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Editorial

Mechanisms through which Chemical Compounds Produced by Mammals or Plants Delay Chronological Aging in Yeast

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Editorial

The budding yeast *Saccharomyces cerevisiae* is a valuable model for uncovering molecular mechanisms of cellular aging in multicellular eukaryotic organisms [1-3]. Because of the relatively short and easily monitored replicative and chronological lifespans of *S. cerevisiae*, this genetically and biochemically manipulable unicellular eukaryote with annotated genome has been successfully used to identify many genes shown to play essential roles in cellular aging not only in yeast but also in multicellular eukaryotes [2,4,5]. Furthermore, studies in *S. cerevisiae* have discovered a nutrient- and energy-sensing network of integrated signaling pathways shown to influence cellular aging and define organismal longevity in multicellular eukaryotes across phyla [2-5]. Moreover, studies in *S. cerevisiae* have led to the discovery of several chemical compounds that delay cellular aging, extend organismal lifespan and health span, and decelerate the onset of age-related pathologies in eukaryotic organisms across species [6-8]. All these studies have provided convincing evidence that the major features of the aging process and mechanisms by which this process can be slowed down by some genetic, dietary and pharmacological interventions are evolutionarily conserved [1-13].

Our research is aimed at unveiling molecular and cellular mechanisms by which certain chemical compounds of mammalian or plant origin can delay chronological aging in *S. cerevisiae*. Using a high-throughput chemical genetic screen of several commercially available compound libraries, we discovered more than 20 molecules that can delay yeast chronological aging and belong to 5 chemical groups [14]. One of these groups includes 6 different bile acids. In mammals, these amphipathic molecules are either synthesized from cholesterol in hepatocytes of the liver or produced by bacteria in the colon [15-18]. In contrast, yeast are unable to synthesize bile acids [15,16,19]. We demonstrated that the most hydrophobic bile acid called Lithocholic Acid (LCA) exhibits the highest aging-delaying efficiency among the 6 bile acids discovered in our chemical genetic screen of chemical compounds capable of decelerating chronological aging in yeast [14]. Our studies have revealed the following mechanism underlying aging-delaying action of LCA in yeast. Exogenously added LCA enters yeast cells, where it is sorted to the inner and outer mitochondrial membranes [20]. Because LCA causes a distinctive remodeling of the synthesis and transfer of phospholipids within both these membranes, it elicits substantial changes in mitochondrial membrane lipidome [20]. These LCA-driven changes in the concentrations of mitochondrial membrane phospholipids lead to characteristic changes in mitochondrial size, number and cristae morphology, thus altering membrane potential, respiration, ATP synthesis and reactive oxygen species concentration in mitochondria of yeast cells that progress through several consecutive stages of the chronological aging process [20]. Such age-related changes in mitochondrial functionality of yeast treated with LCA transform mitochondria into a signaling platform that drives a stepwise establishment of an aging-delaying transcriptional program for many nuclear genes; this transcriptional program is under control of the transcriptional factors Rtg1/Rtg2/Rtg3, Sfp1, Aft1, Yap1, Msn2/Msn4, Skn7 and Hog1 [21].

Importantly, our studies have provided evidence that LCA not only slows yeast chronological aging, but also selectively kills cultured human cells of neuroblastoma, glioma, prostate and breast cancers [22-24].

In a recent screen of a library of Plant Extracts (PEs), we have discovered 6 PEs that delay yeast chronological aging more efficiently that any aging-delaying chemical compound currently known [25]. We call these geroprotectors of plant origin PE4, PE5, PE6, PE8, PE12 and PE21 [25]. Our studies have revealed that each of these 6 PEs delays aging in yeast by triggering a hormetic stress response and eliciting a distinct kind of changes in certain longevity-defining cellular processes [25]. These changes include the following: 1) amplified respiration and membrane potential in mitochondria; 2) increased or decreased concentrations of reactive oxygen species; 3) reduced oxidative damage to cellular proteins, membrane lipids, and mitochondrial and nuclear genomes; 4) enhanced cell resistance to oxidative and thermal stresses; and 5) accelerated degradation of neutral lipids deposited in lipid droplets [25]. We provided evidence that each of the 6 aging-delaying PEs extends yeast chronological lifespan by modulating different hubs, nodes and/or links of the nutrient- and energy-sensing network of integrated signaling pathways and proteins kinases [26]. The effects of these PEs on the network of longevity-defining signaling pathways and proteins kinases include the following:1) PE4 weakens the inhibitory effect of the pro-aging TORC1 (target of rapamycin complex 1) pathway on the anti-aging SNF1 (sucrose non-fermenting) pathway; 2) PE5 attenuates two branches of the pro-aging PKA (protein kinase A) pathway, one of which depends on the anti-aging protein kinase Rim15 whereas

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the other branch is Rim15-independent; 3) PE6 stimulates anti-aging processes and/or inhibits pro-aging processes that are not integrated into the network of signaling pathways/protein kinases; 4) PE8 weakens the inhibitory effect of the pro-aging PKA pathway on the anti-aging SNF1 pathway; 5) PE12 stimulates the anti-aging protein kinase Rim15; and 6) PE21 impedes a PKH1/2(Pkb-activating kinase homolog)-sensitive form of the pro-aging protein kinase Sch9 [26].

The challenge for the future is to investigate whether any of the six age-delaying PEs can slow the onset and progression of chronic diseases associated with human aging. These aging-associated chronic diseases include arthritis, diabetes, heart disease, kidney disease, liver dysfunction, sarcopenia, stroke, Parkinson's neurodegenerative disease, Alzheimer's neurodegenerative disease, Huntington's neurodegenerative disease, and many forms of cancer.

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