Interstitial mesenchymal progenitors are crucial for homeostatic skeletal muscle integrity

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Sarcopenia, comprising the loss of skeletal muscle mass and strength, constitutes an important health problem associated with adverse outcomes such as disability, poor quality of life, and even death. Decline in muscle strength precedes the loss of muscle mass in older adults, suggesting decreased muscle quality as causal factor of sarcopenia. One of the notable changes in muscle quality during aging is the increase in fat infiltration, which is attributable to interstitial mesenchymal progenitors. However, the precise mechanism by which these cells contribute to sarcopenia remains unknown. Here we show the essential role of mesenchymal progenitors in the maintenance of steady state skeletal muscle by generating mesenchymal progenitor-depleted mice. Specific ablation of mesenchymal progenitors led to phenotypes markedly similar to sarcopenia including muscle weakness, myofibre atrophy, fibre type alteration, and denervation at neuromuscular junctions. Through searching for genes responsible for mesenchymal progenitor-dependent muscle maintenance, we found that bone morphogenetic protein 3b (Bmp3b) is specifically expressed in mesenchymal progenitors whereas its expression level is significantly decreased by aging or adipogenic differentiation. The functional importance of Bmp3b in maintaining muscle mass was demonstrated by using knockout mice and cultured muscle cells treated with recombinant BMP3B. Furthermore, administration of BMP3B to aged mice resulted in improved energy metabolism and an increase in muscle mass and strength. These results reveal previously unrecognized mechanisms whereby interstitial mesenchymal progenitors ensure muscle integrity and suggest that age-related changes of mesenchymal progenitors contribute to sarcopenia. Our study highlights a critical role of stromal components to sustain parenchyma, raising the possibility of the broader importance of such mesenchymal-parenchymal interactions in diverse tissue homeostasis.

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