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

is 104.4 ±15.5 cm, fasting glucose is 102.3 ± 10.0 mg/dL, Hemoglobin A1c is 5.8 ±0.3, and glucose at 2 hours during OGTT is 167.3 ± 17.8 mg/dL. Metformin is being examined in this study as a potential therapeutic agent to prevent frailty in older adults with pre-diabetes. Findings from this trial may have future implications for the screening and potential treatment of pre-diabetes in older patients with metformin for the prevention of frailty.

CELL-BASED AND PHARMACOLOGIC HORMONE THERAPY MAINTAIN DIASTOLIC FUNCTION AFTER OVARIECTOMY IN HYPERTENSIVE RATS

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The role for hormone therapy in the maintenance of diastolic function upon ovarian senescence has not been clinically tested due to concerns for off-target health risks. We developed a cell-based hormone therapy (cHT) approach that recapitulates native cell–cell interactions between ovarian granulosa and theca cells in a 3D bioengineered construct to mimic the dynamic release of sex hormones. Our first report in ovariectomized (OVX) rats shows that cHT ameliorates various adverse somatic effects of hormone deficiency (e.g. bone loss). To extend these findings to cardiac health, we sought to determine the efficacy of cHT in preserving diastolic function in OVX-spontaneously hypertensive rats (SHR). 14 SHRs underwent bilateral OVX while 5 SHRs received sham surgery at 12 weeks of age. Following an 8-week washout, OVX rats were randomized to cHT or pharmacologic hormone therapy (pHT: E2 (10 mcg/kg/day) and P4 (2 mg/kg/day, s.c.) for 10 weeks and compared to OVX-vehicle and Sham. While uterine atrophy by OVX was minimized by cHT and pHT, hormone levels across OVX groups were not overtly different. Systolic blood pressure increased progressively over time ($P<0.01$), without a treatment effect. Even so, cHT and pHT prevented OVX-related reductions in myocardial relaxation and increases in Doppler-derived filling ($P<0.05$); paralleling the diastolic profile of Sham. Alongside superior diastolic function, 25% increases in cardiac interferon regulatory factor-4 (Irf-4) gene expression levels occurred in both hormone-treated OVX groups and Sham when compared to OVX-vehicle, suggesting a link between sex hormones and local immune modulation in the regulation of female cardiac health.

CPG METHYLATION IN AGING: TRAJECTORIES OF INDIVIDUAL SITES

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Age-related changes in methylation in a set of genomic CpGs have been shown to form a kind of molecular clocks of aging – DNA methylation (DNAm) clocks. These markers are usually based on a small set of CpGs in every case, but 1) they rarely overlap between different clocks and 2) they are interchangeable, meaning that one can remove all clock sites from a data set and make a new clock of similar precision selecting a new set from the remaining sites. Nonetheless, only a fraction of CpG sites would be suitable for DNAm clocks. We performed an extensive analysis of all CpG sites aging behavior. Previous studies were focused on identifying positions where changes in DNAm correlate with age, but in this case, some of CpGs where DNAm changes occur in a non-linear way can be overlooked. We assessed the aging trajectory of every CpG, clustered CpGs by the type of aging behavior and applied a machine learning approach to construct a new kind of DNAm clocks based on the DNAm of these clusters. Since every cluster is composed of multiple CpGs, it makes this marker resistant to a common problem of missing data. Using blood, brain, skin, colon and liver samples we were also able to investigate tissue specificity of CpGs trajectories.

DETRUSOR UNDERACTIVITY AS AN HCN-MEDIATED FAILURE OF RESILIENCE IN AGING

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Sympathetic relaxation of the bladder wall permits low pressure urine storage and allows central regulation of afferent sensitivity to volume. Impaired regulation of volume sensitivity has been linked to symptoms of underactive bladder and cystometric detrusor underactivity. Hyperpolarization-activated cyclic nucleotide-gated channels (HCN channels) are mediators of sympathomimetic-induced detrusor relaxation in young mouse bladder tissue, however in bladder strips from old female mice, HCN blockade enhanced age-diminished isoproterenol-induced relaxation. We therefore hypothesized that loss of HCN would compromise cystometric function and enhance sympathomimetic responses in old mice. Male HCN1 KO mice (20-22 mo) and their WT littermates underwent pressure-flow cystometry under urethane anesthesia to assess urinary performance at the level of the autonomic nervous system in the absence of cortical control. Following cystometry, bladders were harvested and pharmacomyography was performed on bladder strips to determine tissue-level changes in the absence of CNS input. All mice responded to continuous-fill cystometry by establishing regular filling/voiding cycles. HCN KO mice function showed discrete changes in volume sensitivity vs. WT. Bladder strip studies showed minimal response to isoproterenol regardless of HCN status, and no significant differences in response to carbachol based on HCN status. We conclude that HCN status impacts the brainstem-bladder reflexic control over urine storage/voiding, but not by regulating bladder wall tensions during filling. The absence of HCN influence on the loss of end-organ responsiveness to sympathetic control in old mice points to an increasing dependency on central control mechanisms with aging.

EFFECT OF COMBINED DASATINIB AND FISETIN TREATMENT ON SENESCENT CELL CLEARANCE IN MONKEYS

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