H11. Monocarboxylate transporters expression is influenced by different extracellular conditions determining the effect of 3-bromopyruvate

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Monocarboxylate transporters (MCTs) play a vital role in the glycolytic metabolism in cancer cells, exporting lactate by a proton symport mechanism, maintaining intracellular pH homeostasis and contributing for tumor microenvironment acidification and aggressiveness. 3BP is an analogous of lactate with anti-tumor properties. 3BP uptake occurs via MCTs, acting as a glycolytic inhibitor with already identified targets, including hexokinase (HK) II and glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Indeed, 3BP induces energy depletion and cell death. As tumor cells overexpress MCTs, they can be used as a trap to mediate the uptake of compounds as 3BP. However, the tumor microenvironment may influence the expression of MCTs and consequently affect the toxic effect of 3BP. In this work, we aimed to characterize the effect of 3BP in different colorectal cancer (CRC) cell lines by exploring 3BP cytotoxicity and MCT1 and MCT4 expression upon different extracellular stimuli, including extracellular pH (pHe), glucose and oxygen levels as well as short-chain fatty acids (SCFAs) exposure. Materials and methods: Viability assays: The IC50 of 3BP was determined in basal conditions and in the different conditions: hypoxia, starvation, different pHe and exposure to SCFA. HCT-15 cells were incubated during 24 h with medium containing 200 µM of CoCl2 (chemical hypoxia), free-glucose medium (starvation), complete medium (w/o bicarbonate) adjusted with HEPES buffer to pH 6.6 or 7.4 or with complete medium containing butyrate (10 mM). When cells were incubated with medium containing lactate (50 mM) or acetate (20 mM), cells were incubated during 48 h. After that, cells were exposed to different concentrations of 3BP for 16 hour and cell viability was determined after this period of time by the SRB assay. Metabolites quantification: HCT-15 cells were exposed to different extracellular conditions and lactate and glucose were measured in extracellular medium. Expression assays: MCTs expression was evaluated by Western blot assays. Protein extracts of HCT-15 cells lines, incubated in the different conditions tested, were used. Result/Discussion: In this work, we tested the effect of 3BP in three different CRC derived cell lines: HCT15, Caco-2 and HT-29. HCT-15 cells showed to be the most sensitive cell line to 3BP and also the one that presented the highest basal expression of both MCT1 and CD147, a protein involved in the proper expression and activity of MCT1 and MCT4 at cell surface. Glucose starvation and hypoxia induced an increased resistance to 3BP in HCT-15 cells, in contrast to what happens with at acidic pHe. However, no association with MCT1, MCT4 and CD147 expression was observed, except for glucose starvation, where a decrease in CD147 (but not of MCT1 and MCT4) was detected. Butyrate and acetate (but not lactate) exposure increased the expression of MCT4 (but not MCT1) and CD147. Additionally, it was observed that the metabolic profile was affected by the 3 rd ASPIC International Congress, 10 – 11 May, Lisbon 92 different extracellular conditions. The overall results suggest that MCTs influence 3BP effect in CRC cells, although they are not the only player in its mechanism of action.

No conflict of interest