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Commentary

A Novel Stomach-Pancreas Connection: More than Physical

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The exocrine pancreas and the stomach are on the same team, yet they have differing and sometimes opposing functions. For example, the stomach acidifies chyme whereas the pancreas alkalinizes it. Ultimately however, both organs function with the goal of enhancing nutrient absorption. Interestingly, although the stomach and pancreas are physically connected and share common autonomic innervations, very few humoral mechanisms have been described by which the stomach impacts the exocrine pancreas. It is thus noteworthy that Yu et al. [1], as reported in *EBioMedicine*, have identified a novel gastric-pancreas humoral axis active in health.

The researchers selectively activated the mTORC1 complex in X/A-like cells. X/A-like cells are the ghrelin secreting cells of the stomach. To accomplish this, Yu et al. created ghrelin-Cre mice, selecting a resulting mouse line which expressed Cre in the stomach but not in the pancreas or hypothalamus. These mice were crossed to $TSC1^{flox/flox}$ mice, creating X/A-$TSC1^{-/-}$ ("TG") mice with selective deletion of TSC1 from X/A-like cells of the stomach. As expected, since TSC1 is a major inhibitor of mTORC1, TSC1 deletion increased mTORC1 activity in the X/A-like cells of the TG mice. Also as expected [2], gastric and circulating ghrelin levels were abnormally low in the TG mice. However, this is where the expected results end. Surprisingly, the TG mice exhibited significant pancreatic fibrosis, evident at the molecular and histologic levels, without inflammatory component or organ atrophy. Furthermore, pancreatic insulin mRNA and plasma insulin levels were reduced, and there was a mild impairment in glucose tolerance in these mice.

Naturally, the investigative team wondered whether the low ghrelin levels in these mice may have promoted the unexpected pancreatic fibrosis. To address this possibility, ghrelin was administered to the TG mice continuously for 14 days by osmotic minipump. This ghrelin treatment nearly fully resolved the pancreatic fibrosis and glucose intolerance of the TG mice. Rapamycin, an inhibitor of mTORC1 activity, had similar action to increase ghrelin levels and ameliorate pancreatic fibrosis in the TG mice. Taken together, these results suggest a hitherto unexpected X/A-like cell: pancreas axis whose disruption promotes pancreatic fibrosis. The axis involves X/A-like cell mTORC1 and may be mediated by ghrelin. Although independent confirmation and further characterization are needed to fully establish the function and role of this X/A-like cell: pancreas axis, it perhaps should not be surprising that such a physiological axis might exist. The workload of the pancreas is cyclical with high demand occurring during nutritional intake. What better way for the pancreas to anticipate workload and prepare for use than to sense the hunger and nutritional cues provided by the X/A-like cells of the stomach?

Interestingly, there are no evident reports of pancreatic fibrosis occurring in ghrelin knockout mice or in humans with ghrelin mutations, suggesting there may be more to the story than just ghrelin. In addition to ghrelin, X/A-like cells of the stomach produce several other secreted factors, including obestatin and nesfatin-1. The work presented does not rule out the possibility that these other hormonal peptides created by X/A-like cells might be involved in the uncovered crosstalk with the pancreas. Nonetheless, prior evidence hints at a ghrelin-pancreas axis. Ghrelin administration protects against experimental pancreatitis [3], an effect perhaps mediated by anti-inflammatory actions [4] and dependent upon sensory nerves [5]. Similarly in human patients, lower ghrelin levels are associated with more severe pancreatitis [6]. However, these prior studies finding an impact of ghrelin on active pancreatitis do not necessarily predict that a partial loss of ghrelin secretion would induce pathology in an otherwise unperturbed pancreas. Furthermore, the TG mice did not develop pancreatitis, but rather isolated pancreatic fibrosis.

Subclinical pancreatic fibrosis is very common in humans, being present in up to 44% of pancreases on autopsy [7]. Furthermore, pancreatic fibrosis is thought to play a role as a precursor to chronic pancreatitis and pancreatic malignancy [8]. Thus, the existence of a gastric X/A-like cell: pancreatic fibrosis axis might impact a wide swath of human disease. These new findings provoke a number of important questions. Chiefly, does such an axis exist in humans? What mechanisms mediate the X/A-like cell: exocrine pancreas axis? Might the fibrosis observed upon X/A-like cell mTORC1 activation be related to the fibrosis observed in the recently described exocrine pancreatopathy of diabetes [9]. In any case, these results raise the exciting possibility of a humoral gastric-pancreas axis which more functionally connects these already physically-adjacent organs.

Disclosure

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