Bioscience

Cell Cycle News & Views

More than MAX: Discovering the Myc interactome

Comment on: Agrawal P, et al. Cell Cycle 2010; 9:4908–21

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The proto-oncogene *MYC* encodes an essential master-regulatory protein in normal cells that controls a variety of critical cellular processes, including proliferation, apoptosis and differentiation.[1] When the tightly regulated expression of Myc in normal cells becomes deregulated, Myc becomes a potent oncogene that can drive tumor initiation and progression. Myc deregulation plays a profound role in tumorigenesis and is thought to contribute to the development of over 50% of human cancers of diverse origin.

Defining the molecular mechanisms underlying both proto-oncogenic and oncogenic Myc function promises to yield important advances in the development of useful anticancer therapeutics targeting Myc activity. Past research efforts largely focused on understanding how Myc functions as a regulator of gene transcription, with the identification of target genes taking center stage. Current advances have demonstrated that Myc binds to the promoter regions of many gene targets, yet only a subset are then regulated at the level of expression. Moreover, to add further complexity, Myc has recently been reported in the cytoplasm.[2] The role Myc plays in this new subcellular compartment remains unclear. Although evidence suggests that recruitment of co-regulators is essential for Myc function,[3] further insight into the specific molecular mechanisms controlling Myc-dependent transformation are required.

An important yet understudied strategy to delineate Myc's mechanisms of action is to identify Myc partner proteins, and then to subsequently equate these protein complexes to their functional roles and biological activities. A handful of Myc-binding proteins have been identified to date, with the best-studied example being Max.[4,5] The Myc:Max interaction appears to be essential for Myc activation and repression of gene transcription, as well as for most Myc-related biological activities. Despite the key advance marked by the discovery of Myc and Max as partners in an important functional complex, the identity of additional Myc-binding proteins has not been explored using a global systems-wide approach.

In a previous issue of *Cell Cycle*, the first attempt at a large scale unbiased assessment of Myc interactors was undertaken by Koch et al. in 2007, using the DLD1 colorectal cancer cell line and HEK293T cells, stably and transiently expressing ectopic Myc, respectively.[6] This study utilized a C-terminal tandem affinity purification (TAP)-tag co-immunoprecipitation (Co-IP) approach coupled with multidimentional protein identification technology (MudPIT). This strategy identified 17 known Myc-binding proteins and 204 putative new interactors, of which 12 were selected and further validated.

In the December 15, 2010 issue of *Cell Cycle*, Agrawal et al. utilized several complementary approaches to identify putative Myc interactors in human lung fibroblast LF1/TERT/LT/ST cells stably expressing N-terminally TAP-tagged Myc.[7] In particular, three independent experimental approaches were undertaken: a two-step TAP purification and a one-step Protein A purification and stable isotope labeling with amino acids in cell culture (SILAC) were used and coupled with MudPIT. Notably, this study is the first to characterize the Myc interactome with the use of several distinct experimental approaches. A total of 418 high confidence Myc interactors were identified, with five proteins identified with high confidence by all three methods.

Recently, Kim et al. have also exploited highly sensitive mass spectrometry techniques to characterize the Myc interactome.[8] This group used a biotin-labeling method to isolate Myc complexes in mouse embryonic stem (ES) cells and then analyzed their components by one-dimensional mass spectrometry. This approach identified eight Myc interactors, of which four were not listed in the Human Protein Reference Database (HPRD). All eight were validated by co-immunoprecipitation (co-IP) and mass spectrometry.

These three investigations into the Myc interactome reveal distinct subsets of putative Myc-binding proteins, suggesting that Myc interactions may be cell-type specific and dependent on the experimental conditions, including the isolation procedure employed. Studies using either N- or C-terminally tagged Myc found many differences in putative Myc associations, suggesting that the reported interactions could be further influenced by steric hindrance of the protein. Each of the putative interactors identified in these types of studies, however, remains to be validated in additional experiments to rule out false positives. For example, co-IP studies, fluorescence resonance energy transfer (FRET) and in vitro binding may be useful to confirm complex formation and direct interaction. Additionally, the possibility of signal-dependent or transient interactors remains an important avenue to pursue in future studies, along with the specific biological functions of different Myc complexes. Importantly, these studies have highlighted that there are potentially hundreds of proteins that can interact with Myc (**Fig. 1**). Delineating the role of each complex could provide both exciting insights to explain the diverse array of biological functions regulated by Myc and the potential for novel therapeutics targeting Myc activity in cancer.

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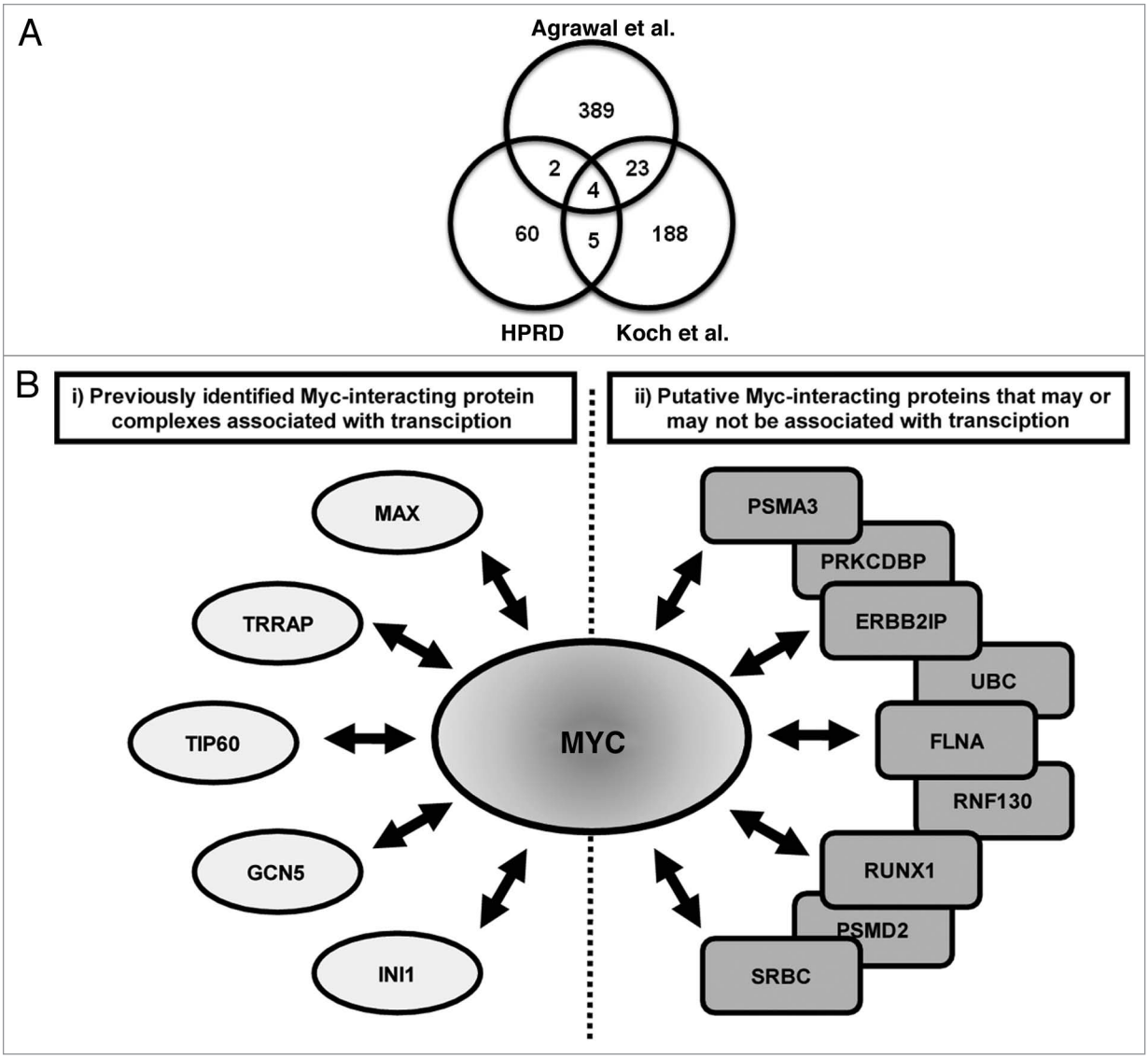

Figure 1. Expanding the Myc interactome. (A) Venn diagram comparing the known Myc interacting proteins (Human Protein Reference Database, HPRD) with recent publications using high-throughput mass spectrometry methods. (B) Schematic diagram representing several of the known Myc-interacting protein complexes and several of the putative interactors identified by Agrawal et al.

Loss of CC3/TIP30 allows tumor cells to cope with low glucose

Comment on: Chen V, et al. Cell Cycle 2010; 9:4941–53

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Glucose metabolism in eukaryotic cells is finely tuned not only to accommodate fluctuations in glucose and oxygen inputs but also to regulate the balance between energy production and the production of the biosynthetic precursors ensuring cell proliferation. Whereas glycolysis yields two molecules of ATP per molecule of glucose, full oxidation of glucose yields up to 38 molecules of ATP. Consequently, resident cells of normal tissues most efficiently extract energy from glucose when the glycolytic flux is coupled to the rate of pyruvate incorporation into the tricarboxylic acid (TCA) cycle. Because oxidative phosphorylation (OXPHOS) is rate-limiting,[1] the glycolytic flux must be repressed to reach high performance energy production and avoid pyruvate leakage. This is achieved by the Pasteur effect, a negative feedback in which high energy metabolites such as citrate and ATP allosterically repress the activity of key glycolytic enzymes.[2] Since oxygen is the final electron acceptor for ATP production in mitochondria, this accurately tuned regulation further ensures metabolic adaptability with respect to local pO_2. The Pasteur effect not only allows cells to accommodate physiological variations in oxygen delivery but also to achieve optimal energy production at increasing distance from blood vessels. To proliferate, cells must undergo a profound metabolic reorganization allowing the effective redistribution of carbohydrate backbones from energy-producing pathways to biosynthetic pathways. A first regulation is through alternative splicing of the *pyruvate kinase M* gene, a c-Myc-dependent on/off mechanism producing either PKM1 or PKM2.[3] PKM2 exists in a catalytically active tetrameric form promoting glycolysis but also in a catalytically inactive dimeric form that creates a metabolic bottleneck redirecting glucose-6-phosphate to the pentose phosphate pathway for ribose and DNA synthesis. A second regulation involves switching to glutamine as a substrate to replenish the TCA cycle leaking out the citrate, malate and oxaloacetate needed for lipid and aminoacid synthesis.[4] Proliferating cells primarily produce ATP from glycolysis.[5] They consume glucose abundantly but few oxygen and release high levels of lactate, a process initially identified in ascite cells of the mouse and termed the Warburg effect.[6]

Cancer is a metabolic disease. Tumor growth indeed depends on the ability of cancer cells to resolve the metabolic equation characterized by highly variable oxygen and glucose inputs on one side and survival and unbridled proliferation on the other side. Adaptation to sustained (or repeated episodes of) hypoxia involves the transcription factor hypoxia-inducible factor-1 (HIF-1), a master regulator of glycolysis. HIF-1 target genes encode glucose transporters, glycolytic enzymes insensitive to (hexokinase-2) or repressing (phosphofructokinase-2) the Pasteur effect, pyruvate dehydrogenase kinase-1 (PDK1), which limits pyruvate oxidation in the TCA cycle, and lactate dehydrogenase-5 (LDH5), which reduces pyruvate to lactate to replenish the NAD^+ pool required to perpetuate glycolysis.[7] The efflux of lactate and protons depends on monocarboxylate transporter-4 (MCT4), the sodium proton exchanger-1 (NHE1) and carbonic anhydrase-9 (CA9), all encoded by HIF-1-target genes. c-Myc cooperates with HIF-1 to promote glycolysis.[8] As for nonmalignant cells, tumor cell proliferation largely relies on the Warburg effect. Consequently, tumor cells survive and are able to proliferate even under hypoxia as long as high amounts of glucose are available. We recently proposed that glucose delivery to hypoxic tumor areas primarily relies on a metabolic symbiosis in which oxygenated tumor cells consume lactate rather than glucose as an oxidative fuel, and hypoxic tumor cells benefit from increased glucose to produce lactate glycolytically.[9] This mechanism implies sufficient glucose delivery from blood vessels.

But then, what is the fate of glycolysis-addicted cells when the vascular glucose input drops down? Cell death? In a previous issue of *Cell Cycle*, Chen and Shtivelman[10] reported on a new mechanism through which CC3/TIP30, an evolutionarily-conserved tumor suppressor, regulates the survival of tumor cells in low glucose. Cells die when CC3/TIP30 is present but they survive when it is silenced. The authors document in vitro that CC3/TIP30 deficiency provides the metabolic flexibility needed to reactivate OXPHOS in Warburg-phenotype tumor cells, thus allowing efficient ATP production from the remaining glucose and/or glutamine. Although the mechanisms are still incompletely understood, loss of CC3/TIP30 is convincingly shown to increase the expression of protein subunits of mitochondrial respiration complexes I, III and IV, promote c-Myc expression and the downstream expression of GLUT1 and PKM2 and, either directly or indirectly as a consequence of increased OXPHOS, represse AMPK activation by low glucose. Loss of CC3/TIP30 thus provides a metabolic advantage to tumor cells receiving few glucose as long as oxygen is present. Is it relevant to human cancer? Part of the answer lies in the fact that CC3/TIP30 is often decreased or absent in a variety of cancers.[10]

Acknowledgements

Works in the author's lab are supported by the European Research Council (FP7/2007-2013 ERC Independent Researcher Starting Grant 243188 TUMETABO), the Fonds National de la Recherche Scientifique (F.R.S.-FNRS), the Communauté Française de Belgique (ARC 09/14-020) and the Fondation Belge Contre le Cancer (200-2008). PS is a F.R.S.-FNRS Research Associate.

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BRCA1, microRNAs and cancer predisposition: Challenging the dogma

Comment on: Pelletier C, et al. Cell Cycle 2011; 10:90–1

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Identifying breast cancer risk in BRCA1-negative (and BRCA2-negative) families is an important medical issue. *BRCA1* is a tumor suppressor gene that is important in the regulation of several cellular functions, such as DNA damage, the cell cycle, recruitment of chromatin-modifying proteins and ubiquitin ligase activity.[1] *BRCA1* mutations are well-known risk factors for developing breast cancer. These mutations may cause wild-type BRCA1 loss of function or create gain-of-function BRCA1-mutated proteins.[1] Although some researchers have focused their attention on understanding how *BRCA1* mutations affect cellular physiology and therefore affect cancer risk,[1] others have focused on finding new genetic markers in the *BRCA1* gene that can help predict breast cancer risk. However, less than 5% of all persons susceptible to breast cancer can be determined by analyzing *BRCA1* mutation status;[2,3] thus, new markers in the *BRCA1* gene must be identified. New players in the predisposition mechanism are microRNAs (miRNAs) (**Fig. 1**, see opposite page). This class of small, noncoding RNAs is approximately 22 nucleotides in length and can regulate gene expression post-transcriptionally by binding the 3′ untranslated region (UTR), the coding sequence or 5′UTR of target messenger RNAs (mRNAs), which can lead to inhibition of translation or mRNA degradation. It is already known that genetic variations in miRNAs or miRNA target sites can interfere with the miRNA-mRNA interaction, which then can affect expression levels of several proteins involved in cancer genesis and development, such as oncogenes and tumor suppressor genes (for a review see ref. 4).

Recently in *Cell Cycle*, Pelletier et al.[3] described rare *BRCA1* halotypes in the 3′UTR associated with breast cancer risk. The authors sequenced the *BRCA1* 3´UTR of breast cancer patients and found three previously reported and one novel single-nucleotide polymorphism (SNP). Using an outstanding normal population repository of 2250 individuals from 46 different geographic populations, the authors determined the variants' frequencies.

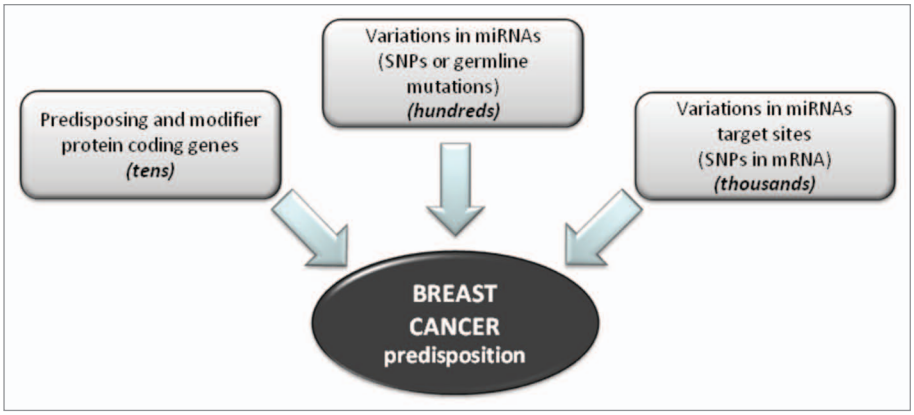

Figure 1. Challenging the dogma—miRNAs and cancer predisposition.

Pelletier et al. analyzed 8 SNPs and identified five haplotypes, three of which were located on the 3′UTR of *BRCA1*, that were present in the breast cancer population but rarely found in the control population. The frequency of these haplotypes also differed according to ethnicity and tumor subtype. Interestingly, these rare haplotypes were not associated with the most common *BRCA1*mutations and therefore might be independent markers of breast cancer risk. Given their potential as biomarkers, further study of the SNPs identified by Pelletier et al. is needed, particularly with respect to any disruptions in the interaction between miRNAs and mRNA that these variations might create.

Another example of a *BRCA1* SNP showing an association with breast cancer risk was reported by Nicoloso et al.[5] Those authors reported that the *BRCA1* SNP rs799917 is associated with susceptibility to breast tumor and that this risk is particularly increased for sporadic breast cancer. The authors showed that miR-638 interacts more strongly with allele [C] of SNP rs79991 than with the [T] allele. This difference in interaction was also confirmed at the protein level.[5]

In addition, miRNA-mRNA interactions dependent on SNPs have also been described in other tumor types. For instance, the laboratories of Slack and Weidhaas were the first to describe a SNP associated with non–small cell lung cancer risk in the *KRAS* 3′UTR that interferes with let-7 binding. The variant allele alters let-7-mediated regulation of KRAS, increasing its expression.[6]

These results demonstrate the importance of SNPs in conveying susceptibility to different kinds of cancer. The study by Pelletier et al.[3] is particularly vital because it describes new genetic markers in *BRCA1* 3′UTR noncoding regions that can improve our determination of breast cancer susceptibility. Inclusion of these SNPs in *BRCA1* haplotypes that are associated with breast cancer risk may guide future studies of functional miRNA interactions and their cellular consequences. This has the potential to greatly increase our ability to diagnose BRCA1-negative breast cancer at an earlier stage.

Acknowledgements

We thank Virginia M. Mohlere (Department of Scientific Publications, The University of Texas MD Anderson Cancer Center) for English editing of the manuscript.

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PKCε paves the way for prostate cancer

Comment on: Benavides F, et al. Cell Cycle 2011; 10:268-77

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Since the discovery that protein kinase C (PKC) is the receptor for tumor promoting phorbol esters, there have been numerous studies that linked PKC with tumor promotion. Subsequent studies revealed that PKC could function both as a tumor promoter and a tumor suppressor. The diverse function of PKC is attributed to distinct PKC isozymes. PKC exists as a family of closely related serine/threonine kinases categorized into three groups: conventional (α, βI, βII and γ), novel (δ, ε, η and θ) and atypical (ζ and λ/ι). PKCε was shown to possess oncogenic potential and is considered a transforming kinase that promotes cell proliferation, confers resistance to apoptosis and contributes to invasion and metastasis.[1,2]

PKCε has also been implicated in the development and progression of prostate cancer.[2-4] It is frequently overexpressed in prostate cancer cell lines and tumor specimens, and is a predictive biomarker of prostate cancer.[2] PKCε overexpression maintained prostate cancer growth following castration and contributed to androgen independence.[2] While these studies suggest the involvement of PKCε in prostate cancer, it is not clear if it is indeed necessary for the initiation of prostate cancer and its progression to neoplastic phenotype.

In the article "Transgenic overexpression of PKCε in the mouse prostate induces preneoplastic lesions," Kazanietz and colleagues investigated the causal role of PKCε upregulation in prostate cancer development and progression.[5] PKCε was specifically overexpressed in mouse prostate epithelium by driving its expression under the control of androgen-responsive rat probasin promoter. The authors made an important observation that targeted overexpression of PKCε but not PKCα or PKCδ in mouse prostate led to the development of preneoplastic lesions, such as prostate hyperplasia and prostate intraepithelial neoplasia (PIN). This observation is consistent with the previous finding that targeted overexpression of PKCε but not PKCα or PKCδ promoted development of skin squamous cell carcinomas (SCC).[5] In addition, PKCε when overexpressed in mouse prostate maintained its prosurvival activity and conferred resistance to apoptosis induced by castration.[5]

While the study by Benavides et al. corroborates previous findings derived from cell culture, tumor xenograft and studies performed with transgenic mouse model of SCC,[1,2],there are also some important differences. For example, PKCε is known to play an important role in invasion and metastasis and targeted overexpression of PKCε in mouse epidermis caused not only development of SCC but also invasion and metastasis to lymph nodes.[6] In contrast, overexpression of PKCε in mouse prostate demonstrated no evidence of invasive or in situ carcinoma up to 16-months of age.[5] This disparity could be due to differences in species, histological type or the model of carcinogenesis. For example, in the skin cancer model, TPA-DMBA or repeated exposure to ultraviolet radiation (UVR) was used to develop SCC.[6] While TPA causes tumor promotion in skin cancer, it induces apoptosis in prostate cancer cells.[7] Moreover, TPA or UVR may activate additional signaling pathways that may cooperate with PKCε to promote metastasis.

The Akt signaling pathway is frequently deregulated in prostate cancer. We have shown that PKCε acts upstream of Akt to promote cell survival.[8] The preneoplastic lesion in PKCε-overexpressing transgenic mice was accompanied by hyperactivation of Akt.[5] Thus, the Akt signaling pathway may mediate resistance to apoptosis following castration in the transgenic mouse model of prostate cancer.

Verma and colleagues have shown that PKCε is also essential for the activation of the transcription factor Stat 3 (signal transducers and activators of transcription 3).[3] Stat3 is constitutively activated in many cancers, including prostate cancer and was shown to interact with PKCε in prostate cancer cell lines, tumor specimens and transgenic adenocarcinoma of the mouse prostate (TRAMP).[3] Moreover, activation of Stat3 was essential for cancer cell invasion.[9] Although overexpression of PKCε in mouse prostate caused activation and induction of Stat3, it was not sufficient to promote invasion and metastasis. Future studies should determine how PKCε cooperates with other signaling pathways to promote aggressive metastatic phenotype. Nevertheless, the study by Benavides et al.[5] establishes the causal role of PKCε in the development of prostate cancer and validates it as a target for prostate cancer therapy.

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A tale of three PKCs: Epsilon emerges as a driver of pre-neoplastic phenotypes

Comment on: Benavides F, et al. Cell Cycle 2011; 10:268-77

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The concept that classical and novel PKCs exert divergent outcomes in cancer has been long appreciated (reviewed in ref. 1). The PKC family of serine-threonine kinases is comprised of ten related members, including "classical" (cPCKs α, β, and γ), "atypical" (aPKCs ι/λ and ζ), and "novel" (nPKC δ, ε, η, and θ) subclasses according to structural motifs, calcium requirement and mechanisms of activation. The individual PKCs regulate diverse and sometimes opposing cellular processes such as proliferation, apoptosis, migration/motility, differentiation and, most notably, are thought to play unique roles in cancer development and progression. The potential impact of PKCs on tumor development was realized almost three decades ago when PKCs were identified as intracellular receptors for tumor-inducing phorbol esters.[2] These initial discoveries ignited a season of discovery for discerning the overall influence of PKCs in tumorigenesis and tumor progression (reviewed in ref. 3).

Elegant in vitro and in vivo studies revealed that PKC functions in cancer are distinct amongst the kinases and show tissue specificity. For example, while PKCα does not alter skin cancer development in animal models, this isoform was identified as a critical mediator of proliferation in squamous cell carcinomas of the head and neck and as a marker of poor clinical outcome in this disease.[4,5] Similarly conflicting data has been observed with PKCδ; this isoform has been shown to be anti-proliferative in animal models of skin cancer and exerts anti-tumor properties in rodent colon epithelia, but evidence supports a pro-survival role for PKCδ in cells derived from lung or breast cancer (reviewed in ref. 6). The divergent and context-specific functions of PKCs in cancer illuminate the urgent need to consider the tumor-specific and clinically relevant effects of PKC alterations using in vivo models.

In a recent study by Benavides, Kazanietz and colleagues,[7] the impact of three distinct PKC isoforms was assessed using novel, prostate-specific transgenic models. Transgene expression was confined to the epithelial compartment, and animals homozygous for transgenic PKCα, PKCδ or PKCε expression were analyzed for histological changes after 12 months. Notably, significant epithelial hyperplasia was observed in PKCε but not PKCα or PKCδ models, and similar results were observed in vitro upon individual expression of the three isoforms into human prostatic epithelial cells immortalized with viral oncoproteins. Combined, these findings reveal specificity of PKCε for inducing pro-proliferative effects in prostatic epithelia.

While no evidence of neoplastic lesion formation was observed in the PKCε animals, dysplastic changes characteristic of mPIN (murine prostatic intraepithelial neoplasia) developed in multiple lobes of the prostate. Subsequent investigation revealed that mPIN lesions in the PKCε-expressing compartments displayed concomitant hyperactivation of AKT. It will be of significant interest to determine if this event is requisite for PKCε-mediated phenotypes, as prostate-specific expression of AKT also drives formation of mPIN lesions that do not progress to neoplasia, and excessive AKT activation is thought to play a major role in human disease.[8] In addition, a subset of PKCε overexpressing mPIN lesions exhibited elevation in total and activated Stat3. Given the putative oncogenic functions of Stat3 in human disease and the impact of Stat3 activation on tumor phenotypes,[9] it is enticing to speculate that PKCε-positive tumors may show altered clinical behavior. Accordingly, the present study showed that PKCε expression conferred moderate resistance to castration. A caveat of the prostate-specific expression model is that the transgene is under control of an androgen-dependent promoter (and is therefore attenuated in response to castration); nonetheless, the PKCε-transgenic epithelia showed a reduced apoptotic index after castration as compared to the PKCα and PKCδ transgenics.

Taken together, this tale of three PKCs defines the epsilon isoform as a driver of pre-neoplastic changes in the prostate, and provides an important new model with which to assess mechanism (including the role of AKT and Stat3), discern specificity of function, identify cooperative oncogenic factors and determine impact on therapeutic intervention. In this age of wisdom, wherein inhibitors of PKCs are both in development and in clinical trial, the present findings provide the impetus for developing PKCε as a putative new target for human prostate cancer.

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