factor DAF-16/FOXO, an event that requires AMP-activated protein kinase under this condition. Importantly, animals treated with SCO are not only long lived but also show improved stress resistance in late adulthood, suggesting that this fat-promoting intervention may enhance some aspects of physiological health in older age. These findings identify SCO as a natural product that can modify fat regulation for longevity benefit and add to growing evidence indicating that elevated fat can be pro-longevity in some circumstances.

FUCOIDANS ARE NOVEL SENOTHERAPEUTICS THAT ENHANCE SIRT6 AND DNA REPAIR ACTIVITY

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With age, senescent cells accumulate in various tissues where they contribute to loss of tissue homeostasis, aging, and age-related diseases through their inflammatory senescence-associated secretory phenotypes (SASPs). Senotherapeutics able to selectively eliminate senescent cells, termed senolytics, or suppress the detrimental SASPs, termed senomorphics, have been demonstrated to improve age-associated comorbidities and aging phenotypes. To discover novel senotherapeutics translatable to promote healthy longevity, we conducted a drug screening of diverse natural products based on the characteristic senescence-associated β-galactosidase activity. Several fucoidans from different brown seaweed were found to exhibit potent senotherapeutic activity. Fucoidans are long-chain sulfated polysaccharides found in various species of brown algae including seaweed. The best senomorphic fucoidan was able to suppress senescence in cultured senescent fibroblasts, in ex vivo human tissue explants, and in vivo in mouse models of natural and accelerated aging. Specifically, fucoidan reduced markers of cellular senescence and SASP in senescent mouse and human cells. Acute treatment of the fucoidan in naturally aged mice reduced tissue senescence, especially in the kidney and lung. Chronic treatment of the fucoidan in Ercc1-/Δ progeria mice attenuated composite aging symptoms and extended healthspan. Interestingly, preliminary mechanistic studies demonstrated that fucoidan can improve non-homologous end-joining-directed DNA damage repair and increase the mono-ADP-ribosylation activity of SIRT6, suggesting a relationship between cellular senescence, DNA repair, and SIRT6 signaling pathways. Collectively, fucoidans were identified as novel senotherapeutics with translational potential for reducing cellular senescence, ameliorating age-associated phenotypes, and extending healthspan as well as able improve DNA repair pathways through modulation of SIRT6 activity.

EFFECT OF L-VALINE TREATMENT ON SIRTUIN (SIRT1 AND SIRT2) ISOFORMS

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L-valine is one of the essential branched-chain amino acids (BCAAs) required for synthesis of proteins in human body. It promotes muscle growth and tissue repair and is important for immune function. Recent data indicate that BCAAs can activate sirtuins expression and elevate mitochondrial biogenesis and fatty acid oxidation in both adipocytes and myotubes thereby increasing life span. Sirtuins are a conserved family of proteins, play a critical role in maintaining metabolic health by deacetylating many target proteins in numerous tissues, and regulate mitochondrial function and the aging process. Due to multiple effect of sirtuins on aging, we sought to determine whether the addition of valine might enhance sirtuin gene expression. We utilized the C2C12 skeletal muscle cell line grown on physiological normal glucose (100mg/dL) media. The cells were treated with two different concentrations of valine (0.5 and 1.0mM) for different time intervals (18 and 24). Gene expression of sirtuin 1 (SIRT1) and sirtuin 2 (SIRT2) isoforms were determined by RT-PCR. The results showed increased expression of the sirtuin gene isoforms after treatment with valine. Relative expression varies with in different isoforms of SIRT1 (v1 and v2) and SIRT2 (v1, v2 and v3). Among all, SIRT1 v1 and SIRT2 v1 showed maximum expression as compared to the other isoforms used in the study. Our study showed that adequate supplementation of L-valine enhanced sirtuin gene expression, which may promote healthy muscles and healthy aging.

LOSS OF HYPOXIA SIGNALING IMPAIRS RESPONSE TO AEROBIC EXERCISE IN AGED MICE

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To assess the differential effects of exercise with age, Young (Y, 10-12 weeks) and Old (O, 23-25 months) mice were subjected to regimented treadmill running or no regimented exercise. Y, trained mice experienced a significant increase in maximal distance running, maximal speed of running, and lean muscle mass in comparison to age-matched, untrained controls. O mice did not improve significantly in any of these measures following training. Transcriptome analysis of gastrocnemius from Y mice demonstrated differential regulation of 120 genes with exercise. None of these genes were similarly regulated in the O group. Genes most upregulated following exercise in Y mice were direct targets of the hypoxia signaling pathway. Immunoblotting demonstrated that aryl hydrocarbon receptor nuclear translocator (ARNT), a critical regulator of hypoxia signaling, increased 3-fold with exercise in Y mice, but this increase was absent in O mice following exercise. To assess whether this loss of ARNT in O muscle impaired the exercise response, we generated a mouse with inducible, skeletal muscle-specific knockout of ARNT (ARNT muscle (m) KO). Following regimented exercise, ARNT mKO mice did not improve maximal distance running, maximal running speed, or lean muscle mass in comparison to untrained ARNT mKO mice. Littermate, age-matched ARNT wild type mice increased significantly in all of these measures following training. Administration of ML228, an ARNT agonist, increased maximal running distance and speed in response to exercise training in O mice. These results suggest that restoration of ARNT and hypoxia signaling may restore the physiologic response to exercise in aging.