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highlighted topics

Exercise Effects on Muscle Insulin Signaling and Action
Invited Review: Autocrine/paracrine IGF-I and skeletal muscle adaptation

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Adams, Gregory R. Invited Review: Autocrine/paracrine IGF-I and skeletal muscle adaptation. *J Appl Physiol* 93: 1159–1167, 2002; 10.1152/japplphysiol.01264.2001.—This brief review presents the basic premises suggesting that insulin-like growth factor I (IGF-I), functioning in an autocrine/paracrine mode, is an important mediator of skeletal muscle adaptation. Key intracellular signaling mechanisms associated with ligation of the primary IGF-I receptor are highlighted to illustrate the mechanisms by which IGF-I may promote muscle hypertrophy. In addition, a number of recent findings are presented that highlight the potential for interactions between IGF-I-related signaling pathways and intracellular signaling mechanisms activated by cytokines or hormonal systems.

insulin-like growth factor I; hypertrophy; cytokine; calcium

INSULIN-LIKE GROWTH FACTOR I (IGF-I) is the primary mediator of many of the responses regulated by growth hormone in tissues throughout the body (15, 116). In addition, it has long been recognized that IGF-I and IGF-II are important for the pre- and postnatal development of skeletal muscle (13, 38). In the specific context of IGF-I as it relates to muscle, the objectives of this review are twofold: *1*) to briefly outline some of the key factors that have led to the continued interest in IGF-I as a potential mediator of loading-induced skeletal muscle adaptation and *2*) to widen the discourse on IGF-I via the inclusion of topics that appear to have received less notice in the muscle-related IGF-I literature. The format will be that of a brief review and thus will not be exhaustive in nature. For readers seeking more depth, there are a number of excellent reviews available in the literature (e.g., Ref. 96).

LOCAL CONTROL OF SKELETAL MUSCLE ADAPTATION

It has become increasingly clear that skeletal muscle is constantly adapting to the functional demands imposed by the load-bearing activities of the individual. In mammalian skeletal muscle, this adaptation process can include changes in both the size and the structural/functional properties of the myofibers. The focus on IGF-I, as well as a number of other growth factors, has been driven in part by the recognition that activity-induced skeletal muscle adaptation is largely mediated by intrinsic mechanisms. Interestingly, a number of studies have demonstrated that adaptations such as muscle hypertrophy can occur even when the somatic milieu would be considered nonanabolic. For example, in rats, the circulating hormone and growth factor milieu can be drastically depressed via surgical hypophysectomy (Hx), which prevents further somatic growth. However, despite this depression of the somatic growth factor environment, the muscles of Hx rats can respond to increased loading with substantial compensatory hypertrophy (40). In this model, the circulating and tissue levels of IGF-I are substantially decreased in Hx rats, but the compensatory hypertrophy process includes a robust increase in the expression of IGF-I mRNA and peptide in the overloaded muscles (2, 30).

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MUSCLE REGENERATION

To understand the importance of intrinsic regulation via autocrine/paracrine signaling, it is instructive to consider some cellular processes, such as myofiber regeneration, which appear to be modulated by IGF-I. In models of severe muscle injury, the death of myofibers leaves behind the basal lamina and some satellite cells. Satellite cells are small mononucleated skeletal muscle stem cells[1] located between the basal lamina of the muscle and the sarcolemma of myofibers. As a result of the injury to myofibers, these satellite cells are mobilized to begin the regeneration process (26, 75, 77, 93). The initial events after satellite cell activation have been reported to be a proliferative response in which some or all of the activated satellite cells undergo at least one mitotic cycle (75, 83, 94). After this initial phase, some of the activated cells and/or their progeny are thought to differentiate into myoblast-like cells. In regenerating muscle, these myoblasts can either fuse with each other to form new myofibers or become incorporated into damaged but surviving myofibers (11, 57, 65, 77, 78). If the capacity of satellite cells to proliferate is eliminated, for example via irradiation, the regeneration process is inhibited (26, 42, 75). There is evidence that locally produced, i.e., autocrine/paracrine IGF-I, may be important in this regeneration process. Jennische et al. demonstrated that increased IGF-I immunoreactivity can be detected in the cytoplasm of myoblasts and myotubes (44) as well as in satellite cells (45) during muscle regeneration. Furthermore, the introduction of neutralizing antibodies, which prevent either IGF-I or fibroblast growth factor (FGF-2) activity, has been shown to reduce the number and size of regenerating myofibers after muscle injury with anti-IGF-I treatment demonstrating a higher potency (53).

INTRACELLULAR IGF-I SIGNALING

With the muscle regeneration process in mind, an examination of the known effects of IGF-I on skeletal muscle cells provides insight into potential mechanisms by which this growth factor may contribute to muscle repair or adaptation. In studies involving both established cell lines and primary satellite cell cultures, ligation of the type 1 IGF-I receptor (IGFR1) has been shown to initiate intracellular signaling cascades involved in key mitogenic and myogenic responses (25, 38, 79). One pathway activated by IGF-I involves Ras-Raf signaling to extracellular response kinases (ERKs), which can activate a number of transcription factors as well as other protein kinases. In muscle cell cultures, this pathway has been shown to promote increased cell proliferation (Fig. 1) (e.g., Ref. 25). A second pathway involves phosphorylation of insulin receptor substrate and leads to the activation of phosphatidylinositol 3-kinase (PI3K) (Fig. 2). PI3K activation is central to a

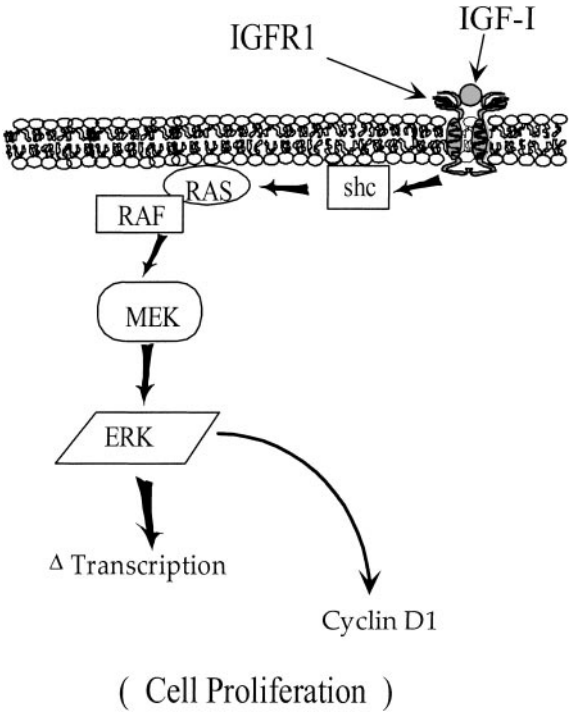

Fig. 1. The Ras-ERK signaling cascade. A simplified diagram of one intracellular signaling pathway associated with tyrosine kinase activity of the type 1 insulin-like growth factor receptor (IGFR1). A number of studies have linked this pathway with the control of muscle cell proliferation in vitro. The phosphorylation targets of ERKs include transcription factors and additional protein kinases. ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase (MAPK)/ERK kinase; Raf, MAPK kinase kinase; Ras protein, member of the Ras GTPase family; Shc, SH2-containing collagen-related proteins (couples IGFR1 tyrosine kinase to Ras).

number of important cellular processes, including protection from apoptosis, increased translation, and alteration in intracellular calcium. PI3K activation increases the initiation of translation via alterations in the phosphorylation state of eukaryotic initiation factor 4 binding protein and the p70 S6 kinase (Fig. 2). The activation of p70 S6-kinase is of particular interest in that it enhances the translation of mRNAs encoding ribosomal proteins and elongation factors, integral components of the protein synthesis machinery (106). In addition to generalized anabolic effects, activation of portions of the PI3K signaling cascade appear to be particularly important for the differentiation of muscle cell lines in culture (16, 17, 25, 52, 105, 107, 110).

It is important to note that the activities of the pathways depicted in Figs. 1 and 2 are conditional, i.e., the outcomes are based on a complex set of interactions yet to be comprehensively identified. For example, there are reports that both ERK and PI3K activity act in concert in some cell types (e.g., Refs. 62, 117) and that both may be required for the differentiation of myoblasts (89). In contrast, others have reported that the activity of one pathway may actually inhibit the other (80, 88, 117, 119). As an example of the conditional nature of the effects of signaling through the PI3K pathway, Chakravarthy et al. (19) recently re-

[1] There is evidence that multiple muscle stem cell populations may be contributing to processes traditionally ascribed to satellite cells (e.g., Refs. 26, 118).

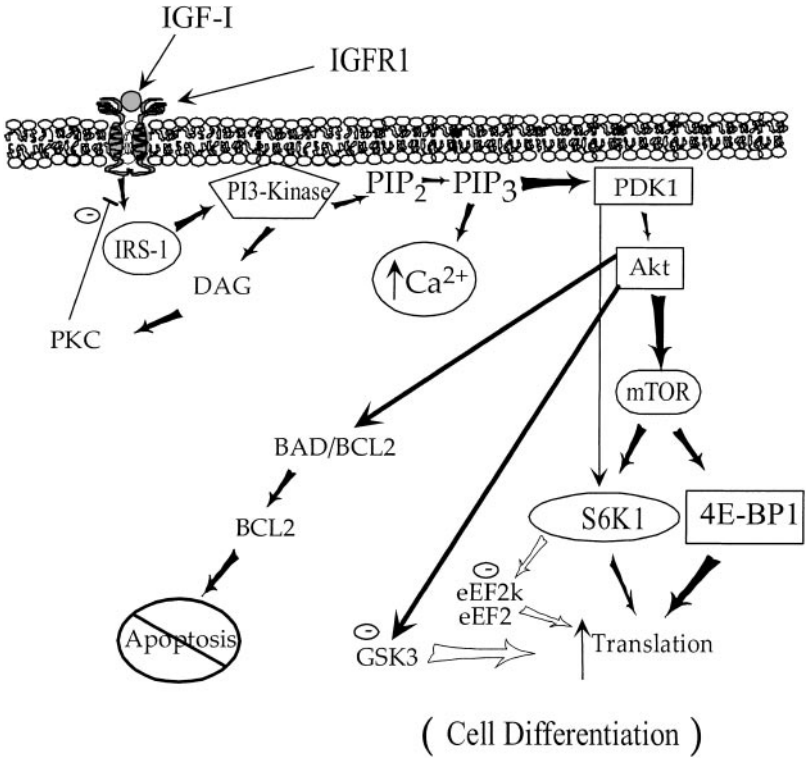

Fig. 2. The IRS-PI3K signaling cascade. Signaling through PI3K is central to a large number of processes in mammalian cells. In this greatly simplified diagram, one of the primary pathways leads to increased translation initiation and increased production of components of the transnational system. Also shown is the pathway for protection from apoptosis and that which can mediate increased cytoplasmic calcium levels. DAG-induced increases in PKC activity have the potential to feed back and prevent the phosphorylation of IRS-1. For clarity, potential interactions between the Ras/ERK pathway (Fig. 1) and calcineurin and G-protein receptor signaling have been omitted. Akt, protein kinase B; BAD, proapoptotic regulator of programmed cell death; Bcl2, regulator of programmed cell death, promotes cell survival; DAG, diacylglycerol; 4E-BP1, eukaryotic initiation factor 4 binding protein; eEF2, eukaryotic elongation factor-2 (k = kinase); GSK3, glycogen synthase kinase 3; IRS, insulin receptor substrate; mTOR, mammalian target of rapamycin; PI3-kinase (PI3K), phosphotidylinositol 3-kinase; PIP_2, phosphatidylinositol 3,4-bisphosphate; PIP_3, phosphatidylinositol 3,4,5-trisphosphate; PDK1, PI3K-dependent kinase; PKC, protein kinase C; S6K1, p70 S6 kinase.

ported that inhibition of PI3K signaling in satellite cell cultures can prevent the completion of the cell cycle, inducing arrest in the G_1 phase. Under physiological conditions, G_1 arrest would be expected to lead to either cell differentiation or apoptosis. The finding that inhibition of this signaling pathway stimulates cell cycle arrest would suggest that, under some conditions, signaling through PI3K is important for the continuation of cellular proliferation as opposed to the commonly ascribed differentiation response.

Interestingly, the processes of cellular proliferation (i.e., mitotic activity) and differentiation (i.e., expression of muscle-specific proteins) are generally thought to be mutually exclusive. In fact, in a number of cell types, activation of one of the two primary signaling pathways associated with ligation of growth factor receptors (e.g., Fig. 1 vs. Fig. 2) will generally inactivate portions of the other (80, 88). Among the well-characterized growth factors, IGF-I is relatively unique in that it has been reported to stimulate both proliferation and differentiation[2], depending on timing and intracellular conditions (84, 108).

The intracellular signaling pathways that subserve IGFR1 ligation also represent potential points for interactions between IGF-I-induced responses and those initiated by other mediators. For example, there is evidence that signaling via G-protein receptors may interact with IGF-I receptor-related pathways modulating or even blocking some responses (e.g., Refs. 48, 58). There is also a growing body of data that suggests that there are interactions between the calcineurin- and IGF-I-signaling pathways in skeletal muscle (e.g., Refs. 29, 67). This is of particular interest in that calcineurin-IGF-I interactions would provide a another mechanism linking cellular calcium homeostasis to IGF-I signaling.

MUSCLE ADAPTATION TO INCREASED LOADING

There is evidence that the mitogenic and myogenic effects of IGF-I that render it useful for muscle regeneration might also be important for the adaptation of muscle to increased loading as well. A number of in vivo activity models, such as increased loading, stretch, and "eccentric contraction," are known to result in increased IGF-I and/or IGF-I mRNA expression in muscle cells (2, 3, 9, 30, 46, 86, 92, 97, 114, 115). Furthermore, experimental manipulations of muscle IGF-I levels have been shown to induce muscle hypertrophy both in vitro and in vivo (4, 24, 109). For example, overexpression (24) or direct infusion (4) of IGF-I in muscle results in hypertrophy, whereas inhibition of intracellular signaling components associated with IGFR1 ligation can prevent this response (14). Overexpression of IGF-I in muscle has also been shown to prevent some of the age-related effects on skeletal muscle, such as the decline in muscle mass (10, 68). However, muscle IGF-I overexpression in a transgenic model did not prevent atrophy due to acute muscle unloading (27).

THE AUTOCRINE/PARACRINE IGF-I SYSTEM

One of the more interesting recent developments in the IGF-I story has been the identification of a unique

[2]A number of growth factors, such as FGF-6 and hepatocyte growth factor, are being actively investigated in this respect, but to date the results have not proved conclusive in in vivo models.

IGF-I isoform that is expressed in response to changes in the loading state of skeletal muscles (115). This isoform, mechanogrowth factor (MGF), has been shown to be markedly upregulated in response to both stretch and increased loading (61, 70). It appears that skeletal muscles produce both a generalized tissue-type IGF-I (1) and the loading-sensitive MGF isoform with differing time courses, suggesting distinct roles for these two growth factor isoforms (70). Expression of both IGF-I and MGF appears to be very sensitive to the loading state of the muscle. For example, we recently found that IGF-I and MGF mRNA increased significantly within a few hours after a single bout of resistance-type exercise in rat muscles (unpublished observations).

In addition to IGF-I itself, there is evidence that cells in muscle produce other components of the IGF-I regulatory system (8, 12, 60). For example, Awede et al. (8) reported that overloaded muscles in mice increased the expression of IGF binding protein 4 (IGFBP4) mRNA, whereas that of IGFBP5 was decreased. In contrast, unloading of mouse muscle resulted in an increase in IGFBP5 mRNA, whereas that of IGFBP4 was unchanged (8). In general, IGFBP4 and IGFBP5 would be expected to modulate the effects of IGF-I via regulation of the free IGF-I concentration in muscle and possibly via competition with IGF receptors for IGF-I (11). These findings provide further support of the idea that the autocrine/paracrine IGF-I system is active in skeletal muscle and sensitive to the loading state of the muscle.

THE "MYOGENIC" COMPONENT OF MUSCLE ADAPTATION

As with myofiber regeneration, a number of processes that IGF-I is known to stimulate would also promote skeletal muscle hypertrophy. The utility of the insulin-like anabolic effects for promoting muscle hypertrophy is obvious (71, 85). However, the importance of IGF-I-induced actions on muscle satellite cells may be less evident. In the case of the hypertrophy response, there appears to be a "myogenic" component wherein satellite cell-derived myoblasts are thought to fuse with existing myofibers much as they would with damaged but still viable myofibers after injury (22, 66, 87, 91, 98). The importance of this response stems from the observations that mature mammalian skeletal muscle fibers appear to maintain a relatively finite, fiber type-specific relationship between the size of the myofiber and the number of myonuclei present in a given myofiber (5, 6, 23, 34, 43, 59, 63, 99, 102, 104). However, mammalian myofibers become permanently differentiated shortly after birth and cannot undergo mitotic division or directly increase their myonuclear number (i.e., myonuclear division) (22). The requirement for additional nuclei to support hypertrophy appears to be met via the proliferation, differentiation, and finally the fusion of muscle satellite cells or their progeny with the enlarging myofibers, providing the new myonuclei needed to support the hypertrophy process (5, 63, 72, 81, 82, 91) (Fig. 3). Among the well-characterized growth factors, IGF-I is the only one that

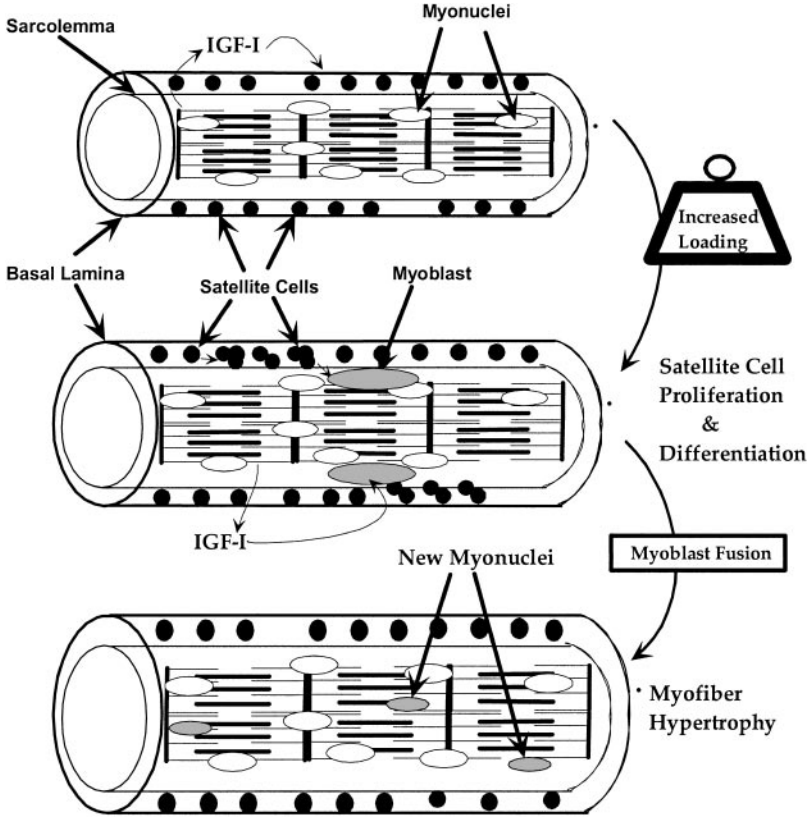

Fig. 3. IGF-I and "myogenesis" during compensatory hypertrophy. Increased loading leads to satellite cell proliferation, differentiation, and fusion. IGF-I has been shown to stimulate these myogeninc processes in skeletal muscles. It is postulated that IGF-I, and/or the loading-sensitive IGF-I isoform mechanogrowth factor (MGF), is produced and released by myofibers in response to increased loading or stretch. The increased local concentration of IGF-I (MGF) would then stimulate the myogenic processes needed to drive the hypertrophy response.

has been consistently reported to facilitate each of these processes.

Interestingly, relatively acute overexpression of IGF-I has been shown to increase the number of times that satellite cells can replicate, possibly explaining some of the palliative effects of this treatment on age-related changes in skeletal muscle cited above (19–21). However, chronic overexpression of IGF-I appears to exhaust the replicative capacity of satellite cell in vivo and thus does not prevent age-related declines in proliferation (21).

IGF-I AND EXCITATION-CONTRACTION COUPLING

In addition to the anabolic and myogenic effects attributed to IGF-I, this growth factor also appears to have the ability to modulate components of the excitation-contraction coupling mechanism in vivo. Skeletal muscle dihydropyridine receptors (DHPR) are L-type calcium channels that act as the voltage sensor in the transverse tubular system. The primary function of these L-type channels appears to be the detection of depolarization and the direct activation of the calcium release channels in the sarcoplasmic reticulum (49). Unlike the cardiac version of DHPR, the inward current carried by these channels in skeletal muscle does not appear to be important in the acute regulation of excitation contraction coupling (49). However, it is possible that the slow inward conductance of Ca^{2+} may have some function with regard to long-term intracellular calcium signaling. In cell culture, IGF-I induces an increase in DHPR that results in a significant increase in charge movement (112). In vivo, overexpression of IGF-I in muscle results in a significant increase in DHPR receptor concentration in both fast-twitch and slow-twitch skeletal muscles (74). In addition, IGF-I-induced increases in DHPR appear to ameliorate age-related effects on contractile function in mice (73). To date, the potential impacts of IGF-I on excitation-contraction coupling have received relatively less attention than the myogenic and anabolic aspects detailed above.

IGF-I AND PROINFLAMMATORY CYTOKINES

There have been reports that prolonged and/or intense exercise may result in significant increases in circulating levels of proinflammatory cytokines such as interleukin (IL)-6 and/or IL-1β (33, 64, 69, 100, 113). Interestingly, there are reports that exercise can increase proinflammatory cytokines and concurrently depress circulating IGF-I in children (35, 90). In general, the cellular and molecular effects of exercise-induced cytokine responses on the IGF-I system have not been extensively evaluated in the context of exercise. However, it is known that in disease states such as sepsis the elevated proinflammatory cytokine levels can either directly or indirectly mediate catabolic effects on skeletal muscle (36, 37, 39, 50, 51, 54, 55). In direct relation to the IGF-I system, Fan et al. (36) found that systemic injection of IL-1β or tumor necrosis factor-α (TNF-α) resulted in a reduction in muscle IGF-I in rats. In a similar finding, Lang et al. (50) reported that systemic sepsis is associated with a decline in skeletal muscle and plasma IGF-I. These authors found that blocking the IL-1 receptor prevented the decline of IGF-I in skeletal muscle and reduced the degree of IGF-I decrease seen in the plasma. The IL-1 blockade also prevented the 43% decrease in skeletal muscle protein synthesis-induced by the septic state. Thus it appears that the anti-anabolic and/or catabolic effects of cytokines such as IL-1β may be mediated at least in part via the IGF-I axis.

In addition to indirect effects such as a decrease in circulating IGF-I, there is evidence that some cytokines may interact with intracellular IGF-I receptor signaling. One area of intersection involves intracellular signaling via the Janus-activated kinases (JAK) and signal transducers and activators of transcription (STAT), which participate in cytokine signaling (47). Recent evidence suggests that the IGF-I receptor may also activate JAK/STAT signaling (41, 56, 103, 120). Among the targets for STATs are a family of suppressors of cytokine signaling, which act as part of a negative feedback loop to the cytokine receptors. This raises the possibility that elevated cytokine signaling could also feedback to and possibly inhibit the IGF-I receptor as well (31, 32, 103). This would provide an indirect mechanism for the inhibition of IGF-I signaling whereby increased proinflammatory cytokine levels might stimulate the production of suppressors of cytokine signaling, which would then feedback to both the cytokine and IGF-I receptors. It is also possible that proinflammatory cytokines modulate IGF-I less directly via increasing circulating corticosteroid levels (51). Both endogenous and exogenous glucocorticoids are known to modulate both IGF-I abundance and IGF-I effects in muscle (28, 36, 51, 95, 96).

In a seemingly paradoxical set of findings, it has been shown that the proinflammatory cytokines IL-6 and TNF-α stimulate the proliferation of satellite cells or myoblasts in vitro (7, 18, 101, 111). This suggests that there may be a role for components of the inflammatory response in muscle adaptation (111). It is tempting to speculate that a potential role of inflammatory responses in muscle adaptation may be a function of the degree of response and as such that this may be one of the mechanisms that separates training from overtraining (97).

SUMMARY

The continued interest in the role of IGF-I in skeletal muscle adaptation is founded on the extensive body of evidence indicating that *1*) IGF-I is both anabolic and mitogenic for skeletal muscle or muscle lineage cells, *2*) IGF-I operates in an autocrine/paracrine mode in skeletal muscle, and *3*) muscle IGF-I and MGF production are sensitive to increases in loading state. In addition to the effects of IGF-I in promoting skeletal muscle hypertrophy or regeneration, there are a number of other systems that may impact or be impacted by IGF-I signaling that should be considered by muscle re-

searchers. Future challenges in this area include the identification of the cellular level mechanisms that transduce mechanical signals leading to changes in IGF-I signaling and elucidation of the relationships between the various intracellular signaling pathways that allow IGF-I signaling to stimulate the competing processes of cellular differentiation and cellular proliferation.

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