Divide et impera: damage retention and rejuvenation in yeast

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Abstract

Ageing of organisms and tissues has been associated with the progressive accumulation of oxidatively damaged macromolecules. Nevertheless, cells have evolved means of providing for the rejuvenation of the progeny even as they age. In the asymmetrically dividing yeast *S. cerevisiae* oxidatively damaged proteins accumulate in the mother cell via a Sir2p-dependent mechanism, which allows the newly formed bud to be born nearly damage-free.

The present work was aimed at elucidating the molecular mechanisms responsible for the asymmetric segregation of oxidized proteins during cytokinesis in budding yeast, as well as its implications for the cells' life span and health span. In addition, I approached the question of whether damage segregation requires an asymmetrical cytokinesis by analyzing the distribution of oxidatively damaged proteins during division in the fission yeast *Schizosaccharomyces pombe*. The data presented and discussed here show that the mother cell-specific accumulation of oxidatively damaged proteins in budding yeast is in fact achieved through the retention of the damaged (aggregated) form of proteins, irrespective of the protein's identity. Evidence suggests that Sir2p acts on damage segregation in two ways: by regulating the functional status of the cell's chaperones, responsible for the recycling of damaged substrates, and the formation of the actin cytoskeleton, which provides a scaffold for trapping oxidatively damages proteins. Failure to retain aggregated damaged proteins in the mother compartment, results in the loss of replicative potential, reduced antioxidant capacity to combat external stress and a compromised fitness of the newly born daughter cells. Accrual of such a situation may lead, according to mathematical modeling, to clonal senescence of the entire population.

It is also demonstrated here that size asymmetry between the progenitor and progeny cell is not a prerequisite for an uneven inheritance of damaged proteins. This is indicated by the preferential segregation of oxidized proteins to one of the *S. pombe* siblings, via a dynamic Sir2p- and actin/microtubule- dependent process. In view of this finding, the significance of damage retention in terms of fitness and aging was modeled. The model predicts that damage segregation increases the fitness of the system at both low and high levels of damage and, at a high damage rate, also prevents the onset of clonal senescence. The data point to sibling-specific aging being the result of a strong selective advantage of damage segregation and that such segregation may be more common than previously anticipated.

Interestingly, life span and health span can be improved also by reducing mitochondrial dynamics, suggesting that damage retention may not be the sole contributor to replicative senescence of the parental lineage and rejuvenation of the progeny.

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