

Organelles enter the game of aging related aggregation and retention of misfolded proteins

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Abstract

Aging is a degenerative process associated with several phenotypes among which are increases in accumulation of misfolded and damaged proteins. Several studies have shown associations of altered mitochondrial DNA and structure, oxidative phosphorylation function, and ROS production with aging. In this study, Zhou et al explore the role of mitochondria in regulating protein aggregate distribution during cell division. This is in fact the first account of a framework mechanism for proteome quality control and its role in aging and cell rejuvenation.

Keywords: aging, cell division, mitochondria, organelle-based aggregation, protein misfolding, protein quality control

Aging is associated with a proteotoxic stress in cells due to formation, accumulation, and aggregation of misfolded proteins. Protein aggregates not only form due to other stresses such as heat but also through inhibition of proteasomal activity.

The cellular site for protein aggregation is initially the surface of ER where most of the active protein translation sites are harbored and later captured by mitochondria. The association of protein aggregates with organelles is the main point of discussion in Zhou et al². In order to do this, Zhou et al first devise several stressing conditions from heat shock at 42° C to oxidation with H₂O₂ or pulsing cells with azetidine-2-carboxylic acid (A2C) to interfere with proper protein folding in cells. These conditions result in aggregation of unstable and misfolded cytosolic GFP-Ubc9 protein species as observed through live-cell fluorescence correlation microscopy. The molecular brightness is an indicator of the oligomeric state of diffusing GFP-Ubc9 species during heat shock stress. These experiments also show that protein species do not form oligomers prior to aggregating spontaneously in the cytosol during stress.

Another important observation made by Zhou et al is that aggregate formation requires active protein translation. Treating cells with cycloheximide to inhibit translation prevented

aggregate formation even under stress conditions.

Due to the interference of protein aggregates with the normal function of cells, sequestration of aggregated proteins into aggresomes (well-confined structures) can reduce the harmful effects in cells.

Majority of protein translation occurs on mRNAs with ER-bound ribosomes. Using confocal and electron microscopy, Zhou et al confirm that close to 75% of active translation occurs on the ER surface. Further, protein aggregates also show prominent association with mitochondria. These aggregates are either formed on mitochondria initially or are captured by the mitochondria upon stress removal. Therefore, the authors show that ER and mitochondria with their extensive contact areas are main organelle hosts for stress-induced protein aggregates. Another important observation made is that depleting cytosolic ATP resulted in a delay in protein aggregate dissolution. This suggests that glycolysis, as the main source of ATP, can play a key role for protein aggregate dissolution.

In a dividing budding yeast *Saccharomyces cerevisiae*, the protein aggregates are distributed asymmetrically between the mother and daughter cells. Zhou et al further report that the mitochondria do not take its associated protein aggregates into the daughter cell. This

asymmetric organelle inheritance during cell division is found to be partly due to Fis1 protein, an evolutionary conserved mitochondrial protein involved in yeast mitochondria fission. Interestingly though, with age, the association of protein aggregates with mitochondria was significantly reduced. The age-dependent decline establishes a framework mechanism for protein aggregation under stress.

Similarly in mammalian cells, a mitochondrion has been found to have high levels of aggregates that is also partitioned unequally during mitosis¹. This organelle-based aggregation in yeast and represents a mechanism of proteome quality control that may be important for development and the aging process in metazoans as well¹. Discovering the molecular mechanism of such asymmetric cell division can aid in understanding both the aging process and hence regulating it for rejuvenation purposes¹.

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