SUMMARY (Basic) 5/16/25 ciT1zen science

Modeling Diabetic Alpha Cell Dysfunction Using Stem Cell-Derived Alpha Cells
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Source: Excerpts from - Stem Cell Reports Article: "Modeling diabetic alpha cell dysfunction using stem cell-derived alpha cells" by Swikriti Shrestha, et al.
Date: May 16. 2025
Subject: Review of a new in vitro model for studying pancreatic alpha cell dysfunction in diabetes and potential therapeutic interventions.
Executive Summary:
This research paper details the development and application of a novel in vitro model using stem cell-derived alpha (SC-α) cells to study the mechanisms of pancreatic alpha cell dysfunction in diabetes. The study highlights the limitations of existing models and demonstrates that inducing endoplasmic reticulum (ER) stress in SC-α cells effectively replicates key diabetic alpha cell phenotypes observed in human patients, including glucagon hypersecretion, altered proglucagon processing, and changes in transcriptional profile related to metabolism and alpha cell identity. Furthermore, the study presents a proof-of-concept that the tyrosine kinase inhibitor sunitinib can mitigate some of these ER stress-induced dysfunctional phenotypes in the SC-α cell model, suggesting its potential as a therapeutic target. This SC-α cell model represents a significant advancement for investigating alpha cell biology in both healthy and diabetic states and for the identification of potential therapeutic compounds.
Key Themes and Important Ideas:

1. **The Critical Role of Alpha Cell Dysfunction in Diabetes:** While beta cell dysfunction and insulin resistance are well-known aspects of diabetes, the study emphasizes the increasing recognition of the importance of dysfunction within glucagon-producing alpha cells.

- "Dysfunction of pancreatic alpha cells contributes to the pathophysiology of diabetes."
- "the importance of dysfunction within glucagon-producing alpha cells is increasingly recognized."
- Defects in diabetic alpha cells include improper glucagon secretion, altered proglucagon processing, and transcriptional changes.

1. **Diabetic Alpha Cell Phenotypes:** The paper identifies specific characteristics of alpha cell dysfunction in diabetes:

- **Glucagon Hypersecretion:** Alpha cells inappropriately secrete high amounts of glucagon at high blood glucose levels, exacerbating hyperglycemia.
- "In diabetic individuals, alpha cells inappropriately secrete high amounts of glucagon when blood glucose levels are high... exacerbating hyperglycemia."
- **Altered Proglucagon Processing:** The normal cleavage of proglucagon by PC2 to produce glucagon is altered. In diabetes, there is increased processing by PC1/3, which produces other peptides like glicentin, GLP-2, and GLP-1.
- "Proglucagon processing is also altered in diabetes."
- "Interestingly, a subpopulation of alpha cells within normal human islets expresses PC1/3 and produces GLP-1... The number of GLP-1-expressing cells is higher in type 2 diabetes (T2D) islets."
- **Transcriptional Changes:** Diabetic alpha cells show altered gene expression, including downregulation of alpha cell-specific transcription factors like MAFB and downregulation of metabolic pathways such as glycolysis and oxidative phosphorylation.

- "Transcriptional changes within alpha cells are also observed in diabetes."
- "Downregulation of alpha cell-specific transcription factors ARX and MAFB is a common feature of alpha cells from diabetic patients."
- "Transcriptomics studies have revealed downregulation in metabolic pathways such as glycolysis and oxidative phosphorylation in alpha cells of diabetic patients."

1. **Limitations of Existing Alpha Cell Models:** Current models, such as rodent islets and immortalized cell lines, do not fully replicate the metabolism and functionality of human islets, hindering detailed investigations of diabetic alpha cell dysfunction.

- "To date, the lack of a suitable human cell model has prevented a better understanding of these phenotypes."
- "Current models such as rodent islets and immortalized cell lines do not fully reflect the metabolism and functionality of human islets."

1. **Development and Characterization of the SC-α Cell Model:** The study introduces a novel model derived from human embryonic stem cells. These SC-α cells are shown to be transcriptionally similar to bona fide human islet alpha cells.

- "To generate a more relevant model of human alpha cells, we have generated stem cell-derived alpha (SC-α) cells..."
- "SC-α cells share transcriptional similarities with human islet alpha cells."
- "SC-α cells are transcriptionally similar to HI-α cells and thus represent a good model in which to assess perturbations to the alpha cell transcriptome."

1. **ER Stress as a Diabetogenic Stressor in SC-α Cells:** Inducing ER stress using tunicamycin (TM) in SC-α cells successfully replicates key diabetic alpha cell phenotypes.

- "Here, we show that induction of endoplasmic reticulum (ER) stress in stem cell-derived alpha (SC-α) cells induces hypersecretion of glucagon."
- "ER stress also increases the secretion of glicentin and the expression of glucagon-like peptide-1 (GLP-1), peptides produced by alternate cleavage of proglucagon by the prohormone convertase 1 (PC1/3) enzyme."
- "Additionally, ER stress establishes a diabetic transcriptional state in SC-α cells characterized by downregulation of MAFB, as well as glycolysis and oxidative phosphorylation pathways."

1. **Glucagon Hypersecretion Induced by ER Stress:** TM-induced ER stress in SC-α cells leads to increased glucagon secretion, mimicking a hallmark of diabetic alpha cells.

- "ER stress results in glucagon hypersecretion in SC-α cells."

1. **ER Stress Alters Proglucagon Processing:** ER stress in SC-α cells increases PC1/3-mediated proglucagon processing, evidenced by increased glicentin secretion and a higher ratio of glicentin to glucagon.

- "ER stress increases PC1/3-mediated processing of proglucagon in SC-α cells."
- "ER stress increased glicentin secretion from SC-α cells at both low and high glucose."
- "The ratio of glicentin to glucagon was higher in ER-stressed SC-α cells than in vehicle-treated SC-α cells... indicating that ER stress increased the proportion of proglucagon processed by PC1/3."

1. **ER Stress Induces Diabetic Transcriptional Signatures:** Bulk RNA sequencing of ER-stressed SC-α cells reveals transcriptional changes consistent with diabetic alpha cells, including downregulation of metabolic pathways and transcription factors like MAFB.

- "ER stress establishes T2D metabolic signatures in SC-α cells."
- "ER-stressed SC-α cells displayed... downregulated genes included transcription factors associated with pancreatic cell lineage... and glucose sensing/tolerance."
- "Negatively enriched biological processes in ER-stressed SC-α cells included glycolysis, oxidative phosphorylation, and mitochondrial electron transport complex."
- "This analysis revealed downregulation of MAFB in the ER-stressed SC-α cells..."

1. **Sunitinib as a Potential Therapeutic:** The study demonstrates that sunitinib, a tyrosine kinase inhibitor, can attenuate ER stress-induced glucagon hypersecretion and upregulate alpha cell identity markers like MAFB in the SC-α cell model.

- "We show that sunitinib, a tyrosine kinase inhibitor, protects SC-α cells against the ER stress-induced glucagon hypersecretion phenotype."
- "Sunitinib, a tyrosine kinase inhibitor, attenuated ER-stress-induced dysfunction in SC-α cells."
- "SC-α cells treated with both TM and sunitinib had much lower glucagon secretion... than cells exposed to TM alone, suggesting that sunitinib treatment mitigated ER stress-induced glucagon hypersecretion."
- "...the alpha cell identity makers IRX1 and MAFB were upregulated in TM and sunitinib co-treated cells compared to TM alone."

Conclusions:

The SC-α cell model developed in this study provides a valuable in vitro platform to investigate the complex mechanisms of diabetic alpha cell dysfunction. By mimicking key diabetic phenotypes through ER stress induction, this model allows for detailed analysis of changes in hormone secretion, proglucagon processing, and gene expression. The preliminary findings with sunitinib highlight the model's utility in identifying compounds that can potentially restore normal alpha cell function in diabetic conditions. This research is a significant step towards a better understanding of alpha cell dysfunction in diabetes and the development of novel therapeutic strategies targeting these cells.

Further Research:

The study suggests further research is needed to explore the precise mechanisms by which sunitinib and other tyrosine kinase inhibitors exert their protective effects on alpha cells. Expansion of studies using additional compounds and further characterization of the SC-α cell model's responses to various diabetogenic stressors will refine our understanding of alpha cell dysfunction.

Relevant Figures and Tables:

- **Figure 1:** Demonstrates the transcriptional similarity between SC-α cells and human islet alpha cells.
- **Figure 2:** Explores proglucagon processing in SC-α cells and human islets.
- **Figure 3:** Shows that ER stress induces glucagon hypersecretion in SC-α cells.
- **Figure 4:** Illustrates the increase in PC1/3-mediated proglucagon processing peptides under ER stress.
- **Figure 5:** Presents the T2D metabolic signatures established by ER stress in SC-α cells.
- **Figure 6:** Details the attenuating effects of sunitinib on ER-stress-induced dysfunction in SC-α cells.
- **Supplemental Information (Tables S1, S2):** Provides additional data, including gene lists and pathway analysis results.

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