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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