Sex-specific trajectories of striated muscle aging

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Sex bias in research poses a significant concern, as most studies tend to focus primarily on males, often neglecting potential sex-specific alterations. Given the well-documented sex differences in the incidence, progression, and treatment response of chronic diseases like cancer and cardiovascular diseases, and of the aging process, it becomes imperative to consider biological sex when tailoring treatment strategies to optimize outcomes.

Aging presents a notable challenge, marked by declining quality of life and premature mortality, and understanding the sex-specific differences in age-related striated muscle remodeling, particularly regarding mitochondrial dynamics, is essential to refine anti-aging interventions. At the cardiac level, males tend to exhibit more pronounced age-related cardiac hypertrophy and fibrosis compared to females, despite no apparent age-related differences in the sex hormone signaling. Conversely, at the skeletal muscle level, females demonstrate a heightened susceptibility to age-related muscle wasting, which was correlated with decreased levels of 17β-estradiol. This muscle wasting in females was further associated with an age-related impaired mitochondrial functionality, contributing to a more severe loss of skeletal muscle mass compared to males. The discovery of sex hormone receptors on skeletal muscle mitochondria underscores the influence of sex hormones in modulating mitochondrial activity. Specifically, the observed decline in mitochondrial activity and increased susceptibility to oxidative damage in the skeletal muscle of old females were associated with decreased mitochondrial levels of the ERα receptor.

Importantly, our research demonstrated, for the first time, the uneven impact of aging on the skeletal muscle mitochondrial proteome according to the biological sex. These findings underline the need of sex-tailored approaches to manage maladaptive striated muscle remodeling, and of mitochondrion-related therapeutics research.

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FIGURE 1
Age-induced sex-specific remodeling of the skeletal muscle, highlighting the higher susceptible of females than males to the adverse effects of aging (more information in FRBM (2024) 218:68-81).