fibroblasts, and four-fold (4.18 ± 0.96 RFU, P=.003) in older cells. This study demonstrates a novel use for the widely prescribed drug combination, Sacubitril and Valsartan, which significantly improves collagen production in older adult fibroblasts.

Session 9110 (Poster)

BIOLOGY OF AGING: MITOCHONDRIA

A STUDY OF C2C12 MYOBLAST BIOENERGETICS IN RESPONSE TO THE CCG-1423 RHO A INHIBITOR

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CCG-1423 is a Rho A pathway inhibitor which has been reported to inhibit Rho/SRF-mediated transcriptional regulation. SRF and SRF cofactors, which include ternary complex factors (TCFs) and myocardin-related transcription factor (MRTF), regulate various cellular functions. The Rho/SRF signaling pathway also regulates the sirtuin 2 (SIRT2) gene that contains a classic serum response element (SRE) sequence. Current research on CCG-1423 focuses on gene expression levels of SRF in response to CCG-1423 and how SRF levels affect the cells; the studies are focused on cell morphology, migration, viability/reproduction, and overall function. The pathways of this inhibitor have yet to be fully elucidated, but several have been suggested with good evidence. Our goal is to study the effect of CCG-1423 on mitochondrial function and gene expression of cells. In this work C2C12 myoblast cells have been used as an in-vitro model to study cellular bioenergetics and variations in gene expressions induced by CCG-1423. The effect of CCG-1423 on mitochondrial function was determined by measuring the mitochondrial oxygen consumption rate and glycolysis rate after treating C2C12 cells with varying concentrations of CCG-1423 overnight. In C2C12 myoblast cells, CCG-1423 treatment significantly reduced mitochondrial oxygen consumption rate (OCR) in a dose-dependent manner. However, treatment of C2C12 cells with CCG-1423 overnight increased the extracellular acidification rate (ECAR) in a dose-dependent manner. By indicating that CCG-1423 represses mitochondrial respiration via the Rho-SRF signaling pathway, the results of this study may enable a better understanding of the bioenergetics of the cell in the aging body.

DEPLETION OF THE MIR-34A "SPONGE" MALAT1 IN AGING SKELETAL MUSCLE: IMPLICATIONS FOR AGE-RELATED MUSCLE LOSS

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We have recently shown that increased levels of reactive oxygen species (ROS) in aging skeletal muscle are associated with increased expression of the senescence-associated microRNA miR-34a-5p (miR-34a). The histone deacetylase Sirt1 is a validated target of miR-34a, and miR-34a expression is induced by the tumor suppressor p53 which is itself stimulated by ROS. Long noncoding RNAs (lncRNAs) are known to function as "sponges" for microRNAs, but the role of such competing endogenous RNAs (ceRNA) in muscle aging is not well understood. We therefore examined in skeletal muscles of young (4-6 mos) and aged (22-24) male and female mice the expression of several lncRNAs that are predicted to bind miR-34a-5p in silico and whose predicted binding has been validated experimentally. Results indicate a significant decrease in lncRNA MALAT1 expression with aging. MALAT1 is known to be highly expressed during the later stages of myoblast differentiation and myotube maturation. We therefore treated C2C12 cells at 48 hrs with hydrogen peroxide (10 uM) and examined changes in MALAT1 expression. MALAT1 was significantly decreased with H2O2 treatment, whereas miR-34a is increased in C2C12 cells after hydrogen peroxide exposure. Age-related muscle atrophy mediated by ROS may therefore result in part from related mechanisms involving miR-34a activity: an increase in miR-34a targeting Sirt1 resulting from p53 activation and an increase in miR-34a bioavailability resulting from a decline in miR-34a "sponging" due to ceRNA MALAT1 depletion. These findings suggest that therapeutic interventions increasing MALAT1 expression in muscle may potentially enhance the preservation of muscle mass with aging.

EFFECTS OF GLYCINE AND N-ACETYLCYSTEINE ON GLUTATHIONE LEVELS AND MITOCHONDRIAL ENERGY METABOLISM IN HEALTHY AGING

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Glutathione is an intracellular antioxidant that neutralizes reactive oxygen species and prevents tissue damage. Dietary supplementation with the glutathione precursors glycine and n-acetylcysteine supports the maintenance of normal glutathione levels in several age-related diseases, but the optimal doses and their efficacy in healthy elderly are not established. We report results from a randomized controlled clinical trial in 114 healthy volunteers (mean age = 65 years) receiving glycine and n-acetylcysteine (GlyNAC) at three different doses for two weeks (1.2g/1.2, 2.4g/2.4g, 3.6g/.3.6g of each amino acid). Older subjects showed increased oxidative damage and a lower reduced-to-oxidized glutathione ratio (GSH:GSSG) compared to young subjects, but unchanged total glutathione levels. GlyNAC did not increase levels of circulating glutathione compared to placebo treatment, the primary study endpoint. However, stratification analyses suggest that subjects with high oxidative stress and low glutathione status responded with glutathione generation. We find that unrelated to glutathione status, healthy aging was associated with lower levels of fasting glycine that can be increased towards those observed in young subjects with supplementation. Using preclinical models, we find