Finding a Therapy for Wolfram Syndrome: Exploring a Calcium Signaling Pathway as a Target for a Disease without a Cure

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An aberrant interaction between wolframin and neuronal calcium sensor 1 (NCS1) explains the clinical implications of Wolfram Syndrome, an orphan disease without a cure. Wolfram Syndrome is an autosomal recessive genetic disorder that is caused by endoplasmic reticulum dysfunction, with typical symptoms being diabetes mellitus, optic nerve atrophy, hearing loss, and neurodegeneration. Patients typically die between the ages of 25-49 with some form of brain stem failure and respiratory complications. NCS1 is important in regulating calcium signaling and maintaining calcium homeostasis within the cell. When wolframin, encoded by the gene WFS1, is mutated, this protein-protein interaction between wolframin and NCS1 is disrupted. Using molecular docking platforms (PyMol and PyDock) I am able to show that these proteins nest so that the calpain cleavage site of NCS1 is protected by the N-terminus of wolframin. When calpain, a calcium dependent protein, cleaves NCS1, NCS1 is dysfunctional which causes reduced calcium signaling throughout the cell. This in silico prediction was supported by the ability of a glutathione S-transferase tagged version wolframin to pull down NCS1 in a calcium dependent manner. Quantitative polymerase chain reaction (qPCR) with hepatocellular carcinoma cell lines demonstrated that expression levels of wolframin and NCS1 levels are coregulated. These results indicate that the functional expression and interaction of the two proteins plays a pivotal role in cell health and provides a pathway for targeting therapeutics to treat Wolfram Syndrome.

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