A novel therapeutic target in pancreatic cancer: Implications for therapy and diagnosis

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BACKGROUND: Pancreatic ductal adenocarcinoma (PDAC) prognosis is very poor and is the result of late diagnosis and high resistance to chemotherapy. Recent evidence suggest that the G-protein coupled receptor 55 (GPR55), is overexpressed in many cancer types, including PDAC, and regulates cancer progression. PDAC chemoresistance is caused in part by overexpression of ATP binding cassette (ABC) transporters. Although so far ABC transporters have been mostly studied as multi-drug resistance proteins, there is evidence that they also directly contribute to cancer progression. Therefore, targeting these proteins may help to improve the effectiveness of current therapies.

METHODS: The effect of modulation of ABCC3 and GPR55 levels (genetically and pharmacologically) and the response to their antagonists was performed on a variety of human PDAC cell lines. Furthermore, GPR55 expression and the response to antagonists were studied in vivo in KRAS/p53 (KPC) transgenic mice and PDX xenografts. New mouse model (KPCG) was also generated by crossing the KPC mice with GPR55(-/-) mice.

RESULTS: Here we demonstrate that, in PDAC, phospholipase A2 (PLA2) produces lysophosphatidylinositol (LPI) that is released by ABCC3 and, once outside the cell, LPI activates GPR55, forming an autocrine loop and enabling continuous stimulation of cancer cell proliferation. We demonstrated that the downregulation and pharmacological inhibition of this loop, highly decreased PDAC cell proliferation and colonisation in vitro and in vivo.

CONCLUSIONS: Collectively, our results indicate that the ABCC3/GPR55 loop has a key role in PDAC progression. Therefore, both ABCC3 and GPR55 are potential targets for novel therapies.

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