

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 ( $\geq 60$  years), obese ( $30\text{--}43\text{ kg/m}^2$ ), sedentary ( $< 2$  strenuous exercises/week) adults with slow gait speed ( $< 1\text{ m/sec}$ ) were randomized to intra-nasal oxytocin (24 IU 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  $67.5 \pm 5.4$  years, 71% female, BMI  $36.0 \pm 3.6\text{ kg/m}^2$ , HbA1c  $5.7 \pm 0.4\%$ , 2-hr OGTT glucose  $140.8 \pm 4.1\text{ mg/dL}$ , SPPB  $9.2 \pm 1.9$ , fat mass  $45,429 \pm 7,037\text{ g}$ , and lean mass was  $49,892 \pm 10,470\text{ g}$ . From baseline to follow-up, total lean mass increased significantly ( $2,250\text{ g}$ ) in the oxytocin group (pre- vs. post-treatment difference of  $-690\text{ g}$  in placebo and  $+1,559\text{ g}$  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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