Islet biology

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Ghrelin regulates pancreatic islet size in mice

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The hormone ghrelin, secreted primarily in the gut, exerts important physiological actions such as regulation of appetite, food intake and glucose homeostasis. According to a new study published in *the Journal of Clinical Investigation*, ghrelin is also involved in the regulation of pancreatic islet size.

Ghrelin achieves its different functions by binding to the growth hormone secretagogue receptor (GHSR), a G protein-coupled receptor expressed in the brain and in different endocrine tissues, including the pituitary and the pancreas. GHSR is expressed by the main pancreatic islet endocrine cell types (including somatostatin-secreting δ cells, glucagon-secreting α cells, insulin-secreting β cells and pancreatic polypeptide-secreting γ cells), supporting a role for ghrelin in blood glucose regulation. Several studies have also provided evidence that ghrelin can regulate blood glucose levels by acting directly on pancreatic α and β cells to stimulate glucagon secretion and to inhibit insulin release, respectively.

Here, Deepali Gupta and colleagues (UT Southwestern Medical Center) used germline and conditional *ghrelin* knockout (KO) mice to further investigate the role of ghrelin on islet biology. Analysis of islet morphology in wild-type and both KO mouse models showed that, while ghrelin reduction had no effect on the overall structural organization of the islets and their distribution throughout the pancreas, mean islet size and β-cell area were increased in KO mice. In addition, adult germline KO mice showed higher increases in islet size and β cell cross-sectional area than KO juvenile mice, indicating that age enhances the effects of ghrelin deletion.

The study also shows that the increase in β-cell area in KO mice was due to an increase in β-cell numbers, most likely mediated by reduced β-cell apoptosis. Single-cell transcriptomics revealed changes in gene expression in several KO islet cell types, including upregulation of *Manf*, *Dnajc3* and *Gnas* expression in β cells, which further supports a decrease in β-cell apoptosis and/or an increase in β-cell proliferation in KO mice.

This is the first report showing that ghrelin deletion alone increases islet size, or β cell mass. In the paper, the authors explain that these findings might open new avenues for the treatment of type 1 or type 2 diabetes as ghrelin reduction could be used to increase β cell numbers in patients with type 1 diabetes and/or to aid type 2 diabetes management by preventing β cell apoptosis.

Alexandra Le Bras

Original reference: Gupta, D. et al. *J. Clin. Invest.* **133**, e169349 (2023)

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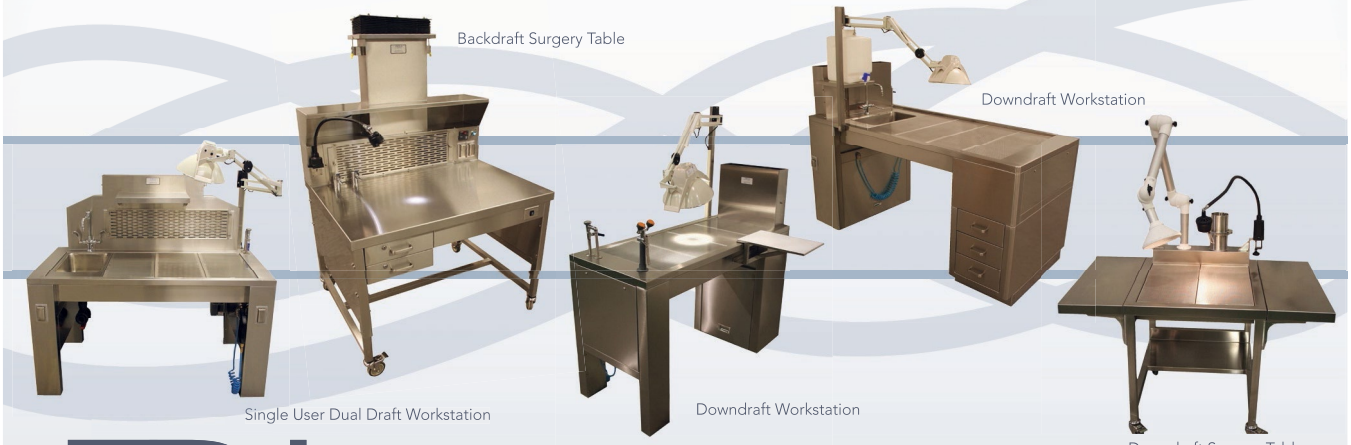

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