Insulin-Like Growth Factor I: The Yin and Yang of Muscle Atrophy

Skeletal muscle is the largest pool of protein in the body. Maintenance of its mass involves a delicate balance between protein synthesis and degradation. The dynamic nature of muscle is evident when one considers that healthy adults turn over 3.5–4.5 g of protein/kg body mass per day (1). Therefore, a small, sustained change in either synthesis or degradation can have a significant impact on muscle mass if not countered by an offsetting change in the reciprocal process. Muscle atrophy, defined as the unintentional loss of 5–10% of muscle mass, is a frequent consequence of many catabolic conditions (e.g., diabetes, cancer, sepsis) and is associated with reduced quality of life and increased morbidity and mortality (2). For example, severe loss of muscle mass is a poor prognostic indicator in cancer patients (3). Several recent studies (4–6), including a report in this issue by Dehoux et al. (4), are beginning to provide insights into the molecular mechanisms that are responsible for muscle wasting. Based on these reports, it is evident that IGF-I and insulin are important determinants of muscle mass by virtue of their ability to promote growth and suppress protein degradation.

IGF-I promotes muscle growth by stimulating muscle satellite cells and their differentiation (7). In mature muscle cells, IGF-I and insulin stimulate protein translation by activating the mammalian target of rapamycin (mTOR), which phosphorylates the translation initiation factor 4E-binding protein (4E-BP1) and the 70-kDa ribosomal protein S6 kinase (p70S6K) (8, 9). Conversely, when the levels of IGF-I and insulin are insufficient or catabolic signals (e.g., glucocorticoids, cytokines) are increased, increases in protein degradation (10–13).

Studies of experimental animals and patients have consistently demonstrated that protein degradation by the ubiquitin-proteasome (UbP) system is increased in muscle undergoing atrophy (1, 14). The 26S proteasome is a large proteolytic complex that degrades proteins that have been modified by the addition of a polyubiquitin chain (15, 16). Conjugation of ubiquitin to proteins occurs in a series of steps involving distinct enzymes or enzyme complexes. The key enzymes in this process are the E3 ubiquitin ligases, one of the largest functional families of proteins in mammals. The E3 ligases act as the substrate recognition component of the ubiquitin conjugation machinery and prevent proteins from undergoing non-specific modification. Notably, two E3s are expressed uniquely in muscle (17, 18). Both proteins were identified during screens for mRNAs whose expression is significantly increased during muscle wasting. Atrogin-1, also known as MAFbx, is a member of the SCF (Skp-cullin-F box protein complex) subfamily of E3 ligases; MuRF1 belongs to the RING (really interesting new gene) finger E3 ligase subfamily. When muscle atrophy was induced by denervation in mice that do not express either MuRF1 or MAFbx/atrogin-1, significant muscle sparing was noted compared with their wild-type littermates (17). This outcome implies that the muscle-specific E3 ligases play important roles in the atrophy process. At the present time, the substrates of these E3s are unknown. Therefore, further study of the MAFbx/atrogin-1 and MuRF1 E3s is needed to better understand their role in muscle atrophy.

A number of diverse signals have been proposed to stimulate muscle proteolysis; however, there do appear to be some common features in the proteolytic responses to different catabolic conditions. For example, a program of transcriptional events occurs including increased expression of genes that encode UbP system components (19–21); MAFbx/atrogin-1 and MuRF1 are two of the most highly regulated genes. In this issue of Endocrinology, Dehoux and colleagues (4) report that giving IGF-I to either fasting rats or rats with acute diabetes induced by streptozotocin attenuated their muscle wasting and reduced the level of several UbP system mRNAs including MAFbx/atrogin-1 mRNA. They then investigated how IGF-I reduces MAFbx/atrogin-1 mRNA expression in C2C12 cells and found that MAFbx/atrogin-1 mRNA stability was unchanged by IGF-I. Others have recently demonstrated that the FOXO (Forkhead box-containing protein, O-subfamily) transcription factors are important regulators of MAFbx/atrogin-1 and MuRF1 expression (5, 6, 22) (Fig. 1). IGF-I or insulin stimulates phosphoinositide 3-kinase and its downstream effector, Akt, which phosphorylates the FOXO proteins (for a review of the metabolic effects of FOXO, see Ref. 23). Phosphorylated FOXO proteins are unable to translocate to the nucleus, where they promote the transcription of muscle-specific E3 ligase genes and perhaps others. Catabolic hormones (e.g., glucocorticoids) or conditions that interfere with IGF-I/insulin signaling decrease the phosphorylation of FOXO and increase the expression of MAFbx/atrogin-1 and MuRF1 (5, 6). Notably, FOXO proteins also may negatively impact protein synthesis, a response that would exacerbate the physiologic effects of FOXOs on protein degradation. A recent study in C. elegans suggests that FOXO homologs may suppress TOR activity by decreasing expression of the homolog of raptor (regulatory-associated protein of mTOR), a protein that associates with mTOR and facilitates substrate interactions (24).

IGF-I/insulin may also inhibit muscle proteolysis by mechanisms independent of FOXO proteins. Both hormones...
act as survival factors that prevent apoptosis, in part, by suppressing the caspase family of proteases in many cell types (25). Recently, caspase-3 was shown to cleave actin into fragments that are degraded by the UbP system (26). Why is this notable? Monomeric actin and myosin can be degraded directly by the UbP system, but surprisingly, actomyosin and contractile proteins in myofibrils are resistant to degradation by this proteolytic pathway (27). These findings raise questions about how muscle contractile proteins are degraded during atrophy. Caspase-3 cleaves actin in actomyosin and myofibrils to produce a characteristic 14-kDa fragment that was abundant in rat muscles undergoing atrophy due to diabetes (26). Depriving cultured muscle cells of serum also increased caspase-3 activity and actin cleavage; both responses were prevented by simply supplementing the serum-starved cells with IGF-I (26). These findings are consistent with the known antiapoptotic actions of IGF-I/insulin, but exactly how these anabolic hormones suppress caspase-3 activity in skeletal muscle is poorly understood. In other cell types, IGF-I/insulin has been reported to block activation of the intrinsic apoptotic caspase cascade by suppressing the activities of BAD/BAX and other pro-apoptotic proteins (25, 28) (Fig. 1). IGF-I/insulin may also enhance the association between the endogenous inhibitors of apoptosis proteins and caspases, an interaction that inhibits the proteolytic activity of the caspases (29).

In summary, IGF-I/insulin is an important regulator of muscle mass. In healthy individuals, these anabolic factors maintain muscle mass by enhancing protein synthesis and suppressing proteolysis. When catabolic conditions that decrease the levels of IGF-I/insulin (or reduce their effectiveness) persist or muscle becomes injured, a number of proteolytic responses occur. The result is the destruction of muscle proteins if there is no offsetting increase in protein synthesis. The reports by Dehoux and others provide tantalizing glimpses into the potential usefulness of IGF-I as an agent to combat muscle atrophy. Future studies will undoubtedly identify more ways that IGF-I/insulin act to preserve muscle mass.

References

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