# SUMMARY (Intro) 5/2/25 ciT1zen science

## Hormone-switching islet cells: parallels to transmitter-switching neurons
## ciT1zen science summary

**Source:** Excerpts from "Frontiers | Hormone-switching islet cells: parallels to transmitter-switching neurons" by Yuval Dor and Nicholas C. Spitzer, published in *Frontiers in Cell and Developmental Biology*, Volume 13, April 27, 2025.

**Purpose:** To review the main themes and important ideas presented in the source regarding the similarities and potential parallels between hormone-switching in pancreatic islet cells and neurotransmitter switching in neurons.

**Key Themes and Ideas:**

- **Shared Physiological and Molecular Similarities:** Despite originating from different germ layers (endoderm for islet cells, ectoderm for neurons), pancreatic islet cells and neurons exhibit significant physiological and molecular similarities. Both cell types are typically post-mitotic and long-lived. They both release bioactive molecules via voltage-dependent processes involving changes in membrane potential, calcium entry, and fusion of secretory granules. Furthermore, they share highly similar transcriptomes, including key transcription factors and structural genes involved in secretion.
- "Although originating from different germ layers, pancreatic islet cells and neurons share extensive similarities, both physiological (e.g., voltage-dependent release of a bioactive molecule) and molecular (e.g., highly similar composition of transcription factors and structural genes)."
- "Both cell types are typically post-mitotic and long-lived. Both are characterized by the release of a signaling molecule through a process involving altered membrane potential, calcium entry, and fusion of secretory granules with the plasma membrane."
- **Dynamic Hormone Expression and Switching in Islet Cells:** Pancreatic islet cells are primarily defined by the expression of a specific hormone (insulin, glucagon, somatostatin, or pancreatic polypeptide). However, the source highlights the phenomenon of multi-hormonal cells and hormone switching.
- During early development, islet cells often co-express multiple hormones. While some studies suggested these were progenitors, recent lineage tracing experiments indicate that most embryonic bi-hormonal cells are eliminated and adult cells originate from mono-hormonal fetal progenitors.
- A more recent study suggests that embryonic islet cells *may* switch the hormone they produce, for example, from glucagon to insulin.
- Multi-hormonal cells are observed in embryonic stem cell differentiation protocols, but are generally considered a "developmental dead end."
- A physiologically more relevant phenomenon occurs under metabolic stress in adult islet cells, leading to "ectopic expression of hormone genes, with or without the downregulation of the original, identity-defining hormone." This process is proposed to contribute to beta cell failure in diabetes and, conversely, could involve alpha or delta cells acquiring beta cell identity for regeneration.
- This hormone expression is discussed at the level of individual cells, distinct from population-wide changes in cell type proportions due to proliferation.
- **Molecular Basis of Islet Cell Plasticity:** While general islet cell identity is stable, the specific hormone expressed is considerably plastic and requires active transcriptional maintenance.
- Key transcription factors act as activators and repressors of specific islet cell programs. Inactivating these TFs can weaken the primary identity and de-repress alternative programs, leading to the expression of other hormones. Examples include the disruption of *Pax6*, Pdx1, Foxo1, and Nkx6.1.
- Some islet TFs, particularly those maintaining beta cell identity, are proposed to be sensitive to hyperglycemia-induced oxidative stress, potentially contributing to identity loss in type 2 diabetes.

- Hormone-negative islet cells, retaining molecular hallmarks but lacking hormone expression, are also mentioned, often in the context of tumors, with unknown origins and mechanisms.
- **Neurotransmitter Switching in Neurons:** Similar to islet cells, neurons are specified to produce a specific neurotransmitter, but they can change their transmitter type, a phenomenon called neurotransmitter switching.
- Neurotransmitter switching has profound effects on brain function and plasticity, with both beneficial (e.g., motor skill learning, social preference modulation) and detrimental (e.g., depression, cognitive deficits, generalized fear) consequences.
- Triggers for neuronal switching are typically external cues like light exposure or altered sensory input, potentially leading to long-term, stable identity changes.
- Sustained changes in neuronal activity are suggested to play a role in the molecular mechanisms.
- Embryonic neurons, like embryonic islet cells, can have a "mixed" phenotype, producing multiple transmitters before potentially switching.
- Neurotransmitter switching involves key transcription factors, several of which (Pax6, Nkx2.2, Lmx1B) are also involved in islet cell identity.
- Adult post-mitotic neurons require active transcriptional maintenance of their identity, including their transmitter.
- Neurotransmitter switching can change the valence of a neuron's signaling (e.g., excitatory to inhibitory), analogous to an islet cell switching between a hormone that increases blood glucose (glucagon) and one that decreases it (insulin).
- **Proposed Parallelism and Mutual Insights:** The central proposal of the source is that hormone switching in islet cells and neurotransmitter switching in neurons share a deep resemblance, potentially reflecting an "ancient molecular circuit of cell plasticity."
- Comparing and contrasting these phenomena can provide insights into their functions and mechanisms.
- The source argues that while altered hormonal identity in islet cells is often viewed as pathological, the understanding of neurotransmitter switching as an active, regulated response to environmental changes should inspire islet biologists to search for physiological contexts where hormone switching is an "adaptive, regulated response," for example, in response to diet changes.
- Conversely, the better-established understanding of transcriptional regulation of hormone expression and repression in islets could inform the study of neuronal transcription factors involved in transmitter switching, suggesting they may also act as both activators and repressors.
- Islet studies on the sensitivity of transcription factors to oxidative stress could also be relevant to neuronal switching.
- Single-cell and single-nucleus sequencing technologies are suggested as valuable tools for exploring gene expression and chromatin accessibility in both switching islet cells and neurons, offering mutually informative insights.

**Important Facts and Concepts:**

- Islet cells primarily produce insulin, glucagon, somatostatin, or pancreatic polypeptide.
- Neurotransmitters are typically small molecules acting short-range, while islet hormones are gene-encoded peptides released into the blood.
- Adult islet cells originate from fetal NeuroG3+ endocrine progenitor cells.
- Metabolic stress is a known trigger for ectopic hormone expression in adult islet cells.
- Disruption of specific transcription factors (e.g., Pax6, Pdx1, Foxo1, Nkx6.1) can lead to altered hormone expression in islet cells.
- Sustained changes in neuronal activity are suggested to be a trigger for neurotransmitter switching.
- Several transcription factors are involved in both islet cell identity and neurotransmitter switching (Pax6, Nkx2.2, Lmx1B).
- The "valence" of a cell's signaling can change with both hormone switching (e.g., glucose regulation) and transmitter switching (excitatory vs. inhibitory).

**Supporting Quotes:**

- "Here we propose that two seemingly unrelated phenomena recognized in these cell types—neurotransmitter switching in neurons and the expression of two or more hormones in individual islet cells—share a deep resemblance, potentially reflecting an ancient molecular circuit of cell plasticity."
- "A key characteristic of pancreatic islet cells is the expression of one of several hormones... which defines their functional identity."
- "Multi-hormonal cells also appear in embryonic stem cell differentiation protocols... but they are regarded as a developmental dead end..."
- "A related phenomenon, likely more relevant physiologically, is observed when adult islet cells are exposed to metabolic stress."
- "Studies of key transcription factors (TFs) in islets revealed that many such TFs act as activators of a transcriptional program of a given islet cell type while repressing the expression of alternative islet cell programs."
- "Neurons and pancreatic islet cells share deep molecular and functional similarities, although they originate in different germ layers..."
- "Like islet cells, neurons of a given type are specified to produce and release a specific neurotransmitter, which defines their identity and function. Importantly, neurons can sometimes change the neurotransmitter that they produce, a phenomenon termed neurotransmitter switching."
- "The triggers for neurotransmitter switching are typically external cues, such as light exposure or altered sensory input, and they may bring about a long-term, stable change in cell identity."
- "transmitter switching may change the valence, e.g., change the product of a cell from excitatory to inhibitory; this resembles a switch in hormone production in an islet cell that flips the metabolic impact of a cell..."
- "Based on knowledge of neurotransmitter switching, we hypothesize that additional environmental triggers may reveal novel physiological aspects of plastic islet cell identity..."
- "In other words, neurotransmitter switching should inspire islet biologists to search for biological contexts in which the appearance of multi-hormonal cells or hormone switching is an adaptive, regulated response."
- "On the other hand, the transcriptional regulation of islet hormone expression and repression appears to be better established than the understanding of the transcriptional program of neurotransmitter switching."

**Conclusion:**

The source posits a compelling parallel between hormone switching in pancreatic islet cells and neurotransmitter switching in neurons. It argues that exploring the underlying molecular mechanisms and triggers of these phenomena in both cell types, particularly through advanced technologies like single-cell sequencing, can lead to valuable reciprocal insights and potentially reveal previously unappreciated adaptive roles for hormone switching in islet cells, similar to the recognized adaptive functions of neurotransmitter switching in neurons. The shared involvement of specific transcription factors further supports the idea of a potentially ancient, conserved mechanism for cell plasticity.