Poster

Protective role of glutathione peroxidase GPX-7 in Caenorhabditis elegans models of protein aggregation

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ABSTRACT

Motivation: Ferroptosis is a regulated form cell death caused by an iron-dependent increase in lipid peroxidation of polyunsatured fatty acid (PUFA) of the plasma membrane. Glutathione peroxidases (GPx's) are a family of enzymes that catalyze the reduction of H2O2 and lipid peroxides using glutathione (GSH) as a cofactor. PUFAs peroxide reduction by glutathione peroxidase 4 (GPX4) is the main pathway in mammals protecting against ferroptotic cell death (1). The objective of this research is to characterize the role of C. elegans GPX-7, an orthologue of mammalian GPX4, in the protection against protein aggregates formation, which we have found sensitizes C.: elegans to ferroptosis.

Methods: By genetic manipulation and crossing in C. elegans, we have created a number of different mutant strains lacking gpx-1, gpx-2, gpx-6 and gpx-7, the four orthologues of mammalian GPX4. These mutant strains were crossed with animals expressing the fusion protein Q40::YFP that forms fluorescent aggregates in muscle cells (2). We quantified these aggregates using a fluorescence microscope. We also used the glutathione depletor diethylmaleate (DEM) to study the impact of glutathione homeostasis in these strains (3). Moreover, we have created a mutant strain unc-52; gpx-7 to determine the effect of depleting gpx-7 on the paralysis phenotype displayed by unc-52 mutants (3).

Results: We have that these two mutant strains gpx-1; gpx-2; gpx-6; gpx-7Q40::YFP and gpx-7 Q40::YFP have half number of aggregates in comparison with Q40::YFP and gpx-1; gpx-2; gpx-6; Q40::YFP control strains. The strains harbouring the gpx-7 mutation are resistant up to 1.5 mM DEM and 2mM DEM, otherwise letal doses in the control of worms. However, unc-52; gpx-7 worms did not show differential paralysis when compared to unc-52 single mutants.

To complement this work we want to investigate if we could obtain these results in an intestinal polyQ model (Q44::YFP). That will be an indicative that gpx-7 protects in the poliQ models.

Conclusions: The deletion of gpx-7 appears to decrease the number of Q40::YFP aggregates in worm muscle cells. In contrast, it does not affect the paralysis of unc-52 mutants.

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