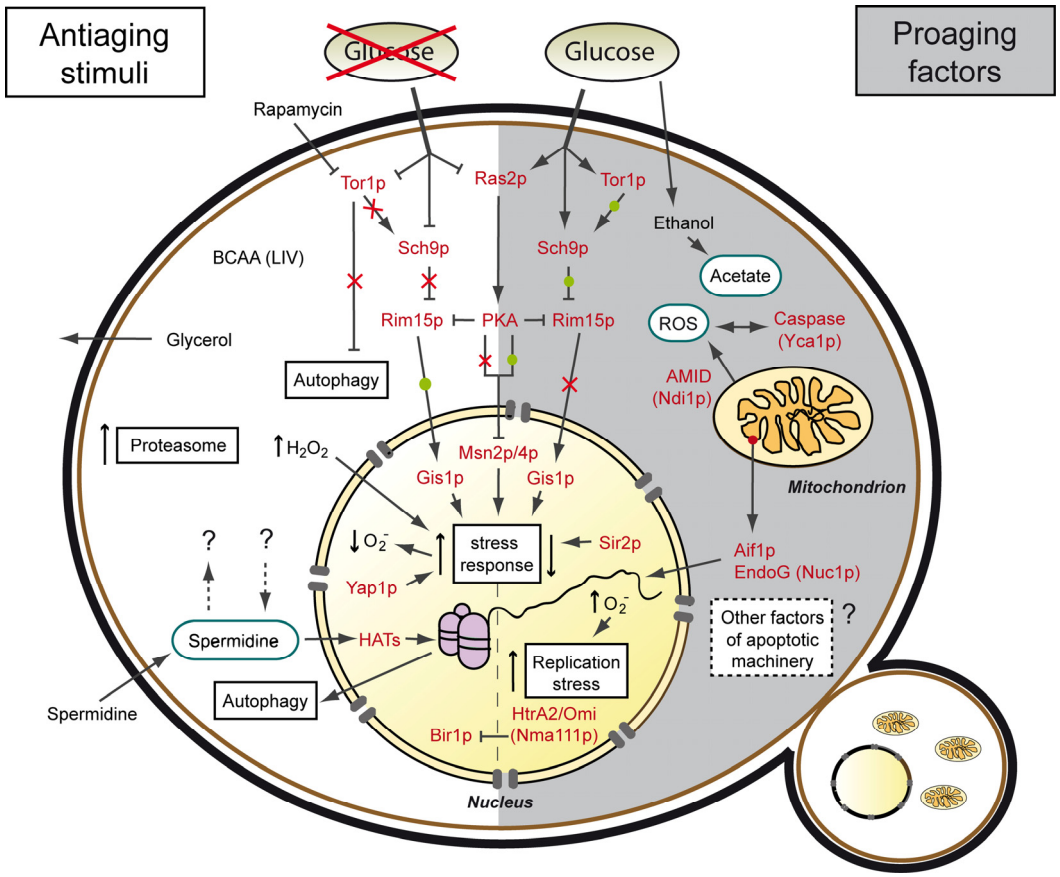

Figure 1. Stimuli and factors involved in yeast chronological aging. The process of chronological aging ultimately relies on a cell's decision to stall or promote its growth in a given scenario. If growth is inhibited, for instance due to low nutrient availability (caloric restriction), the cell enters a state of low metabolic activity (quiescence), thus arresting the aging process (antiaging). If nutrients are available the cell activates growth progression, elevates metabolic rates, promotes its reproduction and progressively ages (non-quiescence or senescence), eventually culminating in its demise (proaging).

Consequently, glucose availability has a major impact on longevity, specifically via the Tor-Sch9p and Ras2-PKA pathways, which require the serine-threonine kinase Rim15p and the transcription factors Gis1p, Msn2p and Msn4p to regulate expression of stress response genes. While longevity is promoted upon low glucose availability (↓glucose → ↓Tor/Sch9p/Ras2 → ↑stress response), it is shortened when glucose availability is high (↑glucose → ↑Tor/Sch9p/Ras2 → ↓stress response). Stress response is also regulated via other factors like the transcription factor Yap1p or the histone deacetylase Sir2.

The Tor1p kinase is also involved in the regulation of autophagy, a self-recycling pathway under nutrient starvation. Upregulation of autophagy may occur via inhibition of the Tor1p kinase (for instance with rapamycin) or elevation of intracellular spermidine levels (by external supplementation or internal regulation mechanisms still to be discerned). Spermidine, which induces autophagy via inhibition of histone acetyl transferases (HATs) and resulting histone hypoacetylation, could also regulate longevity via autophagy-independent alternative pathways. In addition, chronological lifespan is extended by increased availability of branched side chain amino acids (BCAA; leucine, isoleucine and valine) and a rise in synthesis and release of glycerol, which in turn is inhibited by sustained growth signalling (see text).

On the other hand, under conditions where chronological aging is promoted ethanol is metabolized to acetate, which acts as a proaging trigger, in part by influencing internal and external pH as well as TOR signaling. Additionally, growth signaling leads to cell cycle progression and replication stress. Chronological aging-induced cell death has been shown to be regulated by a number of mitochondrial, nuclear and cytosolic lethal effectors and might also involve further factors associated with the yeast apoptotic machinery.