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Wolfram Syndrome iPS Cells: The First Human Cell Model of Endoplasmic Reticulum Disease

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COMMENTARY

Wolfram syndrome is a rare autosomal recessive genetic disorder with clinical signs apparent in early childhood. This condition is characterized by childhood-onset diabetes, optic nerve atrophy, deafness, diabetes insipidus, and neurodegeneration, and it results in death in middle adulthood (1–3). Genetic and experimental evidence strongly suggest that endoplasmic reticulum (ER) dysfunction is a critical pathogenic component of Wolfram syndrome (4,5). However, there is a lack of complete understanding of the pathways and biomarkers involved in the disease process due to the limitations of animal models that do not accurately reflect human patients. As a result, despite the underlying importance of ER dysfunction in Wolfram syndrome, there are currently no therapies that target the ER, a deficiency that points to the urgent need to develop a human cell model of this condition. In this issue, Shang et al. (6) report that this has been successfully accomplished.

ER is a membrane network within the cytoplasm of cells that is involved in protein synthesis, calcium storage, redox regulation, steroid synthesis, and cell death. Recent clinical and genetic evidence indicate that acquired or inherited ER dysfunction can cause rare genetic diseases such as Wolfram syndrome, as well as many common diseases, including type 1 and type 2 diabetes, atherosclerosis, and neurodegenerative diseases (7–11). Thus, ER is an emerging target for both rare and common chronic conditions. However, it has been challenging to study the efficacy of pharmacological agents that could potentially reverse ER dysfunction due to the lack of a human cell model of ER disorders.

In Wolfram syndrome, pancreatic β-cells and neuronal cells are selectively destroyed as a consequence of mutations in the *WFS1* gene. This gene encodes a transmembrane protein localized to the ER, suggesting that ER dysfunction is a major pathogenic component of Wolfram syndrome. In animal and cell models of Wolfram syndrome, WFS1 mutations lead to elevated ER stress levels, pancreatic β-cell dysfunction, and initiation of ER stress–associated cell death (5,12,13). Shang et al. showed that Wolfram syndrome patient induced pluripotent stem (iPS) cell–derived β-cells also showed increased levels of ER stress molecules, as well as decreased insulin content. Upon exposure to experimental ER stress, Wolfram syndrome patient iPS cell–derived β-cells showed impaired insulin processing and failed to increase insulin secretion in response to glucose and other secretagogues. These observations were all consistent with previous findings and could validate the roles of WFS1 in insulin production, secretion, and protection against ER stress (14). Moreover, Shang et al. showed that 4-phenyl butyric acid (4PBA), a chemical protein folding and trafficking chaperone, could restore normal insulin synthesis and the ability to upregulate insulin secretion in Wolfram syndrome patient iPS cell–derived β-cells, a finding that suggested 4PBA is a candidate drug for treating patients with Wolfram syndrome.

We can expect Wolfram syndrome patient iPS cell lines and Wolfram iPS cell–derived β-cells to be cornerstones for developing novel therapeutic modalities for Wolfram syndrome and other diseases involving ER dysfunction. We can use these cells to screen and identify drugs for treating patients with Wolfram syndrome and other ER-associated diseases. Chemical chaperones such as 4PBA and tauroursodeoxycholic acid (TUDCA) are

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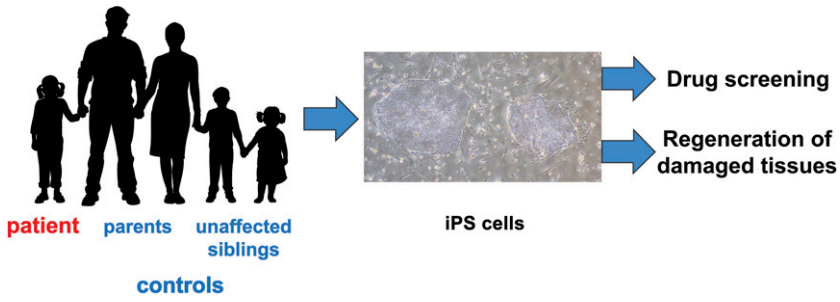

Figure 1—A potential strategy for developing treatments for Wolfram syndrome using patient-derived iPS cells. iPS cells derived from a patient with Wolfram syndrome can be used for drug screening and regeneration of damaged tissues. iPS cells from the patient's parents and unaffected siblings could be the best controls for research.

good candidates. It has been shown that these compounds can mitigate ER stress in peripheral tissues, such as liver, in mouse models of diabetes (15). Glucagon-like peptide 1 agonists and rapamycin are encouraging compounds because they have been shown to prevent ER stress–mediated β-cell death in mouse and cell models (16,17) (Fig. 1). Clinical trials evaluating the efficacy of these drugs should be seriously considered after we carefully test these compounds in β-cells and neurons derived from Wolfram iPS cells. It has been shown that WFS1 polymorphisms and mutations are associated with type 2 diabetes and adult-onset diabetes, suggesting that drugs effective for Wolfram syndrome may also be useful for the treatment of more prevalent forms of diabetes, type 1 and type 2 diabetes (18,19). Thus, the potential public health implications of the new findings are considerable.

In the future, we can use these cells to regenerate damaged tissues including pancreatic β-cells, retinal ganglion cells, and neurons in patients with Wolfram syndrome (Fig. 1). Rapid progress in genetic editing technologies and regenerative medicine will make it possible to correct WFS1 mutations in patient-specific iPS cell lines and regenerate patients' damaged cells. Shang et al. (6) have taken us a step closer toward these goals. As a physician and scientist who is working on Wolfram syndrome, a devastating form of juvenile diabetes, I truly appreciate their important accomplishment. We should make the best use of these cells to develop treatments for Wolfram syndrome—efforts that may lead to breakthroughs in diabetes treatment.

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