ER calcium depletion as a key driver for impaired ER-to-mitochondria calcium transfer and mitochondrial dysfunction in Wolfram syndrome.

Liiv M, Vaarmann A, Safiulina D, et al. Nat Commun. 2024;15(1):6143.

Presenter: Chun-Han Chu **Date/Time:** 2024/11/14, 15:10-16:00pm
Commentator: Wen-Tai Chiu, Ph.D. **Location:** Rm. 601, Med College Building

Background:

Wolfram syndrome (WS) is a rare genetic disorder characterized by mutations in the WFS1 gene (causing the more common type I WS) or the CISD2 gene (causing the rarer type II WS). Wolfram syndrome, also known as DIDMOAD, is a primary defect in the poor handling of calcium ions (Ca^{2+}) in the endoplasmic reticulum (ER), resulting in symptoms such as diabetes insipidus, diabetes mellitus, optic atrophy, and deafness. However, so far, there is no treatment available for the neurological manifestations of WS. Recent findings suggest that mitochondrial dysfunction may be a key driver of WS progression. For example, WFS1 downregulation disrupts mitochondrial dynamics and reduces ATP production in neurons. Further studies showed that loss of WFS1 in patient cells resulted in reduced mitochondria-associated ER membranes (MAMs), impaired mitochondrial Ca^{2+} uptake, and reduced mitochondrial respiration. However, it is unclear why Ca^{2+} flux from the ER to mitochondria is reduced and how reduced Ca^{2+} flux affects mitochondrial function. Furthermore, do WFS1 and CISD2 act synergistically to trigger these abnormalities, or do they act independently to produce similar effects?

Objective:

To investigate the causes of Wolfram syndrome by examining the deficiencies of WFS1 and CISD2 in neurons and finding potential drug targets to restore Ca^{2+} balance and improve mitochondrial and neuronal function.

Results:

The authors used the Ca^{2+} sensors ER-GCaMP6-210 and jGCaMP7b to measure resting Ca^{2+} levels in the ER and axoplasm of WFS1 and CISD2 deficient neurons. They observed that reduced ER Ca^{2+} and increased axoplasmic Ca^{2+} levels, linking these changes to reduced SERCA activity and Ca^{2+} leakage through RyR2 or IP3R1. Overexpression of SERCA2b and the SERCA activator CDN1163 restored ER and axoplasmic Ca^{2+} levels. Inhibition of SERCA through overexpression of phospholipid-bearing protein (PLB) increases axoplasmic Ca^{2+}, but this can be reversed by overexpression of WFS1 or CISD2. Downregulation of RyR2 also restored ER Ca^{2+} levels, whereas IP3R inhibition had minimal effect. Furthermore, reduced ER-mitochondrial calcium flux is associated with decreased mitochondrial function, and GRP75 overexpression restored MAM and mitochondrial Ca^{2+} uptake, further demonstrating that reduced Ca^{2+} flux in the MAM affects mitochondrial function. For example, low ATP levels, the NADH/NAD^+ ratio increases, and PDH activity weakens, pushing metabolism to shift to glycolysis. Finally, WFS1 and CISD2 overexpression have complementary roles, highlighting their synergistic role in Ca^{2+} homeostasis and energy metabolism.

Conclusion:

This study identifies three major impacts of ER Ca^{2+} loss in WFS1-deficient neurons: decreased IP3R-mediated ER-to-mitochondria Ca^{2+} transfer due to reduced SERCA and increased RyR activity, impaired mitochondrial ATP production leading to glycolysis, and the complementary roles of WFS1 and CISD2 in Ca^{2+} regulation. These findings provide insights into the pathogenesis of WFS and suggest new therapeutic targets to improve mitochondrial and neuronal function.