内分泌・代謝学共同利用・共同研究拠点セミナー

O-GlcNAc signaling, the sweet side regulation of β-cell development mass, ER stress, and mitochondrial function.

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Deletion of nutrient sensor O-GlcNAc transferase (OGT) in pancreatic cells, including β-cells, leads to smaller pancreas size (hypoplasia) due to increased cell death during development. Loss of OGT in β-cells triggers stress and cell death involving proteins like p53 and Pdx1. Our research delved into how p53, CHOP (an ER stress protein), and Pdx1 influence pancreas development. We found that reducing p53 or CHOP levels partially improved pancreas size but didn't fully restore it. However, overexpressing Pdx1 increased pancreas size and β-cell mass in OGT-deficient mice, indicating OGT's crucial role in pancreas development through interactions with Pdx1 and p53.

Additionally, we explored OGT's role in regulating β-cell health, focusing on mitochondrial morphology, bioenergetics, and autophagy. While mitigating endoplasmic reticulum stress by deleting CHOP didn't rescue mitochondrial dysfunction, restoring Pdx1 enhanced insulin content and improved mitochondrial morphology and function in OGT-deficient islets. Rescue of TSC2, a negative regulator of mTORC1, restored β-cell mass but not function, whereas ULK deletion improved function but not mass. These findings underscore OGT's critical role in controlling beta cell mitochondrial structure, energy production, and autophagy, linking nutrient signals to mitochondrial function to maintain normal beta cell physiology.

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