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 during 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 pHHT, hormone levels across OVX groups were not overly different. Systolic blood pressure increased progressively over time (P<0.01), without a treatment effect. Even so, cHT and pHHT 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% reduction in 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 carbachol 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 reflex 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 dependence on central control mechanisms with aging.
Aging is the biggest risk factor for the most serious chronic diseases and disabilities. Cellular senescence, a state in which cells stop dividing but release factors that damage other cells, may contribute to both age-related and chronic diseases. Removal of senescent cells from aged mice has been shown to delay aging and age-related disabilities. Our goal was to determine the ability of potential senolytic agents to remove senescent cells in a primate model. Several agents and combinations were tested including Fisetin, Navitoclax, combined Dasatinib and Quercetin, and combined Dasatinib and Fisetin. Here we describe the Dasatinib and Fisetin trial. Dasatinib is an FDA approved oral anticancer drug that has been used to treat chronic myelogenous leukemia in humans. Fisetin is a flavonoid that can be found in many plants, particularly strawberries, and acts as a coloring agent. After baseline measurements, six older (mean age = 21 years) female rhesus monkeys (Macaca mulatta) were given a combined oral dose of Dasatinib (5 mg/kg) and Fisetin (100 mg/kg) on two consecutive days. Animals were additionally assessed at 1- and 7-weeks following dosing. At 7 weeks post dosing, there were fewer (p<0.05) p16+ cells in the epidermis compared to baseline. Similarly, there was a reduction (p<0.05) in p21+ cells in the epidermis at 1- and 7-weeks post dosing compared to baseline. There were no negative outcomes associated with treatment. This study provides preliminary evidence for the senolytic potential of combined Dasatinib and Fisetin treatment and indicates that pharmacological mitigation of age-related changes is possible.

EPIGENETIC SIGNATURES OF CELL STATES IN AGING

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Epigenetic clocks based on DNA methylation (DNAm) show striking age correlations and predict various outcomes. Patterns of DNAm also reflect critical mechanisms in differentiation and proliferation. As such, an outstanding question is whether part of the signal epigenetic clocks are capturing represent shifts in the proportions of somatic stem cells, senescence cells, and/or tumorigenic cells. Here, we assembled various methylation datasets that captured relevant phenomena, including pluripotent stem cells, differentiation, senescence, and cancer, and performed weighted network analysis to cluster and compare DNAm modules. We find overlapping clusters between in vitro samples and in vivo tissue samples, suggesting that cell-level phenomena like cell replication, senescence, and cancer intersect with age-related epigenetic signatures. While the effects of aging manifest at multiple systems levels, from the genome to clinical phenotypes, these analyses may help provide insight to the contribution of cell phenotype dynamics to the general aging phenomenon.

EXOSOMES DERIVED FROM SENESCENT CELLS PROMOTE CELLULAR SENESCENCE

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Exosomes are one type of small-cell extracellular vesicles (sEVs), which together with the senescence-associated secretory phenotype (SASP) mainly constitute the senescent microenvironment and perform remotely intercellular communication. However, the effects of senescence on exosomes biosynthesis and secretion and its role in the cell senescence are still obscure. Here, we used human fetal lung diploid fibroblasts (2BS) passed to PD50 to construct the senescent cells model in vitro, which were confirmed by senescence-related β-galactosidase staining, cell cycle distribution, and intracellular ROS levels. PD30 2BS was used as young control. We evaluated the exosomes derived from senescence and young control group respectively and investigated their regulation of senescence. We found that exosomes released from 2BS had typical sizes and cup-shapes morphology and their surface presented typical exosome-associated proteins. The number of exosomes secreted by senescent cells was significantly higher than that of young cells. Moreover, exosomal markers Alix, TSG101, and CD63 were all more expressed than young cells. Furthermore, we treat young cells with exosomes secreted by senescent cells which can induce senescence-like changes in young cells, including increased SA-β-Gal activity, up-regulated p16 protein expression, and...