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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.

ELEVATED GROWTH DIFFERENTIATION FACTOR-15 IS A BIOMARKER OF SARCOPENIA IN OLDER ADULTS

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Growth differentiation factor 15 (GDF-15) is associated with disease progression, mitochondrial dysfunction and mortality. Elevated GDF-15 level was recently reported to be associated with poorer physical performance in healthy community-dwelling adults. However, the relationship between serum GDF-15 concentration and sarcopenia in community-dwelling older adults has not been well characterized. We analyzed 929 participants (mean age 75.9±8.9 years, 48.0% men) from the Korean Frailty and Aging Cohort Study who underwent assessment of serum GDF-15 concentration and sarcopenia. Participants with an estimated glomerular filtration rate <60 ml/min/1.73 m2 were excluded from this analysis. Sarcopenia status was determined as per the Asian Working Group for Sarcopenia (AWGS) 2019 guidelines. As per the AWGS 2019 algorithm, 154 (16.6%) participants in the study population were classified as having sarcopenia. Median serum GDF-15 concentration was elevated in the sarcopenic group vs. the non-sarcopenic group (920 vs. 793 pg/ml, $p<0.001$). In the multivariate analysis adjusted for potential confounders, the highest GDF-15 tertile (≥1245 pg/ml) was associated with a higher risk of sarcopenia vs. the lowest tertile (<885 pg/ml) (odds ratio [OR] = 1.95, 95% confidence interval [CI] 1.15–3.31). This association remained unchanged (OR = 1.90, 95% CI 1.14–3.23) after further adjustment for potential biomarkers (myostatin, dehydroepiandrosterone, and insulin-like growth factor-1). The OR per unit increase in log-transformed GDF-15 concentration was 3.59 (95% CI 1.21–10.70). To conclude, our results suggest that higher circulating GDF-15 concentration was independently associated with a greater risk of sarcopenia in community-dwelling older adults. Serum GDF-15 concentration can be a promising biomarker for sarcopenia

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) passaged 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

activation of the Notch signaling pathway. The above results imply that exosomes derived from senescent cells can promote cell senescence. The findings expand the current knowledge on exosomes-mediated aging and provide a novel understanding of the relationship between SASP and senescence. This study is supported by National Natural Science Foundation of China (No. 81771520 and 31702144).

INTRANASAL OXYTOCIN IMPROVES LEAN MUSCLE MASS IN OLDER ADULTS WITH SARCOPENIC OBESITY: A PILOT STUDY

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Obese older adults often have sarcopenia with increased functional impairments. Unfortunately, conventional weight loss treatments can lead to further muscle mass loss. Increasing evidence from animal studies suggests that the pituitary hormone oxytocin has trophic effects on skeletal muscle cells and can induce weight loss. We piloted a clinical trial testing whether intranasal oxytocin would decrease adiposity without lowering muscle mass in older adults with sarcopenic obesity. Twenty-one older (≥60years), obese (30-43kg/m2), sedentary (<2 strenuous exercises/week) adults with slow gait speed (<1m/sec) were randomized to intra-nasal oxytocin (24IU four times/day) or placebo for 8 weeks. Pre and post body mass index (BMI), 2-hour oral glucose tolerance test (OGTT), hemoglobin A1c (HbA1c), short physical performance battery (SPPB), and whole body lean and fat mass (via dual-energy X-ray absorptiometry) were assessed. Generalized estimation equation method was used to evaluate effects of oxytocin on these continuous measures. At baseline, results were: age 67.5±5.4years, 71% female, BMI 36.0±3.6kg/m2, HbA1c 5.7±0.4%, 2-hr OGTT glucose 140.8±4.1mg/dL, SPPB 9.2±1.9, fat mass 45,429±7,037g, and lean mass was 49,892±10,470g. From baseline to follow-up, total lean mass increased significantly (2,250g) in the oxytocin group (pre- vs. post-treatment difference of -690g in placebo and +1,559g in oxytocin, $p<0.01$). Oxytocin did not lead to significant changes in other measures. This data suggests that oxytocin leads to significant improvement in whole body lean mass. Future studies in a larger study population will help determine whether older adults with sarcopenic obesity may benefit from intranasal oxytocin to improve lean muscle mass and physical function.

METABOLIC REGULATION OF THE SENESCENCE PROGRAM

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Cellular senescence is a cell fate defined by an irreversible cell-cycle arrest and a pro-inflammatory secretory profile. It is a consequence of a shift in metabolism and rearrangement of chromatin. Accumulation of senescent cells is a universal hallmark of age-related pathologies suggesting these cells contribute to age-related susceptibility to disease. Here, we examine the interplay between two metabolic inhibitors of senescence: Rapamycin treatment and Methionine restriction (metR). We report that a combination of methionine restriction and rapamycin induces a metabolic reprogramming that prevents activation of the senescence program in human fibroblasts. The treated cells continue to divide at a slow rate at a high passage and lack senescence-associated markers and inflammatory cytokines. Genome-wide chromatin accessibility analysis reflects chromatin remodeling with distinctly increased accessibility of heterochromatic regions in treated cells. Further, Transcriptome-wide analysis reveals increased expression of specific methyltransferases which alter the trimethylation of H3, one of the strongest hallmarks of open chromatin. This may represent a mechanistic link between a major hallmark of senescence and nuclear events required for senescence.

METFORMIN IMPROVES COGNITION BY REDUCING LEAKY GUT AND BENEFITING GUT MICROBIOME–GOBLET CELL–MUCIN AXIS

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Older adults are suffering from several aging-related illnesses including cognitive decline and effective strategies to prevent and/or treat them are lacking, because of a poor understanding of therapeutic targets. Low-grade inflammation is a key risk factor of aging-related morbidities and mortalities, and it is often higher in older adults. Although, precise reasons for increased inflammation remain unknown, however, emerging evidence indicates that abnormal (dysbiotic) gut microbiome and dysfunctional gut permeability (leaky gut) are linked with increased inflammation in older adults. However, no drugs are available to treat aging-related microbiome dysbiosis and leaky gut, and little is known about the cellular and molecular processes that can be targeted to reduce leaky gut in older adults. Here, we demonstrated that metformin, a safe FDA approved antidiabetic drug, decreased leaky gut and inflammation in older obese mice, by beneficially modulating the gut microbiota. In addition, metformin increased goblet cell mass and mucin production in the older gut, thereby decreasing leaky gut and inflammation. Mechanistically, metformin increased the goblet cell differentiation markers by suppressing Wnt signaling. Our results suggest that metformin can prevent and treat aging-related leaky gut and inflammation, by beneficially modulating gut microbiome/goblet cell/mucin biology.

MITOCHONDRIAL DYSFUNCTION AND CELLULAR SENESCENCE DUE TO AGING CONTRIBUTES TO PROSTATIC FIBROSIS

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