13:00-13:15 **Antonio Miranda**

Loss of glutathione redox homeostasis impairs proteostasis by inhibiting autophagy-dependent protein degradation

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Under non-stressed conditions, the redox status of the different subcellular compartments is tightly controlled. Hence, the cytoplasm has a reducing environment that favours cysteine protein residues in their dithiol form while the endoplasmic reticulum environment is oxidizing to facilitate the formation of disulfide bonds for protein folding. This situation is reversed in the presence of aggregation-prone proteins, as both compartments undergo a dramatic shift in their respective redox status, with the cytoplasm becoming more oxidized and the endoplasmic reticulum more reducing [1]. However, whether changes in the cellular redox status affect protein aggregation has not yet been addressed.

We approached this hypothesis by using a C. elegans mutant strain lacking the gsr-1 gene, encoding glutathione reductase, the enzyme responsible for recycling oxidized glutathione (GSSG) and thus maintenance of glutathione redox homeostasis [2]. We found that gsr-1 deficiency enhances the deleterious phenotypes of worm disease models caused by aggregating proteins like human b-amyloid peptide, a-synuclein or polyglutamine repeats containing proteins. Importantly, gsr-1 dependent proteostatic disruption is also found in C. elegans strains expressing endogenous UNC-52 and LET-60 aggregate-prone metastable proteins. This deleterious effect is largely phenocopied by the GSH depleting agent diethyl maleate [3].

Protein aggregates can be disposed by autophagy and consistent with a role of GSR-1 in this process, gsr-1 mutants abolish nuclear translocation of the TFEB/HLH-30 transcription factor (a key mediator of autophagy induction) and strongly impair the degradation of the autophagy substrate p62/SQST-1::GFP. In agreement, genetic disruption of autophagy in gsr-1 mutants expressing aggregation prone proteins resulted in strong synthetic developmental phenotypes and in some cases lethality. Downregulation of glutathione reductase and GSH levels in both yeast and mammalian cell models also caused phenotypes associated to protein aggregation and impaired TFEB nuclear translocation [3]. Together, this study demonstrates a novel, evolutionarily conserved role of glutathione redox homeostasis in proteostasis maintenance through autophagy regulation.

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[2] Mora-Lorca JA et al. (2016) Glutathione reductase gsr-1 is an essential gene required for Caenorhabditis elegans early embryonic development. Free Radic Biol Med. 96:446-61.
[3] Guerrero-Gómez D, et al. (2019) Loss of glutathione redox homeostasis impairs proteostasis by inhibiting autophagy-dependent protein degradation. Cell Death Differ, in press.