as compared to carriers of the more common FOXO3 variant (TT – common genotype, m= -33bp/year, P=0.008). Interestingly, telomere shortening was not observed as a function of age for G allele carriers (m= -2bp/year, P>0.1). In an independent study of women (N=6,565) from the Nurses' Health Study cohort, ranging in age from 40 to 70 years, a similar observation was found. Notably, carriers of the TT or GT FOXO3 genotype showed a significant decline in telomere length with age (m= -15.5 bp/year, P0.1). These results mark the first validated longevity gene variant showing an association with negligible loss of telomere length with age in humans.

PICOLINIC ACID, A TRYPTOPHAN METABOLITE, DOESN'T AFFECT BONE MINERAL DENSITY BUT UPREGULATES LIPID STORAGE GENES

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Tryptophan is an essential amino-acid broken down initially to kynurenine (kyn), an immunomodulatory metabolite that we have previously shown to promote bone loss. Kyn levels increase with aging and have also been associated with neurodegenerative disorders. Additional tryptophan metabolites include picolinic acid (PA); however, in contrast to kyn, PA is neuroprotective. Thus, we hypothesized that PA might be osteoprotective. In an IACUC-approved protocol, we fed PA to aged (23-month-old) C57BL/6 mice for eight weeks. In an effort to determine potential interactions of PA with dietary protein, we added PA to both a standard (18%) and a low protein diet (8%). The mice were divided into four groups: control (18% protein), +PA (700 ppm); low protein (8%), +PA (700 ppm). There was no difference in weight among the groups [36.1±4.1, 34.6±3.8, 32.8±3.2, 32.6±3.0 gm, (Means±SD, control vs +PA vs 8% vs +PA, p=ns; n=8-10/group). Mice were sacrificed and bones and stromal cells collected for analysis. We found that addition of PA to the diet had no impact on femoral BMD or BMC (BMD: 0.069±0.008 vs 0.075±0.007 vs 0.069±0.005 vs 0.070±007, p=ns). Addition of PA to the diet had no impact of % body fat as measured by DXA; however, stromal cells isolated from the PA-fed mice showed a significant increase in the expression of the lipid storage genes, Plin1 and Cidec. Thus, although PA is downstream of kyn, the kyn-induced detrimental effects on bone mass are no longer observed with PA but instead this kyn metabolite appears to impact energy balance.

HETEROGENEITY OF SENESCENT RIBOSOME COMPLEX AFFECTS THE TRANSLATIONAL EFFICIENCY OF SENESCENCE RELATED MRNAS

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The ribosome, a protein factory, has a lateral stalk known as the ribosomal P complex made up of rpLP0, rpLP1, and rpLP2. It plays an important role in translation by recruiting translational factors. One of these proteins, rpLP2, was decreased in translating ribosome when cellular senescence was induced. Additionally, Y-box binding protein-1 (YB-1), a multifunctional protein that regulates the transcription and translation, was also reduced in polysomal fraction of senescent cells. We have discovered that rpLP2 depletion in heterogeneous ribosome causes the detachment of YB-1 in polysomes and link to cellular senescence. Here, we also have found that a decrement of CK2α or GRK2 on senescent cells induced an increment of unphosphorylated rpLP2, resulting in the release of YB-1 from a ribosome complex. The heterogeneous senescent ribosome has different translational efficiency for some senescence related genes such as AHR, RAB27B, FEZ1, and DDIT4. Our results revealed that the decrease of rpLP1/rpLP2 and YB-1 in translating senescent ribosomes is not specific to cell type or stress type. Furthermore, the same phenomenon was observed in aged mouse liver. Taken together, our results suggest that the senescent ribosome complex appears to have low levels of rpLP1/ rpLP2 and YB-1, resulting in the alteration of translational efficiency for senescence related genes. (Journals of Gerontology: Biological Sciences, 2019 in press)

PHYSICAL FRAILTY AND ITS ASSOCIATION WITH COGNITION: THE PREDICTIVE VALUE OF A SYNDROME BEYOND ITS COMPONENT PARTS

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The extent to which frailty (PFP) affects cognitive performance and change beyond that expected from its component parts is uncertain. Leveraging NHATS, a nationally-representative cohort of U.S. Medicare beneficiaries, we quantified associations between each PFP criterion and global and domain-specific cognitive level and change (memory: immediate/delayed word-list test, executive function: clock drawing test (CDT), orientation: date, time, president-vice-resident naming), using adjusted mixed effects models with random slopes (time) and intercepts (person). We tested whether presence of frailty was associated with excess cognitive vulnerability (synergistic/excess effects, Cohen's d) above and beyond those found for its criteria by adding an interaction term between each PFP criterion and frailty. Among 7,439 community-dwelling older adults (mean age=75.2 years) followed for a weighted mean of 3.2 years (SE= 0.03), 14.1% were frail. The most prevalent PFP criteria were low activity (30.5%) and exhaustion (29.8%). Associations were strongest for executive function, where frailty added predictive value beyond its criteria (excess effects of cognitive vulnerability ranging from -0.38SD (SE-0.05) for slowness to -0.47SD (SE=0.06) for shrinking). Slowness was a strong predictor of cognitive change in both frail and non-frail participants, especially for executive function (frail: Cohen's d per year=-0.16, SE= 0.02; non-frail: Cohen's d per year=-0.15, SE= 0.02). PFP is an important measure of frailty that

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