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Readthrough Intervention Increases ER Stress in Wolfram Syndrome

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Abstract

Wolfram syndrome (WFS) is an example of inherited endocrine and neurodegenerative disease due to increased ER stress with no causal treatment. WFS is an autosomal recessive syndrome caused by biallelic mutations in WFS1 gene. Some of these mutations result in premature termination codons (PTCs). Some prospects for the causal treatment of WFS patients could give a PTCs readthrough intervention. The use of ataluren (formerly PTC124) can result in bypassing the PTCs and lead to a continuation of translation.

The aim of the study was to evaluate the repairing potential of ataluren in a cell model of WFS caused by PTCs. Diagnosis of WFS was confirmed by Sanger sequencing of the WFS1 gene. ER stress induction (Tunicamycin; Sigma-Aldrich, Germany) with subsequently using PTC124 (Ataluren, Selleckchem, USA) were performed on fibroblasts obtained from skin biopsies of WFS patients and healthy individuals. The evaluation of ER stress induction was conducted by analysis of mRNA expression of recognized markers of the ER stress (7900HT Real Time PCR; Applied Biosystems, USA).

Expression of specific markers of ER stress in patients with WFS was increased after using tunicamycin, with the highest value after 8 hours of the ER stress induction. The highest increase in mRNA expression after application of PTC124 in combination with DMSO in relation to DMSO itself was observed for GRP78 ($p=0.0013$). Fold change was 3.41 ± 0.73. It seems that PTC124 by the ER stress increasing cannot be used as a potential causal treatment for the WFS patients.

Wolfram syndrome (WFS) is an example of a rare genetic syndrome resulting from biallelic mutation of WFS1 gene. The prevalence of WFS in the European population is very low (about 1/500,000 to 1/770,000). In all of the WFS patients diabetes mellitus together with optic nerve atrophy are observed. No causal treatment is currently available in this syndrome .WFS is caused by recessive mutations in the WFS1 gene localized on chromosome 4p16.1 .

Wolframin – as a product of WFS1 gene – is an integral component of the endoplasmic reticulum and is expressed in many tissues and organs (e.g., brain, heart, pancreas, liver, muscles). This wide tissue distribution of wolframin contributes to the pleiotropic effects of mutations of the WFS1 gene. Wolframin is in fact a kind of “gatekeeper” that protects cells from ER (endoplasmic reticulum) stress which occurs due to accumulation of endogenous protein synthesis products .Thus, the loss of its function in particular cells implies an increased ER stress resulting in apoptosis of the affected cells and many neurodegenerative and endocrine symptoms. Currently, above 200 mutations resulting in WFS have been described .

Some of them are the mutations of premature termination codons (PTCs) .It seems that some prospects for the causal treatment of patients with WFS can give a recently discovered phenomenon – a readthrough of PTCs.

The use of a chemical compound that bypasses premature stop codons (stop codons are reading as glycine) results in a continuation of translation. Chemical compounds with the above described properties are e.g. aminoglycosides, including gentamicin. However, they have numerous side effects .Ataluren (formerly PTC124), another readthrough-promoting

compound, is less toxic and was approved to treat patients with Duchenne muscular dystrophy who have a nonsense mutation in the dystrophin gene.

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