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Endocrine–exocrine signals in obesity-associated pancreatic cancer

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Abstract

Obesity is a known risk factor for pancreatic cancer. Now, a new study reports that obesity accelerates early pancreatic cancer development and growth in mice through local perturbations in the pancreatic microenvironment and implicates pancreatic islet-derived cholecystokinin as a driving factor.

One of the deadliest types of cancer has been and still is pancreatic ductal adenocarcinoma (PDAC). In the United States it is currently the third-leading cause of cancer mortality in both men and women[1]. Indeed, deaths due to PDAC are projected to increase dramatically, becoming the second-leading cause of cancer-related deaths in the United States before 2030[2]. Considering the failure to date to efficiently treat advanced PDAC, every effort should be undertaken to prevent this disease or intercept early tumour progression. A clear understanding of the mechanisms underlying the risk factors that lead to PDAC is of utmost importance in identifying preventive and interceptive strategies. A positive correlation between obesity and risk of PDAC has been firmly established[3]. An analysis by the National Institutes of Health reported that 16.9% of all PDAC cases in the Unites States are estimated to be attributable to excess body weight[4]. Several possible mechanisms by which obesity can increase the risk of gastrointestinal cancer have been postulated, including chronic systemic and local tissue inflammation, insulin resistance with hyperinsulinaemia and hyperglycaemia, changes in adipokine and sex hormone metabolism, gut dysbiosis, and others[5]. However, the exact mechanisms that underlie obesity-related PDAC have been largely unclear.

In a new study, Chung and colleagues reported that obesity drives PDAC development and progression in mice through local obesity-associated changes in the tumour microenvironment, and they have discovered a novel endocrine–exocrine signalling pathway in which pancreatic islet-derived cholecystokinin (CCK) has the central role[6]. Using a common mouse model of PDAC (KC; *Pdx1-Cre*;*Kras*$^{LSL\_G12D/+}$) crossed with leptin-deficient (*ob/ob*) mice (KCO mice), the researchers showed, in a series of elegant studies, that genetic obesity greatly accelerated PDAC formation. Pancreatic histology showed a robust fibroinflammatory microenvironment, which was confirmed by RNA sequencing

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Competing interests

The author declares no competing interests.

analysis. The researchers also reported that obesity-accelerated PDAC development in KCO mice was reversible, as exogenous leptin administration or caloric restriction were able to halt or delay PDAC formation. Importantly, their data implied that the effects of obesity are during early stages of PDAC development, as weight loss or leptin administration at later ages failed to affect survival of KCO mice. Similar to the genetic obesity model used by Chung et al., others have shown that KC mice with high-fat diet (HFD)-induced obesity also displayed early and accelerated PDAC development and growth, which was again accompanied by a robust fibroinflammatory pancreatic microenvironment[7]. Interestingly, in both models (KC mice with either genetic or diet-induced obesity) the promotion of PDAC development by obesity was not associated with additional alterations in commonly mutated tumour-suppressor genes, such as *Trp53* (ref.[6,7]). Thus, although additional mutations in tumour-suppressor genes can clearly accelerate PDAC formation and growth in KC mouse models, it is evident that obesity and obesity-induced changes in the pancreatic microenvironment can phenotypically act as ‘substitutes’ for these mutations.

One of the most salient findings of the study by Chung et al. is that islet (β-cell)-produced CCK, and not insulin, seems to be a driver of obesity-accelerated PDAC in KCO mice[6]. Although insulin and insulin-like growth factor have generally been implicated in obesity-associated cancer development[5], knowledge about other pancreatic islet-derived hormones, such as CCK, in driving tumour formation has been scarce. In the study by Chung et al., although KCO mice developed systemic hyperinsulinaemia, they displayed impaired pancreatic islet-derived insulin secretion. In addition, metformin did not attenuate PDAC formation in KCO mice. This observation seems to conflict with studies of KC mice with HFD-induced obesity[8]. In these mice, metformin was able to significantly attenuate PDAC development[8]. There are important differences between the mice with genetic-induced obesity (KCO) and the mice with diet-induced obesity (KC). While KCO mice, in the context of leptin deficiency, display rapid and substantial weight gain early on, HFD models show more gradual weight gain and lower maximum body weight with accompanying hyperleptinaemia[8]. Early metformin administration in the HFD model normalized hyperinsulinaemia and hyperleptinaemia and was associated with weight loss[8], which was not seen in the study by Chung et al. using KCO mice[6]. However, it is still unclear whether the preventive effects of metformin in the HFD model are mediated directly by improving glucose tolerance (and reducing hyperinsulinaemia) or by causing weight loss with corresponding changes in the local pancreatic microenvironment. Nevertheless, differences between both obesity models might explain the distinct responses to metformin (BOX 1).

The study by Chung et al. provides intriguing evidence that local islet (β-cell)-derived CCK is increased in KCO mice, acting on pancreatic acinar cells via the CCK receptor to induce proliferation and formation of acinar-to-ductal metaplasia[6]. This finding is provocative as previously only gut-derived CCK, which physiologically stimulates the release of bile into the intestine and the secretion of pancreatic enzymes, has been implicated in PDAC development in mouse models[9]. Obesity-induced activation of islet macrophages, as evidenced by upregulation of genes associated with proliferation and production of β-cell growth factors[6], might, therefore, have a critical role in β-cell proliferation and CCK secretion. Chung and colleagues speculate that obesity-associated glucotoxicity in islets might be the causative trigger for islet macrophage activation and β-cell proliferation. An

increase in the size of pancreatic islets has also been observed in KC mice with HFD-induced obesity (G.E., unpublished observations). More generally, the data provided by Chung et al. support the existing notion of a critical role for macrophages in early obesity-associated PDAC formation. It has been reported that pancreatic pro-inflammatory macrophages are critically important and indispensable for early acinar-to-ductal metaplasia formation and transition to pancreatic intraepithelial neoplasia[10]. The novel finding reported by Chung et al. is that islet-resident macrophages also seem to have an important role in early PDAC development promoted by obesity.

A major strength of the new study is that the data obtained from mouse models were corroborated by analysing human tissues and The Cancer Genome Atlas. Importantly, pancreatic islets from human donors without known cancer showed a positive correlation between obesity (as measured by BMI) and CCK expression[6], thereby supporting the mechanistic findings in mice.

Taken together, the study by Chung and colleagues discovered a previously unknown pancreatic endocrine–exocrine signalling pathway that drives obesity-related PDAC in mice. Intriguingly, local rather than systemic changes induced by obesity seem to cause the acceleration of PDAC development and growth. It will be important to investigate whether this is a phenomenon that is unique to PDAC or whether obesity drives other types of obesity-related cancers through perturbations in the local tumour microenvironment as well (BOX 1).

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Box 1 |

Obesity-associated pancreatic cancer: unanswered questions

- The exact mechanisms, soluble factors and molecular pathways by which obesity induces cholecystokinin (CCK) expression in pancreatic islets still need to be elucidated. Does obesity accelerate the growth of other tumour types by local processes as well or is this unique to the pancreas?
- It is unclear whether the same pathophysiological processes are operational in high-fat diet-induced obesity models of pancreatic ductal adenocarcinoma (PDAC) development. Does the antitumour efficacy of metformin in these high-fat models, which are accompanied by hyperinsulinaemia and hyperleptinaemia, involve reduction in pancreatic islet CCK secretion?
- Do other drugs that have been shown epidemiologically to reduce risk of PDAC affect this novel exocrine–endocrine pathway?