PANCREATIC CANCER

Not the usual suspect

Obesity is associated with increased risk of developing pancreatic ductal adenocarcinoma (PDAC). High-fat diet (HFD)-induced mouse models of obesity have given limited insight into the underlying mechanisms, and there is still much to be learnt regarding the interventions that can potentially help to improve outcomes in this context. Now, Chung et al. have developed an autochthonous mouse model of obesity-associated PDAC and identified the hormone cholecystokinin (CCK) to be protumorigenic.

The authors crossed *ob*/*ob* mice, which are deficient for the weight regulating hormone leptin and develop early-onset obesity, with *Pdx1*-Cre;*Kras*$^{LSL\text{-}G12D/WT}$ (KC) mice, which are predisposed to develop pancreatic intraepithelial neoplasia. The resulting KCO mice developed early-onset obesity and had a higher pancreatic tumour burden and enhanced progression to PDAC compared with KC or KC;*ob*/+ mice. When obesity in KCO mice was reversed before a significant tumour burden had developed, through intramuscular injection of adeno-associated virus encoding leptin (AAV-leptin), tumour progression was reduced. This reduction was proportional to the degree of weight loss. Having ruled out changes in tumour suppressor protein expression or additional driver gene mutations that could contribute to tumour development in KCO mice, the authors explored the mechanisms by which obesity itself could promote pancreatic tumorigenesis.

Further analysis highlighted obesity-associated changes in the tumour microenvironment, showing that gene expression signatures associated with inflammation and fibrosis, as well as extracellular matrix deposition and tumour immune cell infiltration, were upregulated in KCO mice compared with KC mice or KC mice with additional heterozygous *Trp53* mutations (KPC mice). Bulk RNA sequencing (RNA-seq) of pancreata from KCO, KC and KPC mice showed that genes associated with pancreatic islet cell function were upregulated in KCO mice compared with KC or KPC mice. This was related to increased production and secretion of the hormones glucagon and glucagon-like peptide 1. Contrary to expectations, local insulin production and secretion from islet cells in KCO mice was reduced compared with KC or KPC mice. Indeed, further experiments showed that hyperinsulinemia or insulin-regulated signalling and glucose reabsorption did not seem to be associated with obesity-induced PDAC in KCO mice.

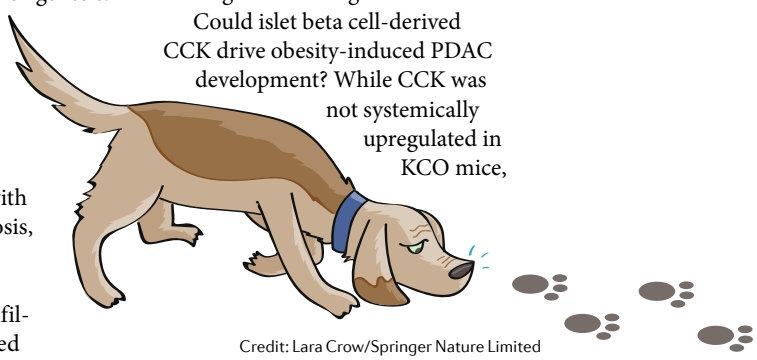
Single cell RNA-seq of islets from wild-type mice or *ob*/*ob* mice showed that obesity resulted in significant changes in gene expression in islet cells. As such, genes that were upregulated in islets from *ob*/*ob* mice included those involved in protein translation, secretion and endoplasmic reticulum stress, with the top upregulated gene encoding CCK. CCK is a hormone usually expressed and secreted by entero-endocrine cells of the duodenum and stimulates the secretion of digestive enzymes from pancreatic acinar cells as well as bile acid from the gall bladder. CCK is known to promote islet survival during insulin resistance, and here, its gene expression in KCO mice was inversely correlated with the expression of the gene encoding insulin.

Could islet beta cell-derived CCK drive obesity-induced PDAC development? While CCK was not systemically upregulated in KCO mice, its expression was increased locally, in islet cells of KCO mice, compared with KC or KPC mice, and was downregulated when KCO mice were treated with AAV-leptin. In tissue samples from patients with PDAC, CCK was expressed in islets in ~60% of samples. CCK expression in islets also correlated with body mass index in donors without malignancy (the same analysis in samples from patients showed no correlation; however weight loss prior to diagnosis might have confounded the analysis in patients with PDAC). When *MIP-Cck* transgenic mice, which express CCK in islet beta cells at levels similar to *ob*/*ob* mice, were crossed with KC mice, the resulting MKC mice showed increased tumour burden compared with KC mice, suggesting that CCK expression in islet beta cells can drive PDAC.

> “CCK expression in islet beta cells can drive PDAC”

Looking into the underlying mechanism, the authors found that *MIP-Cck* mice did not show evidence of inflammation or fibrosis. Conversely, acute or chronic pancreatitis in wild-type mice, induced by cerulin and/or arginine, also did not induce CCK expression in the islets of mice, excluding an inflammation-dependent mechanism of CCK in promoting tumorigenesis or in the induction of CCK in islet beta cells. Moreover, even though CCK has previously been shown to stimulate insulin secretion from islet beta cells in mice, *MIP-Cck* mice did not show increased insulin secretion. These findings suggest that the tumour development in MKC mice was independent of insulin activity or inflammation.

It remains to be conclusively shown whether CCK was required for driving obesity-associated PDAC in KCO mice, or whether inflammation and fibrosis played additional roles. Still, the identification of CCK as a protumorigenic hormone in PDAC provides new potential targeting opportunities in the prevention of obesity-associated PDAC.



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