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Damage Segregation and Cellular Rejuvenation in *Saccharomyces cerevisiae*

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Abstract

The process of aging is defined as a time-dependent decline in cellular functionality, and aging is thought to have evolved as organisms were optimized for reproduction, at the cost of an imperfect repair and maintenance system. As a consequence, different kinds of dysfunctional components and damage accumulate over time. Eventually these dysfunctional components, termed aging factors, reach critical levels at which they interfere with cellular systems, causing the age-related loss of function that ultimately leads to cell death.

The investment in propagation also encompasses the retention of aging factors within the progenitor cell, so that the progeny is born rejuvenated, free from damaging aging factors. The accumulation of oxidized and aggregated proteins has been established to act as aging factors in several organisms. These damaged proteins are asymmetrically distributed during cell division, a process that in yeast relies on the actin cytoskeleton and components of the cellular protein quality control (PQC) system. In my work, I have established that this asymmetric damage segregation is an active and factor-dependent process, accomplished through the actions of two interconnected systems. Mainly, sequestration of protein aggregates into certain quality control sites within the mother cell ensures the retention of damage, but cells have also evolved a process of aggregate removal so that any damage that accidentally leaks into the daughter cell is removed. This removal is achieved either by degradation or by retrograde transport of aggregates back into the mother cell.

In a genome-wide screen we identified functions that are required for this damage distribution, and could further pinpoint several of the asymmetry generating genes (AGGs) regulating this process. Through this approach, we found that the sequestration of aggregates into protective inclusions is dependent on vesicle transport and fusion to the vacuole, and we identified a novel role for the vacuole adaptor Vac17 in this process. Additionally, we found that the process of aggregate removal includes an unexpected role for the metacaspase Mca1, acting in conjunction with the proteasome and PQC system to degrade aggregated proteins. The link between protein aggregation and aging is further reinforced by our data demonstrating that altered levels of these identified AGGs affect cellular fitness and longevity.

Keywords: Aging, protein damage, segregation, quality control, metacaspase, Mca1, protein aggregates, vacuole, endocytosis, Vac17