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iPSZÜRICH

A Lecture Series Focused on Induced Pluripotent Stem Cells

ULB UNIVERSITÉ LIBRE DE BRUXELLES

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STRESS IN THE INSULIN FACTORY: TWELVE MONOGENIC FORMS OF DIABETES AND COUNTING

The heterogeneity in clinical presentation of diabetes points to a complex pathophysiology, with diverse routes leading to pancreatic β cell failure. Genetic and lifestyle factors play essential roles in polygenic types of diabetes. We identified endoplasmic reticulum (ER) stress as an important cellular response contributing to free fatty acid-induced β cell failure in type 2 diabetes. Saturated fatty acids impair ER-to-Golgi protein trafficking and induce signaling in the PERK branch of the ER stress response, thereby leading to β cell demise.

Monogenic forms of diabetes can be viewed as simpler systems, where a single diabetogenic loss-of-function mutation reveals a gene that is essential for pancreatic β cell development, function and/or survival. So far, twelve monogenic forms of diabetes have been described that are caused by mutations in genes with a role in the ER stress response. Five pertain to the PERK branch, providing strong human genetic evidence for the importance of PERK signaling in maintaining β cell integrity. In these diseases, dysregulated eIF2a phosphorylation and mRNA translation lead to β cell demise. Three monogenic forms of diabetes are caused by perturbations in the ER-to-Golgi protein trafficking pathway. The differentiation of patients' induced pluripotent stem cells into pancreatic β cells provides an exciting disease-relevant model to study molecular mechanisms of β cell failure and test β cell protective therapies.