THE ROLE OF RIBOSOMAL COMPOSITION IN SELECTIVE TRANSLATION OF LONGEVITY GENES UNDER DIETARY RESTRICTION

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Dietary restriction influences longevity through changes in gene expression on the level of transcription and translation. Our lab is investigating the changes occurring under dietary restriction in C. elegans on the level of individual ribosomal proteins (RPs) and changes in RP phosphorylation and how they shape gene expression and longevity. To look at the impact of changes in RP expression we used RNAi knockdowns starting at adulthood and assayed lifespan and health span. Two RPs knockdowns that increased longevity, rpl-7A and rpl-22, were then subjected to transcriptome and translatome analysis using polysome profiling and mRNA-seq. Both knockdowns resulted in similar transcriptomic changes with an up-regulation of genes related to translational fidelity and mitochondrion organization. In contrast, the translatome analysis showed minimal changes upon loss of rpl-7A and rpl-22 suggesting that they are not responsible for increase in selective translation previously observed under DR. To look at impact of changes in phosphorylation of rps-6 on DR, we generated mutant lines incapable of being phosphorylated by TOR signaling. These mutants were assayed for changes in lifespan, health span and selective translation. While phenotypically similar to controls under well fed conditions, the mutants were longer lived under DR. Furthermore, preliminary results indicated that the selective translation of the anti-longevity microchondrial electron transport genes cytochrome c oxidase and ubiquinol-cytochrome c reductase binding protein was repressed when rps-6 is not phosphorylated. In summary, our preliminary results that ribosomal protein phosphorylation but not protein composition is responsible for guiding selective translation pf longevity genes under DR.

SENESCENCE-ASSOCIATED SECRETOME COMPONENTS AS BIOMARKERS FOR AGING

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Cellular senescence is a state of stable growth arrest in response to stress, which is a fundamental process of biological aging. They secrete products, the Senescence-Associated Secretory Phenotype (SASP), which consists of inflammatory cytokines, chemokines, growth factors and matrix remodeling proteins. Senescent cells accumulate with advancing age and partial elimination of senescent cells can reverse age-related dysfunction and increase mean lifespan in mice. However, it is not clear whether components of the SASP can be measured in human plasma and serve as aging biomarkers. Here we generated a candidate panel of senescence markers based on a multiplexed bead-based assay of proteins secreted by senescent preadipocytes, endothelial cells, fibroblasts, myoblasts, preadipocytes, and epithelial cells compared to non-senescent controls. The SASP undoubtedly varies by cell type; however, we observed that multiple components of the SASP are conserved. We then assessed circulating SASP components in human plasma samples from Mayo Clinic Biobank participants (n=280, 20 male and 20 female per decade, age 20-90) using the same method. We confirmed that components of the SASP can be quantified in human plasma with the multiplexed bead-based assay and observed several SASP components robustly increase with chronological age in humans. Our study illustrates that senescence-associated secretome components are detectable in human plasma and could potentially serve as biomarkers of systemic aging and senescent cell burden.

SENESCENCE SECRETOME: BIOMARKERS OF BIOLOGICAL AGING AND POSTOPERATIVE OUTCOMES

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Senescent cells drive age-related tissue dysfunction through their potent secretome, termed the senescence associated secretory phenotype (SASP). Circulating concentrations of SASP factors may reflect biological age and serve as clinically useful biomarkers of surgical risk and ultimately, surrogate endpoints in clinical trials. However, they remain largely uncharacterized. We tested associations between circulating concentrations of SASP proteins and biological age, as determined by the accumulation of age-related health deficits, and/or postoperative outcomes in a sample of residents in Olmstead County, MN, age 60-90 years (n = 115) and cohorts of older adults undergoing surgery for severe aortic stenosis (prospective; n = 97) or ovarian cancer (case-control; n = 36). Circulating concentrations of SASP factors were associated with biological age and adverse postoperative outcomes, including risk of any adverse event or rehospitalization within the year following surgery (aortic stenosis group) or admission to an intensive care unit within 30 days of hospital discharge (ovarian cancer group). Gradient boosting machine modeling revealed a panel of SASP factors that predicted adverse outcomes across both surgical groups better than biological age or chronological age and sex. This suggests that the circulating SASP is a robust indicator of age-related health status and may help guide clinical decision making. Furthermore, circulating SASP factors may be harnessed as a readily quantifiable biomarkers in senescence-targeting interventional human studies.

INCREASED HSP25 DRIVES THE TRANSITION FROM PROTEASOME TO AUTOPHAGY-MEDIATED DEGRADATION UNDER PROTEOTOXIC STRESS

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Accumulation of protein aggregates are a common pathology in many neurodegenerative disorders. This accumulation may be due to a function decline in the protein homeostasis network known to occur during the aging process. Small heat shock proteins are a class of molecular chaperones that assist in protein folding and ameliorates the degradation activity of the proteasome and autolysosome