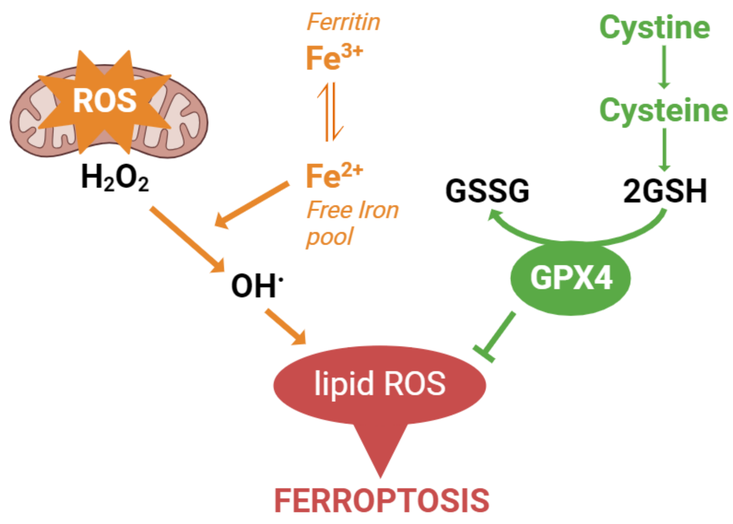
EXPLORING *Caenorhabditis elegans* IN AGING RESEARCH: HEALTHSPAN PARAMETERS AND FERROPTOSIS DURING LIFESPAN

Roberta Pensotti[1], Barbara Sciandrone[1], Laura Schröter[2], Natascia Ventura[2] and Maria Elena Regonesi[1]
[1] Department of Biotechnology and Biosciences, University of Milano Bicocca, Milan, Italy
[2]Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany

Background…

One of the main challenges of the 21st Century is to shed light on the molecular mechanisms underlying the aging process. Indeed, life expectancy has greatly increased in the past few decades, without being accompanied by an increment in healthspan. Moreover, since aging consists in a time dependent progressive decline of physiological functions, the main consequence of this transition include a growing risk of age-related diseases[1]. A promising strategy to reduce frailty is targeting ferroptosis, a newly discovered mode of cell death that is caused by massive lipid peroxidation mediated membrane damage, triggered by the accumulation of intracellular ROS and iron and by the parallel disruption of the main antioxidant systems. Drugs that block lipid peroxidation or scavenge intracellular iron have already been proven to be beneficial at specific late points in *C. elegans*'s lifespan[2].



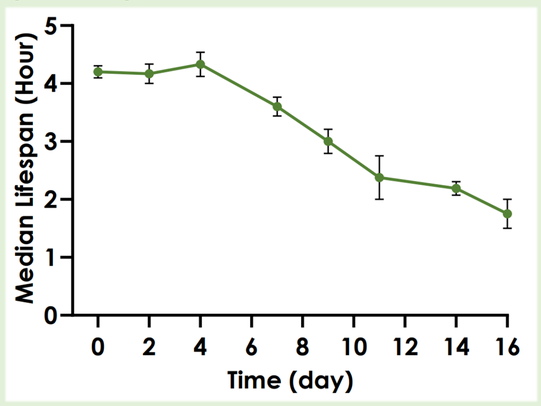
1. Yu M et al. (2021) Cells 10(3), 660). 2. Larrick JW et al. (2020) Rejuvenation Research 23(5), 434-438).

Is ferroptosis implicated in aging? How?

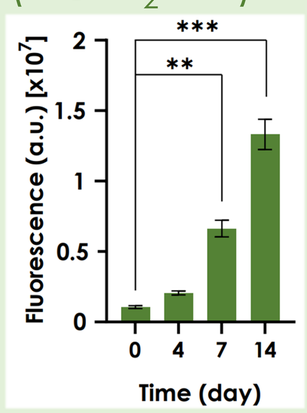
Healthspan parameters

N2 *wild type* strain was maintained at 20°C, on NGM solid plates seeded with alive *E. coli* OP50 strain. Day 0 means the 1st day of adulthood.
Here, heat stress resistance at 37°C, ROS levels and glutathione total amount (together with GSH/GSSG ratio) were measured at specific time points in *C. elegans* lifespan.

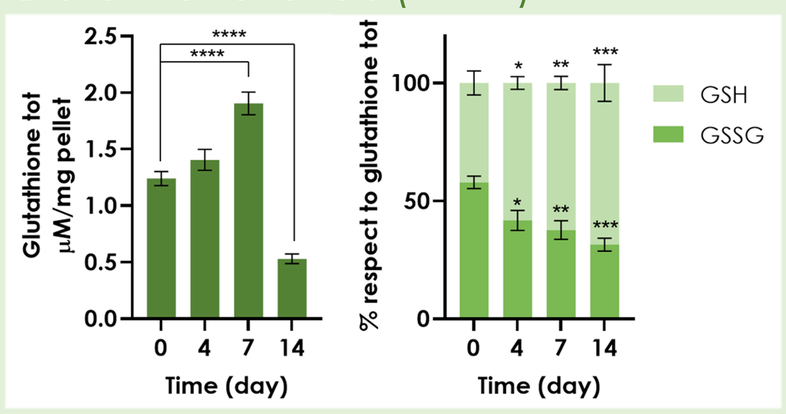
Heat stress resistance (37°C)



ROS total level ($DCFH_2$-DA)



Glutathione levels (DTNB)



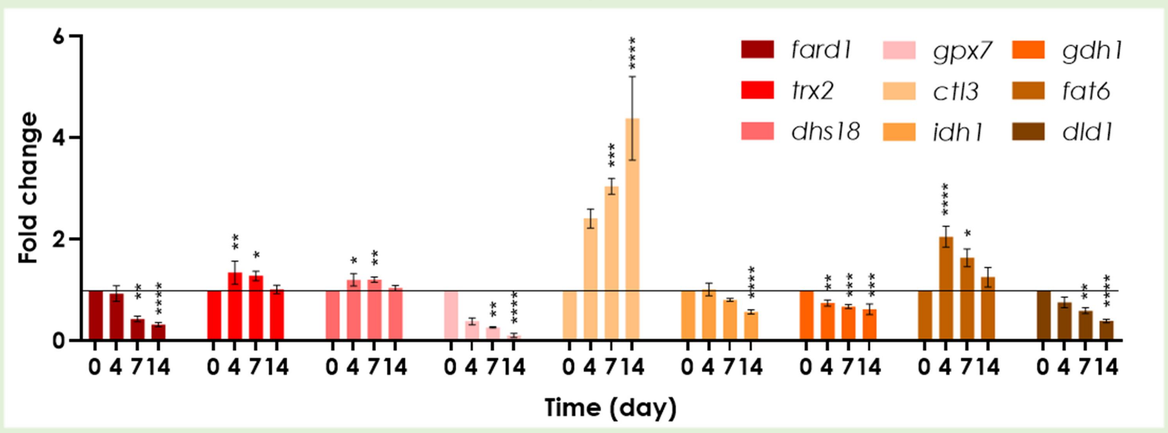
The ability to resist to stressors declines starting from the second week of adulthood, in parallel with the increase in ROS levels and the loss of total glutathione amount, even if the worms try to contrast oxidative stress as shown by the higher GSH/GSSG ratio.

Ferroptosis

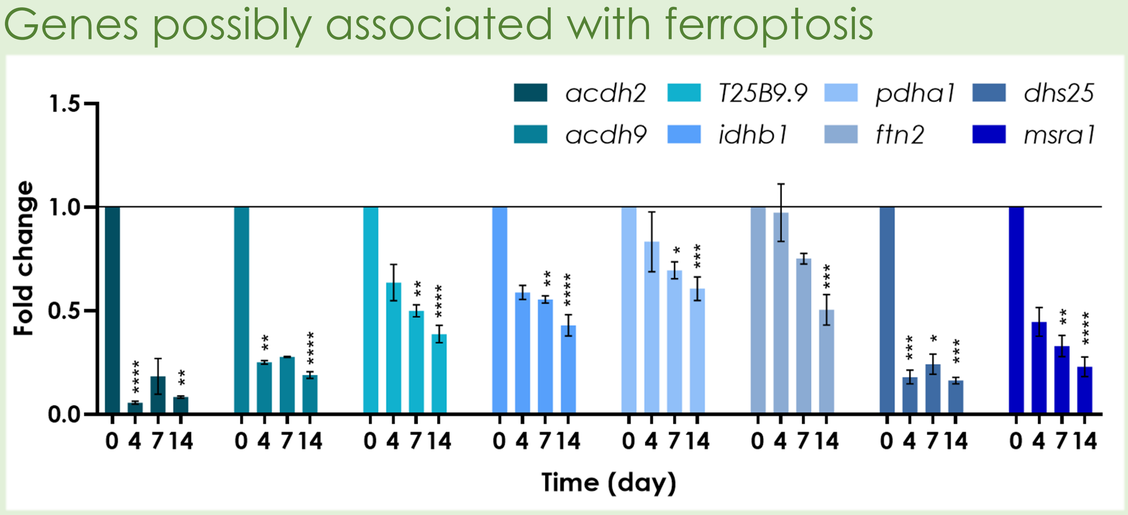
Frataxin (*frh-1*) silencing has been shown to extend *C. elegans* lifespan through the inhibition of ferroptosis[3]. As a consequence, some of the main upregulated genes found in *frh-1* RNAi worms are expected to be downregulated during *C. elegans* lifespan→ suggesting a possible increment of ferroptosis in aging.
Here, Real Time PCRs of genes involved in REDOX, Iron homeostasis and FA metabolism have been carried out at the same time points of the healthspan parameters.

3. Schiavi A et al. (2023) Iscience 26(4).

Genes associated with ferroptosis



Genes possibly associated with ferroptosis



qPCR data support the initial hypothesis, given that most of the selected genes are downregulated over time. To further validate how ferroptosis and aging are linked, lipid peroxidation should be measured on C. elegans KO strains.

To conclude… Ferroptosis might actually impact on the aging process in a straight cross-talk with REDOX homeostasis.

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r.pensotti1@campus.unimib.it
Lab 4045, U3, 4th Floor
BtBs Department of Biotechnology and Biosciences
UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA