EARLY-LIFE PROTEIN TRANSLATION SPIKE DRIVES AGING VIA JUVENILE HORMONE/GERMLINE STEM CELL SIGNALING

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Protein translation (PT) is high in early-adulthood across invertebrates, rodents, and humans but sharply declines thereafter. It has been implicitly assumed that elevated PT at young ages is beneficial to health and PT ends up dropping as a passive byproduct of aging. However, whether this holds true and how dynamic fluctuations in PT over time impact aging remain unknown. In Drosophila, we show that a transient PT spike in early-adulthood exerts long-lasting negative impacts on aging trajectories and proteostasis in later-life. Conversely, blocking the early-life PT spike robustly improves life-/health-span and prevents age-related protein aggregation. Further, greater early-life PT rise strongly predicts shorter future lifespan across fly strains and is observed in neurodegenerative disorders long before symptoms/pathologies appear. Proteomics-guided investigations revealed that during the early-adulthood PT rise, juvenile hormone triggers proteostatic dysfunction and drives aging via aggregation-prone large lipid transfer proteins. The early-life PT spike also transcriptionally represses stress responses essential for proteostasis maintenance and drives aging via germline stem cell signaling. Our findings suggest that PT is thereby suppressed after early-adulthood as an adaptive response to alleviate proteostatic burden, slow down aging, and optimize life-/health-span. We thus propose that the rise and fall in PT over time impact aging in the opposite direction from what was previously assumed. Our work provides a novel theoretical framework for understanding how lifetime PT dynamics regulate the onset of aging. Further, our study provides a foundation for future research, including whether high early-life PT spike is an early biological event driving neurodegeneration/age-related diseases.

A FAT-PROMOTING BOTANICAL EXTRACT ARTEMISIA SCOPARIA EXERTS GEROPROTECTION IN C. ELEGANS

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Like other biological processes, aging is not random but subject to molecular control. Natural products that modify core metabolic parameters, including fat content, may provide entry points to extend animal lifespan and promote healthy aging. Here, we show that a botanical extract from Artemisia scoparia (SCO), which promotes fat storage and metabolic resiliency in mice, extends the lifespan of the nematode Caenorhabditis elegans by up to 40%. Notably, this lifespan extension depends significantly on SCO's effects on fat; SCO-treated worms exhibit heightened levels of unsaturated fat, and inhibiting Δ9 desaturases, which oversee biosynthesis of monounsaturated fatty acids, prevents SCO-dependent fat accumulation and lifespan extension. At an upstream signaling level, SCO prompts changes to C. elegans fat regulation by stimulating nuclear translocation of transcription factor DAF-16/FOXO, an event that requires AMP-activated protein kinase under this condition. Importantly, animals treated with SCO are not only long lived but also show improved stress resistance in late adulthood, suggesting that this fat-promoting intervention may enhance some aspects of physiological health in older age. These findings identify SCO as a natural product that can modify fat regulation for longevity benefit and add to growing evidence indicating that elevated fat can be pro-longevity in some circumstances.

FUCOIDANS ARE NOVEL SENOTHERAPEUTICS THAT ENHANCE SIRT6 AND DNA REPAIR ACTIVITY

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With age, senescent cells accumulate in various tissues where they contribute to loss of tissue homeostasis, aging, and age-related diseases through their inflammatory senescence-associated secretory phenotypes (SASPs). Senotherapeutics able to selectively eliminate senescent cells, termed senolytics, or suppress the detrimental SASPs, termed senomorphics, have been demonstrated to improve age-associated comorbidities and aging phenotypes. To discover novel senotherapeutics translatable to promote healthy longevity, we conducted a drug screening of diverse natural products based on the characteristic senescence-associated β-galactosidase activity. Several fucoidans from different brown seaweed were found to exhibit potent senotherapeutic activity. Fucoidans are long-chain sulfated polysaccharides found in various species of brown algae including seaweed. The best senomorphic fucoidan was able to suppress senescence in cultured senescent fibroblasts, in ex vivo human tissue explants, and in vivo in mouse models of natural and accelerated aging. Specifically, fucoidan reduced markers of cellular senescence and SASP in senescent mouse and human cells. Acute treatment of the fucoidan in naturally aged mice reduced tissue senescence, especially in the kidney and lung. Chronic treatment of the fucoidan in Ercc1-/Δ progeria mice attenuated composite aging symptoms and extended healthspan. Interestingly, preliminary mechanistic studies demonstrated that fucoidan can improve non-homologous end-joining-directed DNA damage repair and increase the mono-ADP-ribosylation activity of SIRT6, suggesting a relationship between cellular senescence, DNA repair, and SIRT6 signaling pathways. Collectively, fucoidans were identified as novel senotherapeutics with translational potential for reducing cellular senescence, ameliorating age-associated phenotypes, and extending healthspan as well as able improve DNA repair pathways through modulation of SIRT6 activity.