ABSTRACT

MECHANISMS OF SKELETAL MUSCLE FIBER TYPE-SPECIFIC ATROPHY AND DYSFUNCTION WITH AGING

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Human aging is accompanied by a decline in skeletal muscle mass that is exceeded by the loss of muscle strength and power, resulting in reduced mobility and functional independence. This age-related phenomenon may be attributed to 1) selective atrophy of muscle fibers expressing fast myosin heavy chain (MyHC) II isoforms and/or 2) impaired intrinsic contractile function of slow MyHC I and fast MyHC II fibers. Although previous studies have reported impaired intrinsic contractile function in older adults, technical limitations in measuring fiber size have made it difficult to determine the relative contributions of reduced intrinsic contractile properties versus fiber atrophy to age-related contractile dysfunction. Because healthy fast fibers generate 5-6x greater power than slow fibers, identifying the mechanisms underlying the divergent effects of aging on slow and fast muscle fiber size and function is critical for preserving muscle power in older adults. Therefore, the purpose of this dissertation was to determine whether intrinsic contractile dysfunction and/or fiber type-specific atrophy contribute to age-related reductions in muscle power. First, we coupled single fiber contractile experiments with three-dimensional imaging to obtain accurate cross-sectional area (CSA) measurements and assessed intrinsic contractile function in young and older males. This approach revealed intrinsic contractile function is preserved with aging in both fiber types, and the age-related reductions in fast fiber absolute force and power are primarily explained by their smaller size. We then investigated whether an increased prevalence of myonuclei expressing senescence-associated markers, γH2AX and HMGB1, contributes to fiber type-specific atrophy. The prevalence of senescent myonuclei did not differ between young and older adults and was not associated with CSA in either fiber type. In contrast, fast fiber myonuclear content was lower in older adults and closely associated with fiber CSA. Finally, we developed an imaging-based quantitative approach to measure myonuclear area positive for γH2AX in isolated muscle fibers, providing a novel method to quantify the extent of fiber type-specific myonuclear DNA damage. Collectively, these studies suggest that the age-related decline in muscle power is due primarily to fast fiber atrophy and identify reduced myonuclear content as a key feature of fiber type-specific atrophy with aging.