adds predictive value beyond its criteria, especially for cognitive levels. Additionally, gait speed remains an important predictor of change in executive function. These results suggest that frailty's contribution to cognitive performance amounts to more than the sum of its component parts.

AGE-RELATED CHANGES IN THE MUSCLE SECRETOME

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Skeletal muscle is one of the most abundant tissues in the body. In addition to its key roles in body support, movement and metabolic homeostasis, muscle also functions as an endocrine/secretory organ producing and releasing proteins into the circulation that modulate distant tissues (i.e. myokines). Considering that muscle mass and function changes with advancing age, here we tested the hypothesis that aging alters the muscle secretome profile. After euthanasia, soleus muscles from sedentary young and old mice were dissected, and incubated in oxygenated KRB buffer for 2 h. The buffer was subjected to in-gel trypsin-digestion and peptides analyzed by mass spectrometry. The concentration of 36 proteins were significantly ($P<0.05$) elevated in the young vs. the old group. In contrast, only 7 proteins were significantly elevated in the old group. Some notable differences include those in HSPA1B and HSPA5 that were detected only in the young group. HSPA8 also was significantly elevated by 1.8-fold ($P<0.05$) in the young versus the old group. Another prominent difference between groups involved translationally controlled tumor protein (TCTP), a critical regulator of apoptosis/carcinogenesis, that was elevated by 7-fold in the young vs. the old group ($P<0.05$). These results indicate that aging alters the muscle secretion profile. Identified differences in the muscle secretome could reflect intrinsic changes in muscle cells with age. Because these myokines are released into the circulation, it is also possible that myokine secretion is a regulated cellular process by which muscle communicates and modulates the aging process in distant tissues.

4-PHENYLBUTYRATE: MOLECULAR MECHANISMS AND AGING INTERVENTION POTENTIAL

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4-Phenylbutyrate (PBA) is a FDA approved drug for treating patients with urea cycle disorders. Additionally, PBA acts upon several pathways thought of as important modifiers of aging including: histone deacetylation, proteostasis as a chemical chaperone, and stress resistance by regulating expression of oxidative stress response proteins. PBA has also been shown to extend lifespan and improve markers of age-related health in Drosophila. Due to its wide range of effects PBA has been investigated for use in numerous age-related disorders including neurodegenerative and cardiovascular diseases. To better understand the effects of PBA on the molecular level, we used both in cellulo and in vivo studies. Treatment of primary mouse fibroblasts, C2C12 mouse muscle cells, and NCTC 1469 mouse liver cells with PBA demonstrated differential responses among cell lines to upregulation of oxidative stress response and histone acetylation. Specifically, upregulation of the oxidative stress response protein DJ-1 by PBA was found to have a corresponding dose response curve to histone H3 acetylation in primary fibroblasts. To study effects of PBA in vivo, four cohorts of HET3 mice were treated with PBA at different doses in drinking water for 4 weeks. PBA was well tolerated and led to different effects on body composition dependent on the sex of mice. We are currently investigating the molecular effects of PBA treatment in multiple tissues samples from these mice. The potential of PBA to alter many fundamental pathways, and specifically those related to stress responses, make it an attractive prospect for treatment of many age-related disorders.

IN VIVO ANALYSIS OF REPORTER ALLELES REVEALS INCREASED VARIABILITY OF GENE EXPRESSION IN CELLS AND ANIMALS WITH AGE

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As a major risk factor for a multitude of chronic diseases aging is being increasingly recognized as a necessary therapeutic target for preventive medicine. Yet, despite tremendous progress in our understanding of the genetic determinants of longevity, proximal causes of aging remain incompletely understood. In part, this may be due to a plethora of factors, such as various types of stochastic macromolecular damage that affect individual cells and individual animals. Indeed, recent studies point to an increase of cell-to-cell variability in gene expression within old tissues, supporting the idea that stochastic events contribute to the aging process. Therefore, more single-cell focused studies are needed for a complete understanding of biological aging. Here, we utilized quantitative microscopy for analysis of gene expression in individual aging cells, in vivo in C. elegans. Using transcriptional reporters, fluorescently tagged proteins and a quantitative analytical framework adapted from yeast, we have found that young C. elegans exhibit very little stochastic or signaling noise in gene expression. However, using quantitative microscopy, we directly observed dysregulation of gene expression with age in vivo. Specifically, the stoichiometric ratios of proteins that are tightly regulated among the youthful populace start deviating in a cell autonomous fashion. Importantly, we find that an increase of gene expression variation is a relatively early event in the aging of C. elegans, readily observed before median lifespan. Hence, we suggest that incoherent cell-to-cell variation in gene expression arising with age can be an immediate causal factor for age-related loss of robust tissue function.

A SYSTEM TO IDENTIFY INHIBITORS OF MTOR SIGNALING USING HIGH-RESOLUTION GROWTH ANALYSIS IN S. CEREVISIAE

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Age is the main risk factor for cancer, cardiovascular disease, neurodegeneration and other diseases prevalent