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GPR55 signalling promotes proliferation of pancreatic cancer cells and tumour growth in mice, and its inhibition increases effects of gemcitabine

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Abstract

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The life expectancy for pancreatic cancer patients has seen no substantial changes in the last 40 years as very few and mostly just palliative treatments are available. As the five years survival rate remains around 5%, the identification of novel pharmacological targets and development of new therapeutic strategies are urgently needed. Here we demonstrate that inhibition of the G protein-coupled receptor GPR55, using genetic and pharmacological approaches, reduces pancreatic cancer cell growth in vitro and in vivo and we propose that this may represent a novel strategy to inhibit pancreatic ductal adenocarcinoma (PDAC) progression. Specifically, we show that genetic ablation of Gpr55 in the $KRAS^{WT/G12D}/TP53^{WT/R172H}$/Pdx1-$Cre^{+/+}$ (KPC) mouse model of PDAC significantly prolonged survival. Importantly, KPC mice treated with a combination of the GPR55 antagonist Cannabidiol (CBD) and gemcitabine (GEM, one of the most used drugs to treat PDAC), survived nearly three times longer compared to mice treated with vehicle or GEM alone. Mechanistically, knockdown or pharmacologic inhibition of GPR55 reduced anchorage-dependent and independent growth, cell cycle progression, activation of mitogen-activated protein kinase (MAPK) signalling and protein levels of ribonucleotide reductases in PDAC cells. Consistent with this, genetic ablation of Gpr55 reduced proliferation of tumour cells, MAPK signalling and ribonucleotide reductase M1 levels in KPC mice. Combination of CBD and GEM inhibited tumour cell proliferation in KPC mice and it opposed mechanisms involved in development of resistance to GEM in vitro and in vivo. Finally, we demonstrate that the tumour suppressor p53 regulates GPR55 protein expression through modulation of the microRNA miR34b-3p. Our results demonstrate the important role played by GPR55 downstream of p53 in PDAC progression. Moreover our data indicate that combination of CBD and GEM, both currently approved for medical use, might be tested in clinical trials as a novel promising treatment to improve PDAC patients' outcome. © 2018, Macmillan Publishers Limited, part of Springer Nature.

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