

METABOLIC REMODELING IN EXTENDED LONGEVITY

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The yeast *Saccharomyces cerevisiae* has been used as a model system to study aging, in which life span can be measured either chronologically or by the replicative capacity of individual cells. Metabolic activity contributes to this replicative life span by providing the substrate for production of daughter cells. Two sorts of studies highlight the importance of metabolism in yeast longevity. Mitochondria lose function during the replicative life span. This triggers an intracellular signaling pathway, the retrograde response, which results in numerous changes in nuclear gene expression. These changes compensate for the mitochondrial dysfunction by altering cell metabolism to maintain the production of biosynthetic intermediates for generation of daughter cells. They also include the induction of stress response genes. Activation of this pathway extends yeast life span. The Rtg2 protein plays a central role in retrograde signaling. It is part of the SLIK transcriptional co-activator complex, which alters chromatin structure through histone acetylation. This activity facilitates the induction of retrograde target genes and life span extension. When Rtg2 protein is not engaged in retrograde signaling, it can participate in the suppression of genome instability. In this way, Rtg2 protein links metabolism with stress resistance, chromatin-dependent gene activation, and genome stability. The results point to the primary role of metabolism in determining life span. Limitation of glucose also extends yeast replicative life span. This effect is distinct from retrograde signaling, but it overlaps the effect on life span of the histone deacetylase Rpd3, which has a genome-wide role in gene silencing. The downstream effects of glucose limitation on metabolism are distinguished from those caused by the retrograde response, although certain features are in common. Thus, there are multiple metabolic adaptations that are compatible with enhanced longevity. However, the provisions of Krebs cycle intermediates appears to be of central importance.