DIABETES

Targeting endoplasmic reticulum to combat juvenile diabetes

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Limited options for clinical management of patients with juvenile-onset diabetes mellitus call for a novel therapeutic paradigm. Two innovative studies support endoplasmic reticulum as an emerging target for combating both autoimmune and heritable forms of this disease.

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Diabetes mellitus comprises a group of disorders characterized by an absolute or relative deficiency of insulin produced by the pancreatic β cells. Dysfunction and stress of the endoplasmic reticulum (ER) are important pathogenic components of both type 1 and type 2 diabetes mellitus, as well as other autoimmune and neurodegenerative diseases.[1] Specifically, mounting evidence now indicates that homeostatic alterations within the ER are directly involved in the β-cell dysfunction and death observed during the development and progression of diabetes mellitus.[2] Targeting the ER, therefore, offers the possibility of a novel therapeutic approach to managing patients with this condition. Two recently published studies have taken a step closer to this goal by establishing a role for ER stress in both autoimmune and heritable diabetes mellitus.[3,4]

The ER is a multitasking subcellular compartment involved in production of secretory proteins, sterol synthesis, calcium storage and regulation of oxidation–reduction reactions. The ER stress response occurs at the cellular level and is designed to help cells survive in the face of an environmental insult that leads to ER dysfunction. Engin and colleagues examined ER stress responses in two mouse models of autoimmune diabetes mellitus and among a group of patients with type 1 diabetes mellitus.[3] The investigators found that dysregulation of the ER stress response occurred during the progression of type 1 diabetes mellitus in both mice and humans. A compound known to counteract ER stress, tauroursodeoxycholic acid (TUDCA), was able to prevent β-cell death in the two mouse models used by Engin and co-workers. This

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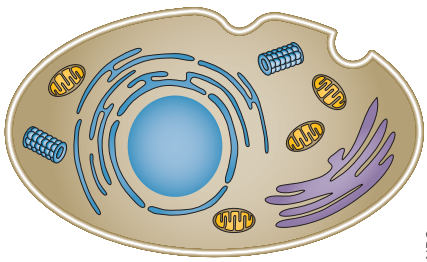
effect of TUDCA was dependent on the activity of ATF6, a critical transcription factor in the ER stress response. In addition, TUDCA did not alter the type and number of immune cells present in the pancreas, but prevented the infiltration of these cells into the islets. These results strongly suggest that maintaining ER homeostasis in pancreatic β cells might prevent lymphocytic infiltration and protect β cells from autoimmune attack, with TUDCA acting like ‘molecular armour’ for the β cells. Consequently, the interesting possibility is raised that individuals whose pancreatic β cells have ‘healthy’ ER stress responses could be more resistant to developing type 1 diabetes mellitus than those with dysfunctional β-cell ER responses.

The findings of Engin *et al.* highlight the importance of identifying biomarkers that define ER health; nevertheless, this goal requires the availability of a suitable experimental model. Wolfram syndrome is a rare autosomal recessive disorder that is considered a prototype of human ER disease.[5] Wolfram syndrome is caused by ER dysfunction owing to the loss of function of a transmembrane protein (wolframin; encoded by the *WFS1* gene) localized to the ER. Despite its rarity (1 in 200,000–500,000 individuals in the general population), Wolfram syndrome probably represents the best model currently available for identifying biomarkers of ER health. Furthermore, this syndrome is characterized by juvenile-onset diabetes mellitus, making it ideal for studying the pathology of β-cell death.[6] Another advantage in using Wolfram syndrome as an experimental model is the fact that it arises from mutation of a single gene (*WFS1*), a gene shown to be also involved in β-cell dysfunction and death in type 2 diabetes mellitus and a heritable form of adult-onset diabetes mellitus.[7,8] Its monogenic aetiology makes Wolfram syndrome more amenable to teasing out the mechanisms underpinning cellular responses to ER dysfunction than other diabetic conditions, such as type 1 diabetes mellitus, in which multiple factors typically interact to produce the disease manifestations. Thus, Wolfram syndrome represents an ideal model to shed new light on the underlying causes of diabetes mellitus.

Shang and co-workers took a cell biology approach and successfully generated β cells *in vitro* using induced pluripotent stem cells (iPSCs) derived from skin cells of patients with Wolfram syndrome.[4] Briefly, iPSCs are artificially derived stem cells that can be induced to differentiate into various types of tissues, including pancreatic β cells and neurons. These ‘Wolfram iPSC-derived β cells’ were found to have increased levels of ER stress and decreased insulin content. Upon exposure to inducers of β-cell ER stress, Wolfram iPSC-derived β cells showed impaired insulin processing and failed to increase insulin secretion in response to glucose and glucagon-like peptide 1 agonists. Moreover, reduction of ER stress by 4-phenyl butyric acid, a chemical chaperone aiding protein folding in the ER, restored both insulin synthesis and the ability to increase insulin secretion in Wolfram iPSC-derived β cells. The study by Shang *et al.* validated the roles of *WFS1* in insulin production, insulin secretion and protection against ER stress in β cells.[9,10]



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The next important step will be to identify biomarkers for ER stress using these cells and to test the efficacy of drugs that might potentially protect β cells from death arising from ER dysfunction.

Taken together, the studies by Engin *et al.* and Shang *et al.* have established a role for ER stress in both autoimmune diabetes mellitus and Wolfram syndrome. Options for treating patients with type 1 diabetes mellitus remain far from ideal, and the results of previous clinical trials have underscored the difficulty of developing novel and effective treatments for this disease. Conducting a clinical trial in a small group of patients with Wolfram syndrome of homogeneous aetiology could potentially lead to a breakthrough in treatments for type 1 diabetes mellitus. Several drugs already approved for use by the FDA and the European Medicines Agency, including glucagon-like peptide 1 agonists and sirolimus, have been shown to protect against ER-stress-mediated cell death. An intervention study targeting the ER should, therefore, be seriously considered for combating Wolfram syndrome; if successful, such a study might then be extended to include a subset of patients with type 1 diabetes mellitus who test positive for biomarkers of ER dysfunction. We all should be aware and appreciate the power of rare diseases, such as Wolfram syndrome, as tools to understand pathogenesis and guide development of novel therapeutic modalities for prevalent diseases, including type 1 diabetes mellitus and neurodegeneration.

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Competing interests
The author declares no competing interests.

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