Islet Cell Biology: Advances in Basic and Translational Research

https://doi.org/10.1038/s41574-024-01073-w

This review by Carmella Evans-Molina MD PhD summarizes key advances in islet cell biology in 2024, highlighting the **fundamental role of intra-islet endocrine cell interactions, particularly δ-cells, in the regulation of glycaemia**. The review also discusses new insights into how **cellular and individual heterogeneity affect hormone secretion**.

Here are the main points of the review:

- The past few years have seen increased interest in understanding the **autocrine and paracrine signaling between β-cells and other cell types in the islet**. This has led to the development of new models of hormone secretion, including the finding that paracrine glucagon signaling amplifies insulin secretion.
- Two studies in 2024 emphasize the **key physiological roles of somatostatin-secreting δ-cells in regulating glycaemia and islet hormone secretion**.
    - Huang and colleagues demonstrated in mouse models that **paracrine signaling from δ-cells via somatostatin is crucial for determining ambient glucose levels**. They found that removing somatostatin expression, ablating δ-cells, or inhibiting somatostatin signaling all lowered the glycaemic setpoint in mice. Furthermore, islet transplantation studies showed that disrupting δ-cells specifically in the pancreas was enough to lower blood glucose in hyperglycaemic mice. Mechanistic studies indicated that the loss of δ-cells or somatostatin signaling significantly lowered the glucose threshold for β-cell calcium responses and insulin secretion.
    - Hill and colleagues highlighted the importance of δ-cells in the context of **hypoglycaemia associated with T1DM and the regulation of glucagon secretion and α-cell function**. In NOD mice with T1DM, they observed decreased insulin and glucagon secretion and a significant increase in circulating somatostatin. Ex vivo and in vivo experiments showed that the impaired glucagon response to low glucose in these mice could be partially restored by blocking the somatostatin receptor. Further investigation suggested that this increased somatostatin secretion in T1DM is likely due to the **loss of an 'electrical break' normally communicated between β-cells and δ-cells**. Importantly, these findings were extended to human islets from donors with T1DM, which also showed impaired glucagon secretion and increased somatostatin secretion in response to hypoglycaemia, with partial recovery of glucagon secretion upon treatment with a somatostatin receptor antagonist. These studies underscore the importance of **paracrine signaling between different islet cell types**.
- Another significant area of discovery in 2024 is the **recognition of islet heterogeneity**, both between β-cells within islets and between islets from different individuals.
    - Peng and colleagues demonstrated **functional heterogeneity within β-cell subpopulations in mouse islets**. They found that only about 40% of β-cells, termed 'readily releasable β-cells' (RRβs), accounted for nearly 80% of insulin secretion, while nearly half of all β-cells were incapable of releasing insulin.

Somatostatin was also shown to play a role in maintaining some β-cells in a release-incompetent state.

- Kolic and colleagues conducted a large-scale evaluation of insulin secretion in human islets from deceased donors (with and without T2DM) in response to various nutrients. They found **statistically significant variability in insulin secretion** in response to glucose, amino acids, and fatty acids among different donor islets, suggesting intrinsic differences in islet function. Transcriptomic and proteomic analysis identified molecular correlates of these nutrient responses and changes occurring in T2DM, with this data being made available as an online resource called HumanIslets. This research lays the groundwork for **personalized nutrient-based therapies for T2DM**.

In conclusion, the review highlights the **complex interplay between islet endocrine cells, with a central role for δ-cells in patterning hormone secretion**. It also emphasizes that **not all β-cells are equal**, and that heterogeneity at both the cellular and individual level significantly influences hormone secretion. Future research is needed to validate these findings in humans and to develop therapies that target paracrine signaling and leverage personalized medicine and nutrition.