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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