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