SUMMARY (Clinical) 6/13/25 ciT1zen science

Endoplasmic Reticulum (ER) Stress and its Key Role in Pancreatic β Cells and Diabetes Mellitus

ciT1zen science summary

Source: Lytrivi, M., Tong, Y., Virgilio, E., Yi, X., & Cnop, M. (2025). Diabetes mellitus and the key role of endoplasmic reticulum stress in pancreatic β cells. *Nature Reviews Endocrinology*.

I. Executive Summary

This review article comprehensively examines the critical and evolving understanding of endoplasmic reticulum (ER) stress in the pathogenesis of diabetes mellitus, particularly focusing on its impact on pancreatic β cells. It highlights that insufficient insulin secretion by β cells is central to diabetes and that perturbations in ER homeostasis lead to ER stress, activating the ER stress response. While ER stress is definitively causal in **15 monogenic forms of diabetes**, its exact causal role versus consequence in polygenic Type 1 and Type 2 diabetes is still under investigation, though strong evidence suggests its contribution. The article also touches upon existing and novel therapeutic strategies aimed at restoring ER homeostasis to improve β cell function.

II. Main Themes and Key Ideas

1. **Centrality of Pancreatic β Cell Dysfunction in Diabetes:**

- Insufficient insulin secretion by pancreatic β cells is identified as a core mechanism in the development of diabetes mellitus.
- As insulin is synthesized in the ER, any disruptions to ER homeostasis directly impact insulin production and β cell health.

1. **Endoplasmic Reticulum (ER) Stress and the Unfolded Protein Response (UPR):**

- **ER Stress:** Occurs when there are "perturbations in ER homeostasis" – essentially, a buildup of misfolded or unfolded proteins in the ER.
- **Unfolded Protein Response (UPR):** This is an "essential adaptive mechanism in β cells" activated in response to ER stress. The UPR aims to restore ER homeostasis by:
- Reducing overall protein synthesis to lessen the burden on the ER.
- Increasing the production of ER chaperones to assist in protein folding.
- Enhancing ER-associated degradation (ERAD) to remove misfolded proteins.
- **Consequences of ER stress on β cells:** The effects are multifaceted and depend on factors such as "the β cell developmental stage, duration of ER stress and genetic background." These consequences can include impacts on:
- Proliferation
- Differentiation
- Function (e.g., insulin secretion)
- Apoptosis (programmed cell death)
- Immune cell crosstalk (particularly relevant in Type 1 diabetes).

1. **Genetic Evidence for ER Stress in Diabetes (Monogenic Forms):**

- A significant and "indisputable genetic evidence" exists for the causal role of ER stress in **15 of approximately 70 known monogenic forms of diabetes mellitus**.
- These monogenic forms are directly caused by "excessive ER stress, perturbed ER stress response signalling or impaired ER–Golgi protein trafficking."
- Specific examples of genes whose mutations cause diabetes by inducing ER stress or dysregulating the UPR include:
- WFS1 (Wolfram syndrome 1)
- EIF2AK3 (Wolcott–Rallison syndrome)
- DNAJC3
- PPP1R15B
- PDIA6
- MANF
- IER3IP1
- YIPF5
- Mutations in the INS gene (proinsulin misfolding)

1. **Role of ER Stress in Polygenic Type 1 and Type 2 Diabetes:**

- ER stress is observed "during both early and late stages in the pathogenesis of polygenic type 1 and type 2 diabetes mellitus."
- While its presence is clear, "causality has yet to be firmly demonstrated" for these common forms. However, the accumulation of data over the past two decades strongly suggests its contribution to β cell failure in both.
- **Type 1 Diabetes (T1D):**Evidence for ER stress markers in human islets and β cells of T1D patients.
- May precede the onset of clinical T1D in animal models.
- Involves "immune cell crosstalk," where ER stress might contribute to β cell antigenicity or vulnerability to immune attack.
- **Type 2 Diabetes (T2D):**ER stress contributes to β cell apoptosis in T2D.
- High expression rates of human islet amyloid polypeptide (IAPP) can induce ER stress-mediated β-cell apoptosis, characteristic of T2D.
- Aging can compromise human islet β cell function and identity by decreasing transcription factor activity and inducing ER stress.

1. **ER-Golgi Protein Trafficking:**

- Impairments in the transport of proteins from the ER to the Golgi apparatus are also recognized as contributing to β cell failure.
- The article lists several genes and their products involved in ER-Golgi trafficking, which, when mutated, can lead to diabetes, emphasizing the interconnectedness of these organelles in β cell function. Examples include COPII, TANGO1, cTAGE5, YIPF5, IER3IP1, and NBAS.

1. **Therapeutic Opportunities:**

- "ER stress modulators have been shown to protect β cells in preclinical studies, and a few early clinical studies are underway."
- **Current and Novel Treatments:GLP-1 receptor agonists:** These are highlighted as a class of drugs that "improve β cell function and survival following induction of endoplasmic reticulum stress," partly by upregulating BiP and JunB. Examples include liraglutide and exendin-4.
- **Imeglimin:** A novel therapeutic agent that "ameliorates β-cell apoptosis by modulating the endoplasmic reticulum homeostasis pathway," showing favorable effects on β-cells by improving mitochondrial morphology and increasing insulin granule numbers.

- **PPAR-γ agonists (e.g., pioglitazone):** Can restore islet function by reducing ER stress and maintaining euchromatin structure.
- **Chemical chaperones (e.g., tauroursodeoxycholic acid (TUDCA), sodium phenylbutyrate):** Known to reduce ER stress and improve insulin sensitivity.
- **Integrated Stress Response (ISR) modulators:PERK inhibitors:** Can enhance glucose-stimulated insulin secretion and reduce autoimmune diabetes risk in mice.
- **ISRIB:** Reverses cognitive deficits and blunts the ISR by antagonizing the inhibitory effect of phosphorylated eIF2 on eIF2B.
- **Halofuginone:** An ISR activator that protects mice from diabetes-like phenotypes.
- **IRE1α modulators:** Both inhibitors (e.g., 4μ8C, KIRA6) and activators (e.g., Imatinib) have shown potential in preserving β cell function or reversing autoimmune diabetes.
- **ATF6 activators:** Compounds that pharmacologically activate ATF6 can remodel the proteostasis network.
- **Targeting ER-Golgi trafficking:** Some drugs might inhibit cargo export at ER exit sites.

III. Supporting Details and Important Facts

- **Insulin Synthesis:** Insulin is synthesized and folded within the ER of β cells, making this organelle crucial for proper insulin production.
- **UPR Branches:** The UPR involves three main transmembrane protein sensors: PERK, IRE1, and ATF6. These pathways are activated by ER stress to regulate gene expression and translation.
- **Causality vs. Consequence:** While clearly causal in monogenic forms, the precise role of ER stress in polygenic diabetes (T1D, T2D) remains a topic of active research, with evidence suggesting it is both a contributor and, at times, a consequence of disease progression.
- **β Cell Plasticity:** The article acknowledges the "adaptive unfolded protein response" and the concept of β-cell plasticity, where cells may dedifferentiate or undergo early senescence in response to stress.
- **Aging:** Aging is identified as a factor that "compromises human islet beta cell function and identity by decreasing transcription factor activity and inducing ER stress."
- **Lipotoxicity and Cytokines:** Metabolic stressors like lipotoxicity (due to fatty acids) and inflammatory cytokines can induce ER stress in β cells.

IV. Gaps and Future Directions (Implicitly within the review's scope)

- **Definitive Causality in Polygenic Diabetes:** More robust proof is needed to firmly establish ER stress as a primary cause rather than solely a consequence in the widespread forms of T1D and T2D.
- **Therapeutic Efficacy:** While preclinical studies are promising, "definitive proof is lacking that ER stress responses can be therapeutically targeted to improve β cell function in diabetes mellitus" in human clinical settings. More advanced clinical trials are required.
- **Targeting Specific UPR Branches:** Understanding which specific UPR pathways to target (e.g., inhibiting PERK or IRE1α RNase, activating ATF6) for optimal therapeutic benefit without adverse effects is a key area for continued research.
- **Combination Therapies:** Exploring the potential of combining ER stress modulators with existing diabetes treatments.
- **Long-term Effects:** Investigating the long-term impact of ER stress modulation on β cell survival, function, and overall disease progression.