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Proteostasis and Aging in *Saccharomyces cerevisiae*
The Role of a Peroxiredoxin

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Abstract

Aging is characterized by a progressive decline in physiological functions that limits biological processes, increases the risk of disease, and ultimately leads to death. At the cellular level, aging is associated with accumulation of damaged components, including proteins, indicating that protein homeostasis (or proteostasis) fails to maintain the integrity and functionality of the proteome as cells age. Reduced caloric intake elevates proteostasis, counteracts the accumulation of damage during cellular aging, and prolongs lifespan in organisms ranging from yeast to primates. Caloric restriction is intimately linked to reduced signaling through nutrient sensing pathways, including the Target-Of-Rapamycin (TOR) and Protein Kinase A (PKA) pathways but which downstream targets of these nutrient-signaling pathways are most important for lifespan control is not known.

In this thesis, using the yeast *Saccharomyces cerevisiae* as a model organism, I found that the peroxiredoxin Tsa1, which belongs to a family of peroxide scavengers, is a downstream target of the PKA pathway and acts as a major modulator of aging. I found that Tsa1 is required for the resistance to hydrogen peroxide and lifespan extension induced by caloric restriction. Further, I traced the beneficial role of Tsa1 in longevity assurance to its involvement in proteostasis; an involvement linked to the hyperoxidized chaperone-like form of Tsa1. This function of Tsa1 in proteostasis entails recruitment of other molecular chaperones to misfolded and damaged proteins under hydrogen peroxide stress and in aged cells, as well as assistance in the clearance of protein aggregates. Our findings suggest that the cell utilizes distinct strategies for managing protein aggregates under different stress conditions, as Tsa1 is important for the management of protein aggregates under hydrogen peroxide stress but not upon elevated temperatures. The data also point to hydrogen peroxide and reduced proteasomal-dependent degradation as contributing factors for the accumulation of protein aggregates in aged cells.

Keywords: Aging, caloric restriction, oxidative stress, peroxiredoxins, proteostasis, protein aggregates, ubiquitin-proteasome system