What Is the Role of Wolframin in the Endoplasmic Reticulum Ca2+ Signaling Network?

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High cytoplasmic calcium (Ca2+) concentrations are toxic to cells. To control Ca2+ concentrations, eukaryotic cells have complex mechanisms for sequestering Ca2+ in the endoplasmic reticulum (ER). When parts of this system are nonfunctional, Ca2+ flow across the ER membrane is dysregulated, causing cell death. Understanding the role of each component protein involved in Ca2+ sequestration is vital to treating diseases involving Ca2+ dysregulation. One poorly-understood protein in this network is wolframin, which is mutated in a fatal disorder of Ca2+ signaling called Wolfram Syndrome, which causes Type 1 diabetes and neurodegeneration. 20 years after its discovery, the mechanism by which wolframin affects Ca2+ concentrations remains unknown. To gain understanding of wolframim's specific function, I took three approaches. First, I constructed a network of known interactions between many ER Ca2+-signaling proteins, including wolframin, to identify proteins that may interact with wolframin. Second, I examined the evolutionary context of wolframin to identify with which proteins wolframin co-evolved. Third, through sequence analysis, I characterized previously unknown globular domains and sequence features of wolframin to suggest mechanisms of wolframin's involvement in ER Ca2+ signaling. Taken together, these approaches suggest that wolframin does not itself bind Ca2+ but rather regulates Ca2+ movement by direct interaction with pumps of Ca2+ into the ER called SERCAs. I also found probable binding mechanisms of wolframin to the cytoplasmic Ca2+ sensor calmodulin and to the ER Ca2+-binding protein calumenin, which suggests a role for wolframin in 'fine-tuning' concentrations of Ca2+ in the ER and the cytoplasm through SERCA regulation.