Poster

Cell death by ferroptosis in Caenorhabditis elegans models of neurodegenerative diseases. Implications of the mitochondria

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ABSTRACT

Ferroptosis is an iron-dependent cell death driven by the peroxidation of membrane phospholipids. To protect themselves from this harm, cells possess several defense systems among which we find peroxiredoxins (Prdxs). This protein family is characterized by the ability to scavenge peroxides and is composed of six members in mammals and three in Caenorhabditis elegans, PRDX-2, -3 and -6 (Ismail et al, 2019). C.elegans is a nematode that is an ideal model for the study of neurodegenerative diseases as it has conserved neurological pathways and simple organ and tissue organization (Caldero-Escudero et al, 2024). Among the three Prdx members in C.elegans, PRDX-2 and PRDX-6 are cytoplasmatic proteins, while PRDX-3 is located in the mitochondria. In this study, we have focused on the effect of these proteins in C. elegans models of polyglutamine-repeats (polyQ) protein aggregation and the possible implication in ferroptosis protection. Bearing this in mind, we have performed genetic crossing strategies to generate all double and triple mutant combinations of prdx-2, prdx-3 and prdx-6 genes. These strains have been used to determine the role of peroxiredoxins in development, progeny generation and effect on PolyQ aggregation in muscle cells using fluorescence. We demonstrate that mutations of peroxiredoxin genes, especially prdx-2, slow down the development of the nematode and reduce egg laying. Combinations of mutations in the other prdx genes enhance this phenotype. Moreover, prdx-2;prdx-3 mutants are letal, being arrested at the L3 state of the development, which might show a possible mitochondrial implication. prdx-6 simple mutants are barely affected when compared with wild type (N2) worms. However, prdx-2; prdx-6 mutants are greatly affected, having a huge decrease in lifespan and egg laying. Furthermore, there is also a reduction in the size of the worms. Finally, microscopy analysis on the integrity of the mitocondrial network are yet to be done in these mutants. In conclusion, the results obtained so far suggest that peroxiredoxins have influence on worms´ developement, maybe protecting them from ferroptosis. Also, mitochondria seem to play its own role during this process. Studies on the implication of ferroptosis and mitochondria, as well as on protein aggregation, are being carried out and need to be completed.

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