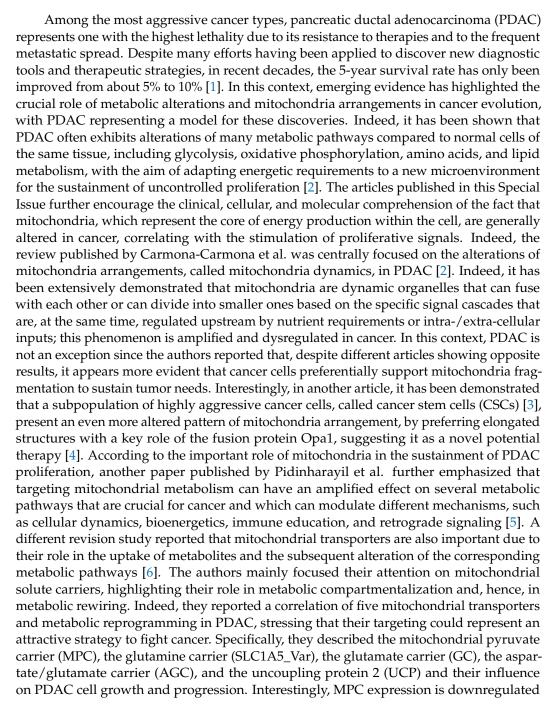




New Insights into Metabolic Alterations and Mitochondria Re-Arrangements in Pancreatic Adenocarcinoma

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Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). in PDAC, whereas the expression of the other four transporters is generally upregulated, with evidence that the loss of one or more of them leads to the detriment of PDAC cell growth and proliferation [6]. Additionally, another study presented in this Special Issue shows that the transcription factor EB (TFEB), which is known to act as a master regulator of lysosomal function and autophagy, is also a nutrient sensor, supporting the responses to cellular stress and immune stimuli. Indeed, based on the data showing that TFEB is overexpressed in PDAC cells compared to normal tissue samples, the authors demonstrated that its genetic inhibition resulted in a significant decrease in both glutamine and mitochondrial metabolism, suppressing PDAC growth in vitro and in vivo [7]. This study added a piece of knowledge to the identification of novel therapeutic approaches based on metabolic targets and, more specifically, on glutaminase-mediated glutamine metabolism, which may represent a key target. Another study that identified metabolic proteins as targets for PDAC growth impairment is that by Pacchiana et al., where they tested the in vitro and in vivo effects of novel inhibitors, 3-bromo-isoxazoline derivatives, of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) [8]. Their results demonstrated that these compounds, in particular AXP-3019, present anti-proliferative effects on PDAC cells and CSCs, without affecting normal fibroblasts. Finally, two other articles presented new insights into the exploitation of metabolic and other pathways, for instance genetic and inflammatory, for cancer treatment by studying two diseases that strictly correlate with PDAC: hepatopancreatobiliary cancer and intraductal papillary mucinous neoplasms (IPMN). Specifically, regarding hepatopancreatobiliary cancer, the authors started from the evidence that in these cancer cells there is a general increase in lipid synthesis and alterations in lipid metabolism associated with lipid droplets' accumulation. Lipid droplets are intracellular structures that store neutral lipids and acts as molecular messengers and signaling factors, thus mediating proliferation, invasion, metastasis, and chemotherapy resistance. The authors discerned the role of different lipid droplet-associated factors, including patatin-like phospholipase domain-containing 3 (PNPLA3), transmembrane 6 superfamily member 2 (TM6SF2), and 17β -hydroxysteroid dehydrogenase (HSD17B) 11 and 13, with the aim of proposing them, and consequently lipid droplets, as new potential therapeutic options [9]. Instead, regarding IPMN, other authors described new factors that could help to diagnose this type of benign neo-formation in order to avoid its evolution into a malignant phenotype. In particular, they structured their work by dividing lowand high-risk factors and identified some potential biomarkers, including some involved in metabolic pathways, that can help to identify IPMNs that have a high risk to become cancerous [10].

In conclusion, new important evidence emerged from this Special Issue, leading us to further encourage the study of the metabolism in PDAC by taking into consideration alterations of specific metabolic proteins and mitochondrial arrangement/function to develop new therapeutic strategies that could improve the survival rate of PDAC patients.

Conflicts of Interest: The authors declare no conflict of interest.

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