Redox-mediated causal connection between ferroptosis and aging in *Caenorhabditis elegans*: a role for *fard-1* and *dhs-25*

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Abstract:
Aging is a natural process characterized by a progressive physiological decline that undermines health and well-being in the elderly population[1]. It is widely accepted that an unbalanced redox state belongs to the hallmarks of aging, but its role as one of the main drivers of ferroptosis is quite recent[2]. Ferroptosis is a form of iron-dependent cell death caused by massive phospholipid peroxidation, triggered by the excessive accumulation of intracellular ROS and the failure of the main cellular antioxidant systems[3]. While roles for ferroptosis in pathological conditions have been described, its physiological roles and regulators are less clearly understood.

Here, using *Caenorhabditis elegans* as a powerful model organism for aging studies, we uncover a role for ferroptosis in physiological aging mediated by disturbed redox homeostasis. We evaluated healthspan parameters in a wild-type strain highlighting how different age-related features differentially decline during aging. A progressive loss of the capability to contrast external stressors, with an increase in hydroxyl radicals and a failure of the glutathione antioxidant system demonstrated the progressive disruption of redox homeostasis in older age. Moreover, we showed that selected genes involved in redox metabolism are downregulated with aging. Among them, knocked out strains of the fatty acyl-CoA reductase, *fard-1*, and of the dehydrogenase, *dhs-25*, displayed higher sensitivity to a ferroptosis inducer, increased lipid peroxidation, anticipated drop in total glutathione and reduced lifespan. Accordingly, the expression of one of the closest mammalian *dhs-25* homolog, the hydroxysteroid 17-Beta Dehydrogenase 8, was downregulated in cells which are more sensitive to ferroptosis due to altered mitochondrial redox homeostasis.

Our results clearly prove a causal role of ferroptosis in *C. elegans* aging driven by oxidative stress, unveiling novel genes involved in this connection that may constitute targets for future interventions to improve healthy aging.

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