While caloric restriction (CR) provides highly robust improvements to longevity and health, dietary restriction of the essential amino acid methionine can provide similar benefits including improved metabolic function and increased longevity. Despite these similarities between CR and methionine restriction (MR), there is growing evidence to suggest they may be mediated by different mechanisms that require further elucidation. The sulfur side-chain of methionine is highly prone to oxidation, even in vivo, with redox changes of these residues potentially altering protein function and interfering with its use as a substrate. An entire family of enzymes, methionine sulfoxide reductases, have evolved in aerobic organisms to regulate the redox status of methionine. We tested the role of methionine sulfoxide reductase A (MsrA) in the physiological and metabolic benefits of MR. After three months of MR, mice lacking MsrA (MsrA KO) showed significant loss of weight, including both fat and lean mass, in comparison to wild-type mice under MR. Both MsrA KO and wild-type mice responded to MR with improvements to both glucose and insulin tolerance. However, MR MsrA KO mice showed lower HbA1c and reduced leptin compared to MR wild-type mice. Overall, our results show mice lacking MsrA have a stronger response to MR suggesting that methionine redox may play an important role in some of the mechanisms responsible for these metabolic outcomes. Further studies clarify whether MsrA could also be a potential regulator of the longevity benefits of MR.

AGE-RELATED PRESERVATION OF MOTOR NERVE CONDUCTION VELOCITY IN NEURONAL MTORC1 KNOCKDOWN MICE

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With age, peripheral nerves undergo demyelination along with overall decrease in peripheral nerve conduction velocity in both sensory and motor nerves. Loss of innervation in muscles is thought to be a major factor in causing age-related sarcopenia including a decrease in muscle function. Dietary restriction attenuates the detrimental effects of aging in mice. Reduction of mTOR signaling is hypothesized to have overlapping mechanisms with dietary restriction. Furthermore, inhibition of mTOR via rapamycin treatment is known to extend lifespan in mice as well as improve peripheral nerve myelination. Therefore, I hypothesized that reducing mTORC1 signaling in neurons would be able to ameliorate the deleterious effects of aging in peripheral nerves. An overall decrease in nerve conduction velocity was observed in both tail sensory and sural nerves with age (15 vs. 30 months). In neuronal mTORC1 KD animals, there was an age-related preservation of both sural and sciatic nerve conduction. Rapamycin treatment produced similar effects with a trend towards increased sciatic nerve conduction velocity in rapamycin-treated wild-type mice at 19 months. The preserve sciatic nerve conduction velocity could be partially explained by preserved myelination. Neuronal mTORC1 knockdown animals had more myelin in the sciatic nerve at 30 mo. as compared to age-matched controls. Overall, these data indicate that mTORC1 signaling plays a role in the age-related decline in peripheral nerve myelination as well as nerve conduction velocity. Future therapeutics could utilize rapamycin or other rapalogs to combat the decline in peripheral nerve function associated with age and other diseases as well.

SKEWED MACROPHAGE POLARIZATION IN AGING SKELETAL MUSCLE

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Skeletal muscle aging is a major cause of disability and frailty in the elderly. The progressive impairment of skeletal muscle with aging was recently linked to a disequilibrium between damage and repair. Macrophages participate in muscle tissue repair first as pro-inflammatory M1 subtype and then as anti-inflammatory M2 subtype. However, information on the presence of macrophages in skeletal muscle is still sporadic and the effect of aging on macrophage phenotype remains unknown. In this study, we sought to characterize the polarization status of macrophages in human skeletal muscle at different ages. We found that most macrophages in human skeletal muscle are M2, and that this number increased with advancing age. On the contrary, M1 macrophages declined with aging, making the total number of macrophages invariant with older age. Notably, M2 macrophages co-localized with increasing intermuscular adipose tissue (IMAT) in aging skeletal muscle. Old BALB/c mice showed increased IMAT and regenerating myofibers in skeletal muscle, accompanied by elevated expression of adipocyte markers and M2 cytokines. Collectively, we report that polarization of macrophages to the major M2 subtype is associated with IMAT, and propose that increased M2 in aged skeletal muscle may reflect active repair of aging-associated muscle damage.

AGE-ASSOCIATED INCREASE IN KYNURENINE SUPPRESSES AUTOPHAGY AND PROMOTES APOPTOSIS IN MESENCHYMAL STEM CELLS

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The age-related increase of the tryptophan metabolite, kynurenine (KYN), has been associated with osteoporosis progression. Increased activity of by Indoleamine-(2,3)-dioxygenase(IDO), are responsible for the elevation of KYN levels in bone tissue. IDO activity is elevated with age and could be a promising therapeutic target forosteopenia and osteoporosis. Previously, our group has shown that the serum level of KYN is elevated with age and correlates with bone loss in vivo. Kynurenine suppress the expression and activity of chemokine CXCL12 essential for osteogenesis, bone marrow stem cells homing. Bone Marrow Stem Cells (BMSC) cultured in 1% FBS were treated with CXCL12