in blood samples of 452 MZ twins (56-80 years of age). Unsupervised IEA were conducted by the KeyPathwayMiner algorithm, while supervised IEA were performed by the KEGG and Reactome databases. No individual CpG site or probe passed correction for multiple testing. Investigating the overlap in genes with p-values<0.01, 0.005 or 0.001 in the EWAS and TWAS, revealed 67, 21 and 2 unique genes, respectively. The latter 2 were TESK2 and VWA1. By the supervised approach, the 67-gene overlap identified three pathways related to "antigen processing and presentation", driven by HLA-A, HLA-B, TAP2 and PSME2. With the unsupervised approach the 21-gene and 67-gene overlaps revealed networks containing 7 and 19 genes, respectively. Exception nodes (added by the algorithm for structure) were CREBBP and CSNK2A2 for the former, and APP and HSP90AB1 for the latter. The remaining IEA revealed no gene sets or networks. Several of these genes have previously been linked to HS relevant traits, e.g. arthritis (HLA-A, HLA-B and TAP2), smooth muscle and cardiovascular function (TESK2, HLA-B and APP) and sarcopenia (HSP90AB1). Hence, this study reports genes and pathways previously reported for physical functioning, yet also novel candidates for further verification.

A PANEL OF DNA METHYLATION AND PROTEOMIC BIOMARKERS FOR SPECIFIC AGING PATHWAYS

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Most aging biomarkers such as DNA methylation and proteomic clocks have focused on measuring overall "biological age," a single number that predicts age-related morbidity and mortality better than absolute chronological age. While intuitive and interpretable, this single biological age number does not account for the possibility that different individuals may preferentially experience aging in different molecular and cellular pathways, and therefore does not suggest personalized aging interventions. We reasoned that a panel of biomarkers each capturing specific aging pathways, such as mitochondrial dysfunction or cellular senescence, may capture the heterogeneity of aging better than existing composite measures. To address this, we employed weighted gene co-expression network analysis to cluster tissue-specific transcriptomes and the serum proteome into specific modules with distinct biological functions and characterized how these modules change with age. We trained DNA methylation proxies of these functional modules that we then applied to independent validation data to identify associations with age-related morbidity and mortality. Clustering analysis using the DNA methylation biomarkers showed that different individuals show distinct patterns of aging. These pathway-specific biomarkers will elucidate how different aging mechanisms interact with each other to produce the larger phenomenon of aging, and for evaluating novel therapeutics targeting specific hallmarks of aging.

AGE-DEPENDENT CHANGES IN NUCLEAR MECHANOTRANSDUCTION AS A DRIVER OF SARCOPENIA

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Informed by evidence that dysregulated nuclear dynamics and nuclear transport may contribute to atrophy in diseased skeletal muscle, the purpose of this study was to assess nuclear deformability, permeability, transport, and mechano-signaling outputs (YAP/TAZ, a marker of mechano-responsiveness, and their downstream genes) in aging skeletal muscle. We hypothesized that aging muscle would show changes in: proteins within LINC (linker of the nucleus to the cytoskeleton) complex, lamina and nuclear pore complex (NPC), and mechano-signaling outputs, with consequent decreased nuclear deformability and increased permeability. We further expected an increase in nuclear strain would increase nuclear YAP/TAZ and downstream indicators of YAP activity (Ankrd1, Cyr61). We used young, adult and aged C57BL6 mice (~4, 14, and 26 months, respectively). Nuclei were less deformable to passive mechanical stretch ex-vivo in adult muscle fibers compared to young muscle fibers. LINC protein gene expression, YAP/TAZ protein, and expression of their downstream genes were significantly increased in adult muscles compared to young muscles. YAP/TAZ protein and their downstream genes were further increased in aged muscles, indicating hyperactivation of YAP/TAZ in aging muscle. Changes with aging in the lamina and NPC included a loss of lamin β1, Nup107 and POM 121, which could underlie the increased nuclear permeability we found in nuclei of aged muscle. In summary, these data highlight a possible role for LINC, lamina and NPC in changes of aging-related nuclear dynamics and mechano-sensing, and may represent therapeutic targets for sarcopenia. Future studies will examine how altering these components affects muscle function during aging.

AGE-RELATED INCREASED ONSET AND PROGRESSION OF PROSTATE CANCER IS REVEALED IN NOVEL PTEN-NULL MOUSE MODELS

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Prostate cancer (PCa) is associated with advanced age. To better understand how age impacts PCa, it is critical to use PCa animal models generated at different ages (aged vs. non-aged). The PB-Cre4 driven phosphatase and tensin homolog (Pten) conditional knockout mouse model, which closely imitates human PCa initiation and progression. However, the Pten deletion is triggered in a 2-week-old prostate, when comparing the extent of PCa between aged and non-aged mice, it is difficult to distinguish the extent to which the onset and progression of PCa are due to the acceleration of the normal aging process or due to the manifestation of PCa pathologies over time. We present here a protocol to inject Cre-expressing adenovirus with luciferin tag intraductally

into the prostate anterior lobes of Pten floxed mice, thus, the Pten-loss will be triggered at different ages post-Cre expression. The in vivo imaging of luciferin signals following viral infection was conducted to confirm the Cre expression and activity. Immunohistochemical staining was performed to confirm the Cre expression, Pten loss, and p-Akt and p-S6 activation. Prostate weight and histopathology were compared between aged and non-aged mice. The results showed that the virus infection was limited in the prostate glands and aged mice had significantly increased PCa onset and progression compared to young mice. Although technical skill is required to carry out this procedure and the success rate of viral infection is about 80%, this model of PCa is of great use to all investigators in the aging and cancer research field.

AN APPROACH TO IDENTIFY NEW PLEIOTROPIC GENETIC LOCI FROM PUBLICLY AVAILABLE UNIVARIATE GWAS RESULTS

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The connections between genes and multifactorial polygenic age-related traits are not trivial due to complexity of metabolic networks in an organism, which were primarily adapted to maximize fitness at reproductive age in ancient environments. Given this complexity, pleiotropy in predisposition to complex traits appears to be common phenomenon. Identifying mechanisms of pleiotropic predisposition to multiple age-related traits can be a key factor in developing strategies for extending health-span and lifespan. Correlation between complex traits may be a factor shedding light on these mechanisms. Recently, we used an omnibus test leveraging correlation between multiple age-related traits to gain insights into pleiotropic predisposition to them. The analysis using individual-level data identified large number of new pleiotropic loci and highlighted a novel phenomenon of antagonistic genetic heterogeneity, which was characterized by antagonistic directions of genetic effects for directly correlated traits. Here, we demonstrate feasibility of our approach using summary statistics from univariate genome-wide (GW) association studies (GWAS). Our analysis focused on the results for high density lipoprotein cholesterol (HDL-C) and triglycerides (TG) from the Global Lipids Genetic Consortium, which reported 94 GW significant loci ($p \leq 5 \times 10\text{-}8$). The traits' correlation was estimated from the individual level data. Our approach identified 28 loci with pleiotropic predisposition to HDL-C and TG at $p \leq 5 \times 10\text{-}8$, which did not attain univariate GW significance with either of these traits. Fifteen of them (53%) demonstrated antagonistic heterogeneity. These results show that our approach can be efficiently used in the analysis of summary statistics from published studies to identify novel pleiotropic loci.

ANTI-AGING EFFECTS OF HYDROPHOBIC AND HYDROPHILIC COMPONENTS FROM IMMATURE PEAR FRUITS EXTRACT

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Cellular senescence, the decline of cellular function due to aging, causes gradual loss of physiological functions and induces some chronic diseases, which negatively affect the quality of human life. Intervention in the cellular senescence process may reduce these incidences and delay the progression of age-related diseases, thereby contributing to the longevity of human lifespan. The budding yeast, Saccharomyces cerevisiae, is a model system that can provide significant insights into the genetics and molecular biology of senescence and is a suitable cellular model for research on mammalian cells. In the 2019 GSA meeting, we had revealed that the prolongation of yeast cell lifespan was induced by the addition of immature pear fruits extracts (iPE). In this study, we have focused on investigating the anti-senescence effects of hydrophilic (WiPE) and hydrophobic (OiPE) components of iPE on yeast cells and their genes and their possible application in extending human lifespan. The anti-aging effects of iPE were investigated using a chronological lifespan assay on S. cerevisiae cells. The chronological lifespan of the yeast was significantly extended in those treated with both WiPE and OiPE at 1% (v/v). The expression of sirtuin-related genes, which regulate cellular senescence, was examined by RT-PCR. Interestingly, gene expression was found to be significantly increased only in WiPE treated cells. The results suggested that the different polarity components from iPE exhibited anti-aging effects on the cells via different mechanisms. Research on the identification of useful components in iPE and the possibility of application to mammalian cells is ongoing.

BASELINE CHARACTERISTICS OF PARTICIPANTS IN A RANDOMIZED CONTROLLED TRIAL OF METFORMIN FOR FRAILTY PREVENTION

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We are conducting a double-blind, randomized controlled trial of metformin for frailty prevention. Participants are adults aged 65+ years with pre-diabetes assessed by 2-hour oral glucose tolerance test (OGTT). Those who are frail (Fried criteria) are excluded. Participants are randomized to metformin (maximum dose of 2,000 mg/day) vs. placebo and followed for 2 years. The primary outcome is frailty (category and score); secondary outcomes are physical performance and function (short physical performance battery, 6-minute walk, lower extremity strength), systemic and skeletal muscle tissue inflammation, muscle insulin signaling, insulin sensitivity (insulin clamp), glucose tolerance (OGTT), and body composition (dual-energy x-ray absorptiometry). Safety assessments occur every 3 months; frailty, systemic inflammation, and OGTT are assessed at baseline and every 6 months, and insulin clamp with muscle biopsies are assessed at baseline and every 12 months. To date, 85 subjects have been randomized; 120 completers are planned. Mean age is 72.8 ± 5.7 years, 55.3% are male, and 43.5% were Hispanic. Mean BMI is 30.2±5.8 kg/m2, waist circumference