Beyond secretion of insulin, the novel function of beta cells in regulating glucose homeostasis

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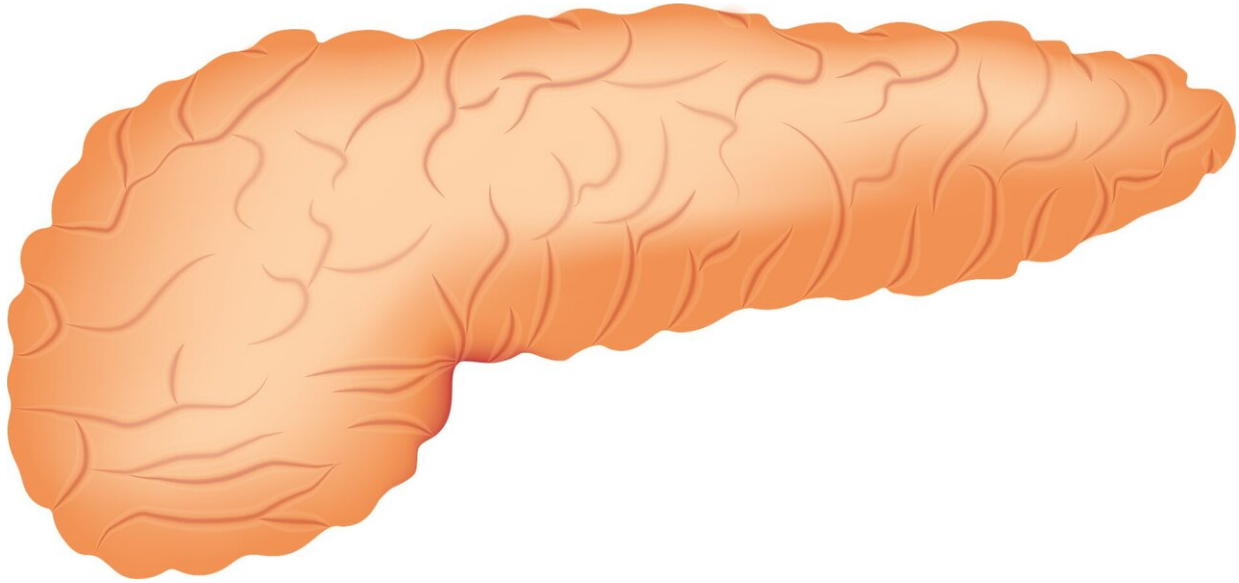

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In a new study published in *Journal of Extracellular Vesicles*, Chen-Yu Zhang's group and Antonio Vidal-Puig's group at University of Cambridge report that pancreatic β cells secrete miR-29 family members (miR-29a, miR-29b and miR-29c) in response to high levels of free fatty acids (FFAs). These β cell-derived miR-29s are delivered to the liver, promoting insulin resistance and enhancing hepatic glucose

output.

Over 100 years after insulin was discovered, it was believed that pancreatic β cells only secreted a single hormone—insulin. Pancreatic β cell-derived insulin regulates glucose homeostasis by binding with the insulin receptors located in the liver, skeletal muscle, adipose tissues and other peripheral organs. The discovery of insulin and its receptor was essential to understand the mechanisms controlling glucose homeostasis and the pathogenesis of type 2 diabetes defined by defective insulin secretion, signal transduction and insulin resistance. However, glucose homeostasis also depends on the integrated coordination of multiple organs, talking to each other to effectively control glucose metabolism. Understanding the crosstalk between organs is still incomplete, which has greatly limited the rational approach to type 2 diabetes treatment.

Previous work from Chen-Yu Zhang's group has identified extracellular miRNA as a new form of cell-to-cell communication. This group was the first reporting the different secretion of miRNAs in response to physiological or pathological states and the uptake and function of secreted miRNAs in recipient cells. In the current study, this group used three independent animal models (ob/ob, HFD and fasted mice) to show that pathological- and physiological- high levels of FFAs induce the secretion of miR-29s from pancreatic β cells. Of relevance, miR-29s is increased in the plasma of obese humans in comparison to lean humans. To address the target organ and functional role of secreted miR-29s, they generated three kinds of transgenic mice. First, mice overexpressed miR-29s or a traceable mutant miR-29a in pancreatic β cells showed that β cell-derived miR-29s is taken by the liver attenuating the normal suppression of insulin on glucose output mediated by targeting p85 α (a regulatory subunit of PI3K) promoting systemic insulin resistance. More importantly, miR-29s deficiency in β cells significantly improved the insulin sensitivity in mice fed on HFD, indicating that β cell-derived miR-29s play an essential role in the development of liver insulin

resistance.

This work is essential for the following reasons:

1. This study finds a novel, unexpected function of the islet controlling glucose homeostasis. Beyond the secretion of insulin, β cells also secrete functional exosomal miRNAs that contribute to an integrated glucose homeostasis loop, which largely extends our understanding of islet function.
2. This study also reveals a new mechanism linking obesity/FFAs-induced insulin resistance in type 2 diabetes's pathogenesis. Obesity or high levels of FFAs may not only directly affect liver, skeletal muscle and white adipose tissue and cause insulin resistance, but also regulate exogenous secreted miRNAs to indirectly result in pathophysiology as well.
3. This study first time demonstrates that pancreatic β cell contributes to insulin resistance development at a very early stage. More importantly, the secreted miR-29s are increased before the onset of insulin resistance in ob/ob or DIO mice, indicating secreted miR-29s may be the factors that initiate the development of insulin resistance;
4. This study reveals the new functions of secreted miRNAs;
5. This study provides an alternative strategy for the treatment of insulin resistance and type 2 diabetes. Given the obvious significance of insulin, current treatments predominantly concentrate on mechanisms of insulin action. This study suggests that it might be insufficient to treat insulin resistance by only targeting insulin and its direct signal transduction and offers an alternative strategy involving secreted miRNAs from the β cell.

Chen-Yu Zhang believes that pancreatic islet-derived miRNAs might contribute to a diversified functional spectrum. Thus, more studies are needed to discover the functional roles of pancreatic islet-derived

miRNAs and subsequently establish mechanisms that underlie integrated multi-organ regulation on glucose homeostasis.

More information: Li et al.: "Pancreatic β cells control glucose homeostasis via the secretion of exosomal miR-29 family" published on Journal of Extracellular Vesicle, 21 January 2021.

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