Expressional and functional studies of Wolframin, the gene function deficient in Wolfram syndrome, in mice and patient cells.

Abstract:
Wolfram Syndrome is an autosomal recessive degenerative disorder of the neuroendocrine system. Diabetes mellitus is its lead symptom. Patients show mutations in the wolframin (WFS1) gene coding for a hydrophobic transmembrane protein of 890 amino acids. This protein was preliminarily localised in the endoplasmatic reticulum (ER) in cells of mice and rats. Mice lacking the WFS1 gene display degeneration of pancreatic beta-cells following induction of ER stress. We here used antibodies against substructures of the wolframin protein in order to analyse its expression and localisation. Expression was detected in both pancreatic beta-cells and the limbic system of mice. Using the rat insulinoma cell line RIN 5AH and fractionated mouse brain tissue, we confirmed wolframin localisation to the endoplasmic reticulum. Expression profiling on patient’s primary fibroblasts revealed down-regulation of the diabetes associated plasma membrane glycoprotein (PC-1) gene, and up-regulation of fibulin-3, a gene connected to senescence. However, cell proliferation was indistinguishable from non-mutated cells. In contrast to data obtained on murine pancreatic islets, we found no increased apoptosis following induction of ER stress but rather by staurosporine treatment in the absence of WFS1 function. This indicates a new role of WFS1 deficiency in programmed cell death.