Muscle Atrophy and the Sestrins

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Major loss of muscle protein (atrophy, or wasting) is commonly seen in old age (sarcopenia), in cases of muscle disuse or denervation, and in systemic inflammatory catabolic states. Loss of skeletal muscle mass and function has mental, social, and physical health consequences that diminish quality of life and increase the risk of additional complications and death. Its treatment remains unresolved. In this regard, two reports on skeletal muscle metabolism by Segalés et al. and Kim et al. provide data that may extend our understanding of the dynamics involved in muscle wasting.

As the largest and most labile reserve of protein in the body, skeletal muscle constantly adapts its mass and function to both physiologic and pathologic stimuli by altering flux through signaling pathways that influence protein turnover. Although several signaling pathways that regulate muscle atrophy have been identified (Fig. 1A), attempts to halt atrophic signaling have been unable to clinically mitigate muscle atrophy. In addition, mitochondrial metabolic dysfunction is a concomitant feature in pathologic muscle proteolysis. Using transcriptome, metabolism analyses, and genetic techniques in fly and rodent models, Segalés and Kim and their colleagues shed light on previously unrecognized roles of three proteins, the sestrins, in muscle mass and function. Sestrins are the products of three genes: SESN1, SESN2, and SESN3. They are stress-inducible metabolic regulators that effect antioxidant functions and bring about metabolic benefits by inhibiting signaling of the mechanistic target of rapamycin (mTOR) complex 1 (mTORC1), which senses and integrates nutritional and environmental cues and affects cell growth, metabolism, and inflammation.

Muscle wasting, including sarcopenia, occurs when the activity of protein degradation pathways exceeds that of synthetic pathways. Muscle proteolysis occurs mainly through the actions of E3 ubiquitin ligases (enzymes that mark proteins for degradation). Knocking out ubiquitin ligase in a mouse model was effective in mitigating disuse atrophy. On the other hand, autophagy (a process that removes damaged or redundant cellular components, which is often disrupted in pathologic states) is like a double-edged sword: impaired autophagy induces profound muscle wasting in mice, whereas excessive autophagy also contributes to muscle wasting by augmenting protein breakdown. Two endogenous hormones, insulin and insulin-like growth factor 1 (IGF-1), can restrain autophagy by activating the Akt–mTORC1 signaling pathway and its downstream effectors. In addition, activated Akt inhibits proteolysis by phosphorylating forkhead box O transcription factor (FOXO) proteins, preventing them from entering the nucleus, where they activate the transcription of muscle-specific E3 ubiquitin ligases (Fig. 1A). Unfortunately, Akt–mTORC1 activation with exogenous insulin or IGF-1 has shown limited success in counteracting pathologic muscle wasting in a rat model, partly because skeletal muscle cells become insulin resistant during atrophy. In addition, persistent Akt–mTORC1 activation has been linked to obesity-associated metabolic syndromes, some cancers, and cardiac dysfunction.

Endurance exercise has been shown to have remarkable metabolic benefits (e.g., increased insulin sensitivity and decreased inflammation) and muscle hypertrophy, in part through activating 5′ adenosine monophosphate-activated protein kinase (AMPK) and a transcriptional coactivator, peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α), which promotes mitochondrial function and biogenesis.
How do the sestrins benefit muscle? Segalés reports that the expression of sestrin 1 is decreased in muscle-atrophy models (disuse, denervation, or aging) in concert with activation of FOXO proteins and thus with the activation of muscle-specific E3 ubiquitin ligases and proteolytic processes. Consistent with these findings is the observation that the expression of sestrins is
comparatively low in the skeletal muscle of aged and frail humans. Moreover, the researchers found that muscle-specific knockout of sestrins in mice exaggerated the breakdown of muscle protein and that the overexpression of muscle-specific sestrins prevented muscle changes in the models tested. This protection was associated with activated Akt, phosphorylation of FOXO proteins, and decreased expression of the FOXO-mediated catabolic genes. Thus, the study by Segalés and colleagues identified sestrins (sestrin 1 and sestrin 2) as integrators of both anabolic and catabolic pathways and as protectors of muscle against atrophy.

Using fly and mouse models, Kim et al. elucidated sestrins as molecular transducers of the beneficial effects of exercise, including enhanced endurance and improved insulin signaling. Chemical inhibition or genetic ablation of sestrins prevented the organism from acquiring exercise benefits in terms of time and intensity of voluntary or forced exercise. Conversely, overexpression of sestrin 1 or sestrin 2 was sufficient to partially reverse the negative effect of immobility and old age, including loss of muscle mass and strength (Fig. 1B).

Conventional thinking has it that Akt-mediated mTORC1 activation benefits muscle by driving protein synthetic pathways. However, the effects of mTORC1 activation on protein synthesis are dependent on upstream activators (e.g., insulin, amino acids, and proinflammatory cytokines), timing (transient or persistent), and the magnitude of activation and cellular context. Persistent mTORC1 activation suppresses Akt-pathway activity and autophagy. Previous studies have also indicated that mTORC1 activation that is not accompanied by Akt activation promotes denervation-induced muscle atrophy9 and sarcopenia,10 partly by inhibiting Akt-mediated phos-
phorylation of FOXO proteins. Consistent with these findings, Segalés et al. found that sestrin expression in immobilization and old age dialed down Akt-unrelated mTORC1 hyperactivation to normal levels. This process promoted increased Akt activity and FOXO phosphorylation, which in turn led to decreased expression of major FOXO-regulated atrogenes (i.e., genes encoding proteolytic enzymes that promote muscle atrophy) and mitigated suppressed autophagy flux while enhancing mitochondrial biogenesis and function.

The use of endurance training to improve muscle function is not a viable option for many patients with muscle wasting, including sarcopenia, owing to disease-related apathy, age-related frailty, morbid obesity, or limited physical capacity. Drugs to reverse muscle wasting have been found to be effective in animal models, but none have been approved by the Food and Drug Administration for the reversal of muscle atrophy in clinical practice. The work of Segalés and Kim and their respective colleagues support further investigation of small-molecule inducers or activators to target sestrins in muscle as part of the search to find ways to reverse pathologic muscle wasting.

Disclosure forms provided by the authors are available at NEJM.org.

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