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The metabolic facet of pancreatic cancer

How hypoxia shapes fatal cancer cells

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Worldwide, among cancers in critical clinical need, pancreatic ductal adenocarcinoma (PDAC) is the most challenging to treat, representing the most fatal solid cancer (based on the ratio "case/dead").[1] As a silent killer, its symptoms are so insidious that most people are not diagnosed until the disease has advanced beyond the stage where surgical resection is possible. Moreover, standard chemo- and radiotherapy protocols improving cancer patient survival appeared to be inefficient in PDAC patients. Pancreatic adenocarcinoma is referred to as a hypovascular tumor, and previous studies demonstrated that hypoxic pancreatic cancer cells are resistant to gemcitabine-induced apoptosis.[2,3] Hence, until now, this population of cancer cells represents specific niches of aggressive cells impossible to target, harboring specific tumoral properties that are still not fully understood. Among characteristics yet to be discovered, molecular understanding of metabolic adaptation of these cells submitted to oxygen- and nutrient-deprived environment, could provide new insight into mechanisms leading to their selection as aggressive pancreatic cancer cells.

In our recent paper in *PNAS*, using the well-known *Pdx1-Cre;LSL-Kras^{G12D};Ink4a/Arf$^{fl/fl}$* PDAC-mouse model, we showed that hypoxia promotes a metabolic switch of pancreatic tumoral cells toward excessive glucose consumption which is used for the purpose of fuel supply, or of by-product for post-translational modifications (PTMs).[4] In these mice, up to 17% of the tumor area is hypoxic and is constituted of epithelial cells harboring mesenchymal invasive characteristics. Indeed, the majority of these cells harbor the N-Cadherin marker to the detriment of the E-Cadherin one, suggesting that they entered into an epithelial-to-mesenchymal transition (EMT) program. Regarding their metabolic activity, these hypoxic cells demonstrate an exacerbated glycolytic potential leading to a 2-fold increase of glucose uptake and lactate release into the extracellular compartment, compared with normoxic cells. Consequences of such a massive lactate release by epithelial hypoxic cells are double. Firstly, it promotes an acidic microenvironment and facilitates the degradation of extracellular matrix close to hypoxic cells. Consequently, the latter will be able to disseminate in the tumor and to adjacent tissues thanks to invasive markers they acquired through the hypoxic-driven EMT process. Secondly, normoxic neighboring cells use this excess of lactate as a substrate to fuel their growth. Therefore, we can consider that a two-speed glycolysis exists within pancreatic tumor. The massive glycolysis occurring in epithelial cells in the hypoxic compartment that partly feeds normoxic cells located close to hypoxic area, and the "routine" glycolytic activity, namely the Warburg effect, occurring in tumoral cells in normoxic regions.

But use of glucose by cancer cells under hypoxia is not restricted to lactate production. So what are the alternative routes of glucose in hypoxic tumoral cells? A recent study demonstrated that glucose is also channeled toward glycogen in response to acute hypoxia, and that subsequent breakdown of this pool of accumulated glycogen under prolonged exposure to hypoxia sustains cancer cells proliferation, while impairment of glucose release from glycogen leads to senescence.[5] In our investigations, we propose a model in which channeling of glucose toward the hexosamine biosynthetic pathway (HBP) is essential for the survival of pancreatic cancer cells under hypoxia. This pathway, fueled not solely by glucose by-products but also by glutamine, supplies cancer cells with UDP-N-acetylglucosamine (UDP-GlcNAc) residues for O-linked GlcNAc PTMs. Besides their avidity for glucose, we demonstrated that hypoxic pancreatic cancer cells effectively consume glutamine, and its conversion into glutamate through glutaminolysis is required for their proliferation. Moreover, we showed that viability of hypoxic pancreatic cancer cells is highly dependent on HBP activation. Interestingly, we identified specific key limiting enzymes of glutaminolysis and HBP, such as glutaminase (GLS) 2 and glutamine fructose-6-phosphate amidotransferase (GFPT) 2, respectively, that are preferentially expressed in hypoxic regions of PDAC. On the other hand, previous report indicated that the GFPT1 enzyme supports activation of HBP in normoxic pancreatic tumoral cells, suggesting that, according to oxygen levels in PDAC, the HBP is driven by two different GFPTs.[6] Considering that levels of O-GlcNAc proteins are higher in hypoxic pancreatic tumor cells than normoxic ones, it is conceivable that maintenance of an elevated rate of PTMs needed for hypoxic cell survival depends on GFPT2. In our ongoing studies, we are now investigating which O-GlcNAc proteins could be responsible for hypoxic pancreatic cell survival. In addition to their role in O-GlcNAc PTMs, UDP-GlcNAc residues also serve for N-Glycan branching of cytokine receptors, transporters and consequently act as upstream regulators of numerous signaling pathways. Hence,

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in the hypoxic context of PDAC, it will be of great interest to identify acceptor substrates of O-/N-Glycan branching, which could participate in biological events leading to PDAC progression and dissemination.

While a lot of efforts have been made on many fronts to better understand PDAC, a new window is open for considering hypoxic pancreatic cancer cells as important targets to eradicate in selective cancer therapy. We showed that besides acquiring aggressive and invasive characteristics, they develop specific metabolic features allowing them to resist to the hostile oxygen- and nutrient-deprived microenvironment. Therapeutic metabolic targeting of pancreatic hypoxic cancer cells is thus a new issue to consider.

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