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Series: Trends in Rare Disease Therapeutics

Science & Society

Current Landscape of Treatments for Wolfram Syndrome

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Wolfram syndrome is a rare genetic spectrum disorder characterized by insulin-dependent diabetes mellitus, optic nerve atrophy, and progressive neurodegeneration, and ranges from mild to severe clinical symptoms. There is currently no treatment to delay, halt, or reverse the progression of Wolfram syndrome, raising the urgency for innovative therapeutics for this disease. Here, we summarize our vision for developing novel treatment strategies and achieving a cure for Wolfram-syndrome-spectrum disorder.

Clinical Manifestations of Wolfram Syndrome

Wolfram syndrome is a rare, monogenic life-threatening disease caused largely by mutations in the *WFS1* gene or, in a small fraction of patients, pathogenic variants in the *CISD2* gene [1]. While insulin-dependent diabetes mellitus, optic nerve atrophy, and neurodegeneration are cardinal features of this disease, many patients also develop other symptoms, ranging from hearing loss and endocrine deficiencies to neurological and psychiatric conditions [1]. Accordingly, recent clinical and genetic findings have revealed that Wolfram syndrome is best characterized as a spectrum disorder. Most Wolfram syndrome patients carry two recessive pathogenic variants in the *WFS1* gene. The disease begins to manifest with the clinical onset of insulin-dependent diabetes mellitus at around age 6 years and optic nerve atrophy at age 10 years. Diabetes insipidus, neurogenic bladder, obstructive

sleep apnea, and deafness may also develop in the next two decades of life, along with symptoms of brainstem and cerebellar atrophy, such as dysphagia, ataxia, and central sleep apnea [1–4]. Some pathogenic variants of *WFS1*, particularly dominant variants, cause deafness or diabetes alone [5,6]. Other dominant *WFS1* variants give rise to deafness and optic nerve atrophy or autosomal dominant congenital cataracts [7,8]. Recently, Dr. Hattersley's team and ours identified several dominant *de novo* *WFS1* variants associated with a genetic syndrome of neonatal/infancy-onset diabetes, congenital sensorineural deafness, and congenital cataracts [9]. Consequently, *WFS1* is a locus of broad interest to various disease processes, highlighting the need for therapeutics targeting the gene towards potential treatments for Wolfram-syndrome-spectrum disorders.

Wolfram syndrome is recognized as a prototype of endoplasmic reticulum (ER) disorder [10]. The ER plays a critical role in the proper folding of secretory and membrane proteins, calcium homeostasis, and lipid biosynthesis. In Wolfram syndrome, dysregulation of calcium homeostasis and misfolding of pathogenic *WFS1* variants causes ER stress in pancreatic β cells, neurons, retinal ganglion cells and oligodendrocytes, resulting in the dysfunction and degeneration of affected tissues. ER dysfunction can also alter mitochondrial dynamics, thereby contributing to neuropsychiatric aspects of this disease [11]. Wolfram syndrome is thus a systemic disorder caused by ER dysfunction with no treatments available to delay, halt, or reverse disease progression. Nevertheless, numerous avenues of therapeutic development are currently under study, heralding the possibility of new treatments on the horizon (Figure 1). Below, we discuss the

ongoing efforts on the development of novel treatments for Wolfram syndrome.

Chemical Chaperones

A common molecular signature of Wolfram syndrome is cellular stress caused by the expression of mutant Wolfram syndrome 1 (*WFS1*) proteins derived from pathogenic *WFS1* alleles. To resolve this, we are testing chemical chaperones that can optimize the structure of mutant *WFS1* proteins. Chemical chaperones, such as 4-phenylbutyric acid and tauroursodeoxycholic acid, are drugs that are known to mitigate ER stress by rescuing or stabilizing the native conformation of mutant *WFS1* proteins, thereby reducing protein aggregation and ER stress [12] (Figure 1). Such designer chemical chaperones hold the potential to delay Wolfram syndrome disease progression by reducing the misfolded *WFS1* protein load in affected cell types, thereby salvaging remaining tissue function.

ER Calcium Stabilizers

To target calcium dyshomeostasis for the treatment of Wolfram syndrome, we are developing and repurposing putative ER calcium stabilizers. We recently discovered, for example, that dantrolene sodium, a US Food and Drug Administration (FDA)-approved drug for malignant hyperthermia and muscle spasm, can act as an ER calcium stabilizer by targeting ER calcium transporters, specifically ryanodine receptors. Dantrolene sodium can suppress cell death and dysfunction in neuronal and β cell mouse models of Wolfram syndrome, as well as in induced pluripotent stem cell (iPSC) models of this disease [13] (Figure 1). These results prompted us to initiate an ongoing phase 1b/2 clinical trial of dantrolene sodium to assess its safety, tolerability, and efficacy in pediatric and adult



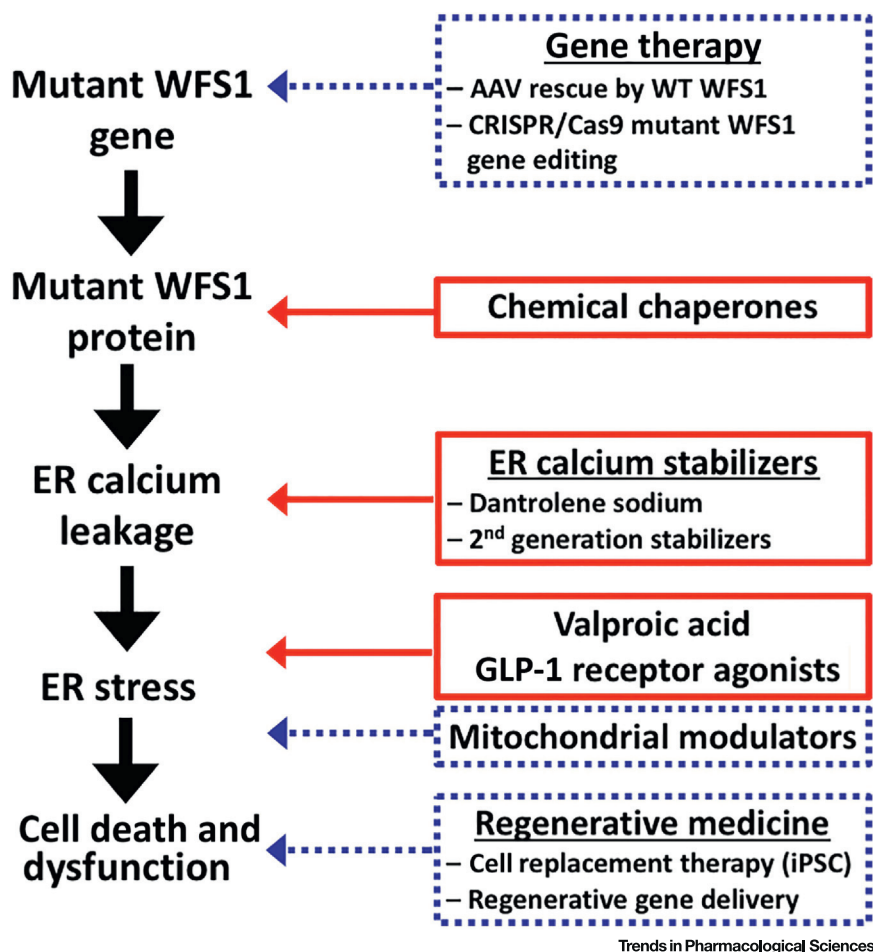


Figure 1. Current and Potential Therapeutic Strategies for Wolfram Syndrome.

Schematic shows various pathophysiological steps in development of Wolfram syndrome. The discussed therapies are shown at the step that they target. Therapies currently in clinical trials and being developed preclinically are in solid red and dashed blue boxes, respectively. Abbreviations: AAV, adeno-associated virus; ER, endoplasmic reticulum; GLP-1, glucagon-like peptide 1; iPSC, induced pluripotent stem cell; WFS1, Wolfram syndrome 1.

patients with Wolfram syndrome (Clinical Trial Number: NCT02829268).

We are also now developing novel ER calcium stabilizers tailored for Wolfram together with the National Center for Advancing Translational Sciences (NCATS)ⁱⁱ. These second-generation ER calcium stabilizers also target ER calcium transporters, but are intended to be safer, more potent and have greater bioavailability to the central nervous system and eyes than dantrolene sodium.

Targeting ER Stress

An interesting molecular target for therapeutic development is p21, which plays a role in cell proliferation and survival after ER stress. Valproic acid, a well-known mood stabilizer, has been shown to increase the expression of p21 and confer protection against cell death in a cell of Wolfram syndrome [14]. Valproic acid also induces WFS1 expression and modulates the ER stress response [15]. A phase 2 double-blind, placebo-controlled drug repurposing

trial is currently underway to evaluate valproic acid in patients with Wolfram syndrome (Clinical Trial Number: NCT03717909).

Glucagon-like peptide (GLP)-1 receptor agonists are another promising treatment for preventing ER-stress-mediated cell death in Wolfram syndrome. It has been previously shown that GLP-1 can suppress apoptosis in cell models of Wolfram syndrome [13]. Now, data from two rodent models of Wolfram syndrome and one patient case report have confirmed that GLP-1 receptor agonists may improve diabetes in Wolfram syndrome [16,17]. Further pre-clinical and clinical studies are needed to assess the broader efficacy of GLP-1 agonists in patients with Wolfram syndrome.

Potential Other Approaches

Recent reports indicate that WFS1 loss of function is associated with mitochondrial dysfunction [11,18]. This likely stems from ER calcium leakage/ER stress causing mitochondrial calcium overload, which results in aberrant organellar function and decreased ATP production. In light of these reports, mitochondrial modulators aimed at restoring mitochondrial function may merit further investigation in the context of Wolfram syndrome, as they may be able to delay neurodegeneration by reducing neuronal dysfunction.

Gene Therapy

One of the approaches to provide a cure to Wolframs syndrome could be via gene therapy. Using adeno-associated viral (AAV) systems, wild-type WFS1 could be transferred into the retinal ganglion cells of patients with Wolfram syndrome (Figure 1) to supplement the production of correct protein in the human body. We also envision using CRISPR/CAS9 gene editing technology for replacing pathogenic WFS1

variants with wild-type *WFS1* alleles in Wolfram syndrome patients' iPSCs and then create iPSC-derived organoids to further determine whether this approach can be used in combination with regenerative cell-replacement efforts (discussed below).

Regenerative Medicine

Given the deleterious effects of chronic ER stress on specific cell types in Wolfram syndrome, there is a need for regenerative medicine efforts aimed at replacing these damaged tissues. More specifically, there is a need for replacing pancreatic β cells and retinal ganglion cells in patients, as defects in these cell types have the greatest impact on patients' quality of life. To this end, regenerative therapy options using iPSCs have been developed [19]. iPSCs from patients with Wolfram syndrome and their respective siblings and/or parents have been generated [13], which could potentially be differentiated into neural progenitor cells, retinal ganglion cells, oligodendrocytes, and pancreatic β cells for therapeutic testing and molecular investigation. These iPSC-derived cell types may one day be used for cell-based replacement therapy.

In addition to developing cell-replacement therapeutic strategies, the regenerative properties of factors such as mesencephalic astrocyte-derived neurotrophic factor (MANF), can be tested on tissues especially sensitive to *WFS1* loss of function. MANF has been shown to activate proliferation of primary islets and confer protection against ER-stress-mediated cell death [20]. A therapeutic strategy could be to directly deliver MANF to neurons, pancreatic β cells and retinal ganglion cells via AAV systems, with the goal of suppressing neurodegeneration and improving β cell mass, glucose tolerance, and visual acuity. Further safety and efficacy

studies will be required to optimize delivery, minimize adverse effects and maximize therapeutic benefit.

Concluding Remarks and Future Perspectives

Wolfram syndrome is a rare genetic disorder with more than 200 pathogenic variants reported in association with disease. Clinical and genetic heterogeneity, as well as variable expressivity, pose a challenge for designing effective therapies in this population. We should therefore aim to design personalized treatments for Wolfram syndrome patients in the future. The first step towards this goal is to stratify patients based on their genetics. Genetic testing based on next-generation sequencing (NGS) technology, including exome and genome sequencing, has the ability to do this by identifying DNA variants that highly correlate with each patient's clinical signs and symptoms. Routine use of NGS-based genetic testing will not only facilitate patient counseling by medical geneticists and genetic counselors, but also serve as a first step towards designing personalized treatments for patients with Wolfram syndrome.

Notably, although Wolfram syndrome is an ultra-rare genetic disorder, its constituent medical components (e.g., diabetes mellitus, deafness, and retinal degeneration) and underlying ER pathophysiology are not as rare. Consequently, novel treatments designed for this ultra-rare disorder may have broader implications for more common medical conditions related to ER stress and dysfunction. Thus, by leveraging the tools and therapeutic efforts targeting Wolfram syndrome, we may identify novel treatment modalities for more prevalent disorders such as diabetes mellitus and neurodegenerative diseases.

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Resources

ⁱwww.clinicaltrials.gov

ⁱⁱ<https://ncats.nih.gov/ntu/projects/2017#calcium>

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Spotlight

Interleukin-13 Is Unlucky for Allergy Sufferers

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Anaphylaxis, a life-threatening allergic reaction, is dependent on high affinity allergen-specific IgE. **Gowthaman et al.** now show that a new interleukin (IL)-13-expressing T helper cell subset specifically promotes high-affinity IgE responses. The discovery of T follicular helper (Tfh)13 cells defines potential new targets for allergy therapies.

The increase in atopic and allergic diseases over the past 30–40 years is of epidemic proportions and these diseases affect millions of people in the USA [1,2]. Allergic reactions can lead to anaphylaxis, a severe and life-threatening form of allergic immune response. Anaphylaxis is a systemic inflammatory response that results in a

dramatic loss of blood pressure and can lead to organ failure. Food allergies, especially to peanut proteins, often involve anaphylactic reactions [3].

During the priming phase of an allergic immune reaction, Interleukin-4 (IL-4) is produced by T helper (Th) cells that promote the production of antigen-specific IgE antibody from B cells. Most IgE then binds strongly to Fc ϵ receptors on mast cells. IgE with low affinity for the allergen protein is not sufficient to fully activate mast cells and cannot provoke anaphylaxis in the presence of allergen (Figure 1A). However, the interaction of allergen proteins with high-affinity allergen-specific IgE on the mast cell surface causes crosslinking of the Fc ϵ receptors, triggering a signaling cascade that leads to mast cell degranulation and release of preformed inflammatory mediators stored in cytoplasmic granules, including histamine, proteases, cytokines, and chemokines (Figure 1B) [4]. Release of these inflammatory mediators in a systemic response leads to the severe allergic reaction of anaphylaxis.

Recent studies have revealed that specialized IL-4-secreting T follicular helper (Tfh) cells are essential for the development of antigen-specific IgE from activated B cells within a cellular structure found in lymphoid tissues called the germinal center [5]. The discovery that Tfh cells control IgE responses has expanded our knowledge of mechanisms that control the development of allergies. However, a crucial aspect of the anaphylactic response is that it is dependent on the development of high-affinity IgE specific for the allergen [6] and despite the clinical significance of anaphylaxis, the question of how high-affinity, allergen-specific IgE develops in the germinal center has been unclear. Now, investigators from Yale University and the Jackson

