Baker's Yeast as a model to study aging and find conditions to

delay aging and extend a disease-free healthspan

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It is unfortunate that the ongoing and impressive increase in human lifespan is accompanied by the devastating emergence of many aging-related diseases, mostly neurodegenerative disorders. Therefore, in an attempt to improve the disease-free healthspan, our research is focused on understanding underlying processes involved in aging. It is well established that aging, a complex biological process, is programmed genetically and conserved in evolution. In addition to its manifestation by whole organisms, aging occurs at the molecular level of individual cells. To address aging at the molecular and cellular level, we selected the baker's yeast as a model, exploiting the awesome power of yeast genetics and relying on the evolutionary conservation of fundamental biological processes. Although aging is usually measured as lifespan, we are looking for aging readouts that are independent of lifespan, because death can be caused by reasons other than old age. To obtain lifespan-independent readouts for the aging process, we examined protein aggregation, a common hallmark for many aging-related neurodegenerative disorders, most notably Alzheimer's, Parkinson's, and Huntington's diseases, as well as ALS. We expressed in yeast recombinant versions of human huntingtin, the protein implicated in Huntington's disease. We followed the aging-dependent aggregation of these huntingtin-derived proteins using visual and biochemical tools, and tested the effects of different genetic backgrounds and a variety of environmental conditions on this aggregation. We identified genes, proteins and systems that both are affected by, and affect, aging, and found condition to slow the aging process. In particular, we implicated key cellular systems that are dedicated to combating stress through their ability to handle aberrant proteins and prevent their aggregation. We found that these systems (heat shock response (HSR), unfolded protein response (UPR), endoplasmic reticulum-associated protein degradation (ERAD)) are functionally linked, forming a coordinated network. Interestingly, the individual systems of this network, HSR, UPR and ERAD, deteriorated with age. However, extreme dietary restriction, namely transfer from rich medium to pure water, slowed this deterioration, delayed the aggregation of the huntingtin-derived proteins and prolonged the yeast lifespan. We conclude that aging is an active process that involves a genetic plan, yet external conditions and lifestyle can delay aging and extend a disease-free healthspan.