Peroxiredoxins in Redox Signaling and Aging

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Abstract

Peroxiredoxins have emerged as conserved modulators of the rate of aging in yeast and multicellular organisms and play a role in lifespan extension through the anti-aging intervention caloric restriction. Yet, it is not clear through what mechanism peroxiredoxins extend lifespan. First discovered as hydrogen peroxide scavengers, peroxiredoxins have been shown to have a genome protective function, to act as chaperones, to play a role in circadian rhythms and to be involved in redox signaling.

In this thesis, I tried to identify the underlying mechanisms for peroxiredoxin mediated lifespan extension and its role in redox signaling. Using the yeast *Saccharomyces cerevisiae* as a model organism, we could show that the lifespan extension by the peroxiredoxin Tsa1 is not linked to increased genome stability. Our data indicates that Tsa1 recruits molecular chaperones to protein aggregates formed during oxidative stress and reduces the number of protein aggregates that accumulate during aging. Surprisingly, this contributes just to a limited extend to lifespan extension, as a mutant not able to form a chaperone still has a normal lifespan. Instead, redox-signaling that reduces protein kinase A (PKA) activity through Tsa1 mediated oxidation seems to be preeminently responsible for lifespan extension.

Interestingly, the same signaling pathway is used in yeast to react to light stress. Hydrogen peroxide formed upon illumination by a conserved peroxisomal oxidase leads to increased redox cycling of Tsa1. Tsa1 then reduces PKA activity allowing the subsequent nuclear localization of the transcription factors Msn2 and Msn4 that induce transcription of stress related genes. Our data thus clarify an important aspect of the role of peroxiredoxins in circadian rhythms, namely they mediate an organismal light response.

**Keywords:** Aging, caloric restriction, peroxiredoxins, protein aggregates, redox signaling, PKA signaling, light stress