Nicotinamide cofactors and longevity: relationship between NAD and oxidative stress during chronological aging in yeast

Abbiati F.[1], Garagnani S. A.[1], Orlandi I.[1], Vai M. [1]
E-mail: f.abbiati1@campus.unimib.it
[1] Department of Biotechnologies and Biosciences, University of Milano-Bicocca, Milan 20126, Italy

Keywords: NAD metabolism, mitochondrial respiration, ROS, antioxidant response, pentose phosphate pathway, aging, yeast

Abstract:
Several studies indicate that a progressive decrease of intracellular NAD^+ takes place from yeast to humans during aging[1]. This reduction appears to contribute to the metabolic decline of tissues and the development of age-related diseases[2].

To study the effects of NAD^+ on cellular aging, we used the yeast *Saccharomyces cerevisiae* as a model organism in the context of chronological aging. This work focuses on two mitochondrial NAD^+ carrier-mutants. The two mutants have different total NAD^+ level and a different intracellular NAD^+ distribution. Specifically, one mutant has higher cellular/mitochondrial NAD^+ levels and an unexpected reduced longevity. The other mutant, despite the low intracellular/mitochondrial NAD^+ levels, has a longer lifespan[3].

Analyses of enzymatic activities, metabolite content and mitochondrial respiratory parameters were performed. We found that in the mutant, characterized by the higher NAD^+ content and a shorter longevity, the mitochondrial respiration was less efficient and the ROS content was higher. These features correlated with an imbalance of NADPH/$NADP^+$ ratio and a low accumulation of the reserve carbohydrate trehalose contributing to shorten its lifespan. On the contrary, the other mutant, despite the low levels of NAD^+, had a more efficient respiration and a reduced ROS accumulation. This took place in concert with the maintenance of a correct NADPH/$NADP^+$ ratio and more trehalose, in line with longer lifespan.

In perspective, this work suggests that, in mitotically quiescent but metabolically active cells, such as neurons and myocytes, the chronological aging is not only influenced by the level of intracellular NAD^+ but by ratios between couples of other cellular redox metabolites, such as NADP(H).

1. Yaku, K., Okabe, K., and Nakagawa, T. (2018). Ageing Res. Rev. **47**: 1-17.
2. Strømland, Ø., et al. (2021). Mech Ageing Dev. **199**:111569.
3. Orlandi, I., Stamerra, G., and Vai, M. (2018). Metabolism. Front Genet. **9**:676.