**Wolfram Syndrome Treatments and New Discoveries about other Degenerative Diseases**

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With advancements in treatments for Wolfram syndrome come new ways to possibly treat and further understand other degenerative diseases such as Alzheimer’s, ALS, and Parkinson’s. There are multiple forms of treatments being devised, one path is to limit the frequency of cell death and halt further symptoms, the other to prevent or replace the mutated cells. Treatments to limit cell death include clinical trials conducted with Dantrolene which helps to preserve cells that may be suffering from ER stress. Another treatment is the use of sodium valproate which keeps cells with defective wolframin from dying. Gene therapy is a new treatment that has yielded promising results as well as expanding the knowledge on other degenerative diseases. Researchers have also employed the use of gene editing through CRISPR to determine if the defects can be located and amended to eliminate the mutation. With the new gene-editing, data researchers have found that when corrected stem cells are developed into beta cells and placed back into mice suffering from diabetes their blood sugar returned to normal. Researchers are working on implementing this technique to develop healthy wolfram genes. With all these new discoveries and advancements with Wolfram Syndrome other similar degenerative diseases will be easier to study. The main issues that confront further progress are funding and limits to our current scientific understanding and tools.

**Introduction**

Wolfram Syndrome (WFS) is considered a rare form of diabetes caused by mutations to the *WFS1* gene that is found on the 4th chromosome. This gene encodes for a protein called wolframin that is found in the endoplasmic reticulum and regulates calcium, protein folding, and processing as well as other physiological processes. It is an autosomal recessively inherited disease that is relatively rare, 15,000-30,000 people currently suffer from Wolfram’s Syndrome. (Leslie, 2021) Symptoms of the disease can be seen in children as young as 11 and usually present in vision impairment and inability to see color. Many individuals suffer from diabetes insipidus which presents around age 14. As the disease progresses it continues to cause other symptoms that ravage the body and eventually lead to death by the age of 40. Other symptoms include impaired hearing, ataxia, dysphagia, unable to control bladder, and mental disorder concerns.

Research into treatments for WFS has gained considerable traction when the link between WFS and Endoplasmic Reticulum stress was discovered. This gave scientists an area to focus their research on and opened the door to possible drugs that could be used as a treatment or further support. ER stress is a major contributor to this degenerative disease because when cells become stressed and there is no way to alleviate it and the cell will eventually destroy itself. Scientists believe this is why there are so many beta cell and neuron deaths. The endoplasmic reticulum is also a large part of many important physiological processes and one of its main responsibilities in keeping the body in homeostasis is calcium regulation. It regulates calcium to keep the levels of cytoplasm at equilibrium, to keep the heart muscle cells deprotonated, to help contract the heart muscles and neurons' ability to transmit neurotransmitters. Healthy beta cells can release adequate insulin when prompted by a large amount of sugar but beta cells with faulty wolframin hold too much calcium and are unable to release enough insulin and eventually go through apoptosis.

**Recent Progress**

There are two main focuses for researchers when studying Wolfram’s Syndrome, the first is limiting, supporting, or replacing dying or dead cells. The other is to develop therapies that replace the genes that have either been damaged or mutated. Currently, a clinical trial being conducted by medical geneticist Fumihiko Urano in the United States to study the effects that a muscle relaxer, Dantrolene, has on the preservation of cells dying from Endoplasmic Reticulum stress. From reported data, the drug did not help to improve the vision of the 22 subjects but in some individuals, there was an increase in beta cell functionality and a rise in insulin production. Scientists are finding that a possible major cause of WFS is ER stress and calcium levels. In 2018, a clinical trial was established to study sodium valproates' effect on the prevention of cell death in cells suffering from defective wolframin. Molecular chaperones are being tested on their ability to reduce ER stress and help the ER to fold proteins properly. A few of these are tauroursodeoxycholic acid and 4-phenylbutyric acid and are of further importance in slowing pancreatic beta-cell and neurologic regression. In Birmingham, UK a study that is in its second stage is examining Valproic-acid (VPA) in treating adults and infants suffering from WFS. VPA is being used because of its ability to limit the amount of cell death. The mechanism is thought to stimulate *WFS1* expression which aids in further reducing ER stress with a special focus on nervous tissue. Some signs combining this therapy with molecular chaperones are effective even with exceptionally rare forms of WFS.

A focus for Urano, is to develop a cure and not just treatments. To delve further into the causes and possible cures for this disease Urano has employed the use of gene editing hoping to replicate healthy cells and replace them in humans to eliminate the disease. Urano is collaborating with other geneticists and stem cell biologist, Catherine Verfaillie, to use CRISPR to amend faulty genes in stem cells and then to promote the growth of beta cells. These cells are then placed into diabetic mice where the blood sugar of the mice returned to normal levels. These results are promising but there are still further tests needed to see if these results are long-lasting or there are eventual negative side effects. Urano believes that gene therapy is a closer possibility due to scientists having more experience and knowledge of the technique. He hopes that gene therapy is only 3-10 years away from clinical trials compared to genetic editing which is an estimated 10-20 years from clinical trials.

**Discussion**

Although clinical trials with Dantrolene show improvements researchers want to collect more data to determine proper dosages, possible side effects, and possible long-term repercussions. Combining therapies seems to yield good results for the rarer types of WFS, but there was no data on how well they did with the common types of WFS. Other drugs are being prepared for possible clinical trials that were not listed and pharmaceutical companies that want their medications considered as well for possible tax exemption reasons. The data provided on the current trials seem valid, but there is always a concern about the spread of incorrect data or misinformation. In the second article by Felix Reschke, he reported a study had “reported gene therapy to cure WFS in affected people.” (Reschke, 2021) This study was done with the CRISPR technique that took the defective *WFS1* gene and corrected it CRISPR-Cas9 in human stem cells. Reschke follows this hopeful statement with “However, further studies are needed to confirm the validity of these findings.” (Reschke, 2021) Those reporting on the data must be well research and certain of their sources. In Leslie’s article, he reports that both Urano and Verfaillie believe that genetic editing using CRISPR will not be fully developed for another 10 to 20 years. While reading these articles and learning all the research that goes into understanding degenerative diseases, I wonder how research like this could further different types of cancer research. How much will data from studies like these expedite studies into neurodegenerative diseases? These new clinical trials are yielding exciting and promising results and it will be very interesting to see how this information is integrated into new studies for other similar diseases.

**References**

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