Editorial

Stressing for sugar: a new role of serotonin for glycolysis in pancreatic cancer cells

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Pancreatic ductal adenocarcinoma (PDAC) is characterized by a prominent desmoplastic stroma in the tumor microenvironment. This histologic feature arises from deposition of extracellular matrix that increases tissue stiffness and limits vascularity (1,2). This stromal architecture offers an advantage to tumor cell survival and metastasis via several mechanisms, including secretion of growth factors between stromal and malignant cells, promoting an immune suppressive microenvironment and acting as a physical barrier, limiting access of therapeutic agents (1-4). A recent publication by Jiang *et al.* explores a novel mechanism whereby desmoplasia is linked to metabolic stress in PDAC cells (5). The authors demonstrate that under metabolic stress, the neuromodulator, serotonin plays a role as an autocrine mediator of PDAC survival and resistance to apoptosis. Using a series of relevant agonists, antagonists and genetic approaches, the authors validated a role for HTR2B, one key receptor for serotonin that regulates the growth and survival of PDAC cells. To further support the relationship between serotonin signaling and tumor progression, they utilized a series of tissue microarrays comprising more than 300 unique PDAC specimens that were obtained from treatment naïve patients. This study links the ability of PDAC cells to metabolize glucose via glycolysis (i.e., the Warburg effect) to a new mechanism that imparts a viability advantage.

Metabolic features of the PDAC tumor microenvironment are regulated by numerous redundant mechanisms. Given these new data, we can now appreciate the serotonin/HTR2B axis as a clever means by which tumor cells can commandeer neuroregulatory pathways in response to metabolic shifts arising from exposure to desmoplastic changes and poor oxygenation. These results are aligned, but still distinct from other reports implying a role for this axis in PDAC. For example, other independent studies have explored the consequences of modulating serotonin receptors (5-HT-1B and 5-HT1D). Namely, down-regulation of these receptors can inhibit proliferation, clonogenicity and invasion of human PDAC cells *in vitro*.(6) In this report by Jiang *et al.* (5), it is worth noting the presence of some degree in variability as to the role of serotonin across individual PDAC cell lines. This inability to rescue certain cell lines from apoptosis induced by serum deprivation points to the need for continued study that may highlight key differences that can be used for better understanding the mechanism on an individual level.

It remains important to consider whether this axis plays a role in cell populations aside from malignant PDAC cells. Indeed, serotonin may impact other cells of relevance in the tumor microenvironment. Notably, serotonin has immunomodulatory properties as a regulator of chemotaxis, lymphocyte activation, and cytokine secretion among others (7). This observation is of particular relevance as other cell types including tumor associated macrophages (TAMs) can promote the Warburg effect in PDAC via distinct mechanisms (8), and the TAMs themselves exhibit prominent glycolytic phenotypic properties (9). Serotonin has also been shown to play a role in regulating acinar dedifferentiation in the pancreas following pancreatitis, and may play a role in accelerating the process of acinar-to-ductal metaplasia by facilitating recruitment of type 2

macrophages (10). Finally, understanding the impact of the serotonin/HTR2B axis on pancreatic stellate cells (PSCs) may also lend further insight into dysregulated metabolic features of PDAC tumors. PSC themselves have glucose intolerance (11) and can facilitate cross-talk that results in rewired metabolic networks of PDAC cells. Of particular relevance is the relationship between *KRAS*-dependent signaling pathways and metabolic properties of these tumors. Prior studies indicate that reprogramming of glutamine metabolism is mediated by oncogenic *KRAS* to become a major carbon source for survival of tumor cells (12). This mechanism is thought to involve interactions between PSC and PDAC via the IGF1R/AKL axis, which in turn elevates mitochondrial respiration in tumor cells (13,14), PSCs can also support tumor metabolism through autophagic alanine secretion (15). Curiously, some metabolic parameters can also be altered in a paracrine manner via exosome mediated communication (16). These findings highlight a complex metabolic network within PDAC tumors capable of utilizing several nutrients as fuel to withstand the hostile pressures of fibrosis, hypoxia and chronic inflammatory processes.

This new understanding of serotonin in the PDAC microenvironment could catalyze further interest in pharmacologic inhibition of this pathway. While these results (5) certainly support serotonin/HTR2B signaling as a viable target, the authors wisely point out that prior attempts at inhibiting pathways downstream of HTR2B have had limited success in PDAC. Together these data suggest that interference with serotonin might be considered in the context of combinatorial approaches at least in pre-clinical studies for proof of principle data. The pleiotropic actions of serotonin across multiple cellular compartments could also be better characterized through well-designed gain or loss of function studies using genetically manipulated cell lines or animals to dissect its tumor-intrinsic or tumor-extrinsic role. Finally, it may be informative to expand this line of study into tumors from patients who have been previously exposed to chemotherapy as standard of care for their disease. The interactions of ongoing or prior exposure to cytotoxic drugs could potentially impact receptor expression and integrity of pathways that signal in response to serotonin.

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