PANCREATIC CANCER

Disrupted lipid metabolic pathways in PDAC identified

In mice, pancreatic ductal adenocarcinoma (PDAC) is characterized by the disruption of several lipid metabolic pathways, reports a recent study in *Proceedings of the National Academy of Sciences of the USA*.

Patients with PDAC generally have a poor response to chemotherapy, which is largely due to the dense stroma associated with the tumour that compresses the vasculature and limits drug delivery to the tumour. As a result of these environmental changes, the tumour cells undergo metabolic reprogramming, which can vary greatly. “Defining the metabolic network signature of PDAC might shed light on key and novel therapeutic targets,” explains Sophie Vasseur, corresponding author of the study. “We want to highlight the main metabolic routes used by pancreatic cancer cells to survive, proliferate and disseminate in distinct healthy tissues.”

In this project, led by Fabienne Guillaumond, DNA microarray technology was used to identify which transcripts involved in metabolic processes were differentially expressed between samples of invasive PDAC and samples from the pancreata of control mice. 427 metabolic transcripts were upregulated and 320 transcripts were downregulated in PDAC mice compared with control mice. The PDAC metabolic signature featured pathways associated with lipid, amino acid and carbohydrate metabolism, with the lipid class containing the greatest number of disrupted pathways. Within the lipid class, most changes were seen in the pathways involved in lipoprotein catabolism and its negative regulation, as well as those that regulated cholesterol homeostasis. “Lipids have long been recognized as important aspects of the rewired metabolism of cancer

LDLR (red in top and brown in bottom images) is restricted to epithelial cells in mouse PDAC. Image courtesy of S. Vasseur.

cells, but their contribution to pancreatic tumorigenesis is not yet fully determined although they appear, in this study, as essential in PDAC-associated metabolic reprogramming,” comments Vasseur.

Vasseur and colleagues also showed that expression of *Ldlr* (which encodes the LDL receptor) is increased in PDAC compared with control mice, suggesting that cholesterol uptake is increased in the tumour tissue. Furthermore, silencing of the LDL receptor decreased cell proliferation and enhanced the chemotoxic effects of common chemotherapeutics in mouse PDAC cells.

“Our work highlights cholesterol uptake, through LDLR, as a key metabolic pathway for the maintenance of cholesterol distribution, which is essential for progression of PDAC,” concludes Vasseur. “This finding supports the development of new clinically relevant LDLR-inactivating agents.”

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Original article

Guillaumond, F. *et al.* Cholesterol uptake disruption, in association with chemotherapy, is a promising combined metabolic therapy for pancreatic adenocarcinoma. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1421601112