Similar to bone, skeletal muscle responds and adapts to changes in loading state via mechanisms that appear to be intrinsic to the muscle. One of the mechanisms modulating skeletal muscle adaptation thought to involve the autocrine and/or paracrine production of insulin-like growth factor-I. This brief review outlines components of the insulin-like growth factor-I system as it relates to skeletal muscle and provides the rationale for the theory that insulin-like growth factor-I is involved with muscle adaptation.

List of Abbreviations Used

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>4E-BP</td>
<td>eukaryotic initiation factor-4E binding protein</td>
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<tr>
<td>eIF-4E</td>
<td>eukaryotic initiation factor 4E</td>
</tr>
<tr>
<td>FGF</td>
<td>fibroblast growth factor</td>
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<tr>
<td>GH</td>
<td>growth hormone</td>
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<td>IGF-I</td>
<td>insulin-like growth factor-I</td>
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<tr>
<td>IGFR1</td>
<td>insulin-like growth factor type 1 receptor</td>
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<tr>
<td>IP3</td>
<td>inositol 3,4,5-trisphosphate</td>
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<tr>
<td>IRS-1</td>
<td>insulin receptor substrate</td>
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<tr>
<td>MAPK</td>
<td>mitogen activated protein kinases, also known as ERKs</td>
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<tr>
<td>MGF</td>
<td>mechanogrowth factor</td>
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<tr>
<td>mRNA</td>
<td>messenger ribonucleic acid</td>
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<tr>
<td>mTOR</td>
<td>mammalian target of rapamycin</td>
</tr>
<tr>
<td>PIP2</td>
<td>phosphatidylinositol 3,4-bisphosphate</td>
</tr>
<tr>
<td>HMGCoA</td>
<td>β-hydroxy-β-methylglutaryl-Coenzyme A</td>
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Glossary

18s = A ribosomal ribonucleic acid of approximately 1900 nucleotides; Identified by rate of sedimentation in ultracentrifugation (s value), this RNA in combination with a number of proteins forms the small ribosomal subunit in eukaryotes.

AKT = cellular homolog of the v-akt oncogene also known as protein kinase B. AKT is an important member of numerous intracellular signaling cascades including one providing protection from programmed cell death (apoptosis).

ERK = members of a family of mitogen activated protein kinases, these enzymes are key members of signaling cascades that transmit receptor mediated signals from the cell membrane to initiate changes in effector enzyme activity including alterations in gene transcription. ERK activity is associated with cell proliferation in numerous tissues.
It has long been recognized that bone can adapt to changes in loading via mechanisms that are, at least in part, intrinsic to the bone tissue. In this context, the presence and importance of autocrine and paracrine growth factor signaling, in particular signaling involving IGF-I has been recognized for some time. Similar to bone, skeletal muscle is a highly plastic tissue that constantly adapts to the functional demands imposed by the activities of the individual. In mammalian skeletal muscle, this adaptation can include changes in the size and the qualities of the myofibers that comprise the muscle. This cellular level adaptation is specific to the muscle that is experiencing the alteration in activity pattern. For example, a program of focused arm resistance training will not result in adaptation in the leg musculature (Fig 1). The simplest explanation for this observation is that the regulatory mechanisms that modulate the cellular level adaptation in a given muscle most likely reside within that muscle. To elicit adaptation of a specific muscle via some central mechanism, for example changes in the circulating levels of some hormone, would require that all nontarget tissues must in some way down regulate their response to the circulating signal leaving only the impacted muscle to respond and adapt. This local control hypothesis has been verified in vivo. For example, in rats the circulating hormone and growth factor milieu can be depressed drastically via surgical hypophysectomy that prevents additional growth (Fig 2). However, the muscles of these hypophysectomized rats can respond to increased loading with substantial compensatory hypertrophy. Insulinlike growth factor-I peptide and mRNA expression also is substantially increased in the overloaded muscles from hypophysectomized and control rats. However, the circulating IGF-I is very low in the hypophysectomized rats. Insulin-Like Growth Factor-I Activity in Skeletal Muscle

MEK = a kinase upstream from the ERK signaling. MEK has been viewed as a promising target for pharmaceutical intervention to inhibit cell proliferation.

PI3K = a family of enzymes fundamental to a myriad of cellular signaling pathways in eukaryotes. Signaling via class I PI3Ks generally is linked to cell surface receptors. Downstream processes mediated by PI3K activation can include cellular proliferation or differentiation depending on context.

RAS = a family of proteins that are key links in the transmission of cell surface receptor signals to intracellular signaling pathways.

Raf = this kinase is activated by binding with activated RAS. Raf kinase activity can initiate a series of phosphorylations that transmit signals from the cell surface receptor via the ERKs.

S6K1 = an enzyme activated by phosphorylation of elements downstream from PI3K. Activated S6K1 phosphorylates the S6 protein of ribosomes. This event promotes the initiation of translation of messenger ribonucleic acids.

SHC = proteins containing SH2 domains act as adaptors that recognize proteins that have been phosphorylated on tyrosine residues and link them to other proteins such as receptors to promote intracellular signaling.

Fig 1. The specificity of adaptation is shown. Although it may seem like a simple concept, it is important to remember that changes in the loading state of individual muscles or muscle groups elicit adaptation specific to the affected muscles.
pophysectomized rats. The low circulating levels of IGF-I most likely account for much of the somatic growth deficit in these rats.

In traditional endocrinology, IGF-I (originally called somatomedin C) appears as a component of the somatic growth and development system mediated by GH (originally Somatomotrophin). Much of the literature concerning the role of IGF-I in relation to skeletal muscle appears in two major contexts: (1) IGF-I as a component of the GH control axis; and (2) the role of IGF-I in myogenesis during the process of development. In the GH context, much of the emphasis has been on the insulin-like metabolic and anabolic effects of IGF-I. In developmental scenarios, the role of IGF-I in stimulating mitotic and myogenic processes has been the major point of emphasis. In contrast to these established theories the concept of a major role for GH-independent, autocrine and/or paracrine functions of IGF-I has been developed relatively recently.

To understand the importance of intrinsic regulation via autocrine and/or paracrine signaling, it is instructive to consider some cellular processes such as myofiber regeneration, that appear to be regulated or modulated by IGF-I. Severe myofibrillar injury results in the death of some myofibers leaving behind the basal lamina and some satellite cells. Satellite cells are small mononucleated skeletal muscle stem cells located between the basal lamina of the muscle and the sarcolemma of myofibers (There is evidence that multiple muscle stem cell populations may be contributing to processes traditionally ascribed to satellite cells). As a result of the injury to myofibers, satellite cells are mobilized to begin regeneration. The initial events after satellite cell activation have been reported to be a proliferative response in that some or all of the activated satellite cells undergo at least one mitotic cycle. After this initial phase, some of the activated cells and/or their progeny are thought to differentiate.

Fig 2. Muscle hypertrophy in a nongrowth environment is shown. Hypophysectomy drastically reduces the circulating levels of numerous growth factors and hormones thereby preventing somatic growth. However, the muscles of nongrowing hypophysectomized rats will hypertrophy in response to overloading. Percent change values are based on muscle mass, which is normalized to body weight.
into myoblast-like cells. In regenerating muscle, these myoblasts either can fuse with each other to form new myofibers or become incorporated into surviving myofibers9,39,43,49 (Fig 3). If the capacity of satellite cells to proliferate is eliminated, for example via irradiation, the regeneration process is inhibited.16,27,50 There is evidence that locally produced, autocrine and/or paracrine IGF-I, may be important in the regeneration process. Jennische et al30,31 showed that IGF-I immunoreactivity was detected in the cytoplasm of myoblasts and myotubes and in satellite cells during muscle regeneration. LeFaucheur and Sebille36 reported that antibodies that neutralized either IGF-I or FGF activity, reduced the number and size of regenerating myofibers after muscle injury and that the anti-IGF-I treatment had a higher potency.

With the muscle regeneration process in mind, an examination of the known effects of IGF-I on skeletal muscle cell types provides insight into the potential importance of this growth factor. In studies involving established cell lines and primary satellite cell cultures, ligation of the IGF-I receptor has been shown to initiate intracellular signaling cascades involved in key mitogenic and myogenic responses11,15,23 (Fig 4). One pathway activated by IGF-I involves Ras-Raf signaling to extracellular response kinases and has been shown to promote increased cell proliferation.23 A second important pathway activates PI3K. Phosphatidylinositol 3-kinase activation is central to numerous important cellular processes including protection from apoptosis via AKT activation and alteration in intracellular calcium via the inositol phosphate cascade. In addition, PI3K activation increases the initiation of translation via alter-

Fig 3. Satellite cells and myofiber regeneration is shown. Severely injured myofibers degenerate. In response to the injury satellite cells proliferate, differentiate, and fuse to form new multinucleated myofibers.
ations in the phosphorylation state of 4E-BP1 and S6K1. The activation of S6K1 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.70 In addition to generalized anabolic effects, the activation of portions of the PI3K signaling cascade is associated with the differentiation of muscle cells in culture.11,15 Interestingly, the processes of cellular proliferation and differentiation generally are thought to be mutually exclusive. In fact, studies have shown that activation of one of the two primary signaling pathways (Ras-Raf versus PI3K) generally will inactivate portions of the other.24,52

Among the well-characterized growth factors, IGF-I is relatively unique in that it has been reported to stimulate both of these processes, possibly via temporal modulation.56

There is evidence that the mitogenic and myogenic effects of IGF-I that render it useful for muscle regeneration also might be important for the adaptation of muscle to increased loading. Numerous in vivo activity models, such as increased loading, stretch and eccentric contraction are known to result in myofibrillar increases in IGF-I and IGF-I mRNA expression.1,2,7,17,18,28,32,57,72,73 Experimental manipulation of muscle IGF-I levels, in the absence of changes in loading state, also has been shown to induce muscle hypertrophy.3,14,71

As with myofiber regeneration, IGF-I is known to stimulate numerous processes that would promote skeletal muscle hypertrophy. The utility of insulinlike anabolic effects for promoting muscle hypertrophy is obvious.46 However, the impact of IGF-I on muscle satellite cells is of particular interest. In the case of

Fig 4. Insulinlike growth factor-I receptor related intracellular signaling pathways are shown. Ligation of the IGF-I receptor results in anabolic, mitogenic (proliferation of satellite cells) and myogenic (differentiation of satellite cells) processes. In addition, IGF-I may provide protection from apoptosis and may stimulate increases in cellular calcium. 4E-BP-eIF-4E binding protein; AKT-Cellular homolog of the v-akt oncogene, an S/T protein kinase-Ca²⁺-Calcium; ERK-Extracellular signal-regulated kinase; IGF-I-insulinlike growth factor-I; IGFR1-insulinlike growth factor type 1 receptor; IP3-Inositol 3,4,5-trisphosphate; IRS-1-Insulin receptor substrate; MEK-MAPK/ERK kinase; mTOR-Mammalian target of rapamycin; PI3K-Phosphoinositide-3 kinase; PIP2-Phosphatidylinositol 3,4-bisphosphate; RAF-a serine/threonine kinase; S6K1-p70 S6 kinase; Shc-SH2-containing collagen-related proteins.
the hypertrophy response, satellite cell-derived myoblasts are thought to fuse with existing myofibers much as they would with damaged but still viable myofibers after injury. The importance of this response is suggested by the fact that: (1) mature mammalian skeletal muscle fibers maintain a relatively finite, fiber type specific, relationship between the size of the myofiber and the number of myonuclei present in a given myofiber; (2) mammalian myofibers become permanently differentiated shortly after birth and do not undergo mitotic division or directly increase their myonuclear number (myonuclear division). Therefore, the requirement for additional nuclei to support hypertrophy appears to be met via the proliferation, differentiation, and fusion of muscle satellite cells providing the new myonuclei needed to support the hypertrophy process.

One of the more interesting recent developments regarding IGF-I has been the identification of an unique IGF-I isoform that is expressed in response to changes in the loading state of skeletal muscles. This isoform, MGF, has been shown to be upregulated markedly in response to stretch and increased loading. It appears that muscles produce a generalized tissue type IGF-I and the loading sensitive MGF isoform with differing time courses suggesting distinct roles for these two growth factors.

The key role of IGF-I in muscle regeneration and adaptation argues for an increased awareness of the potential for injury, illness, or iatrogenic impacts on the functioning of this system. For example, the IGF-I receptor seems to be sensitive to inhibition by components of proinflammatory cytokine intracellular signaling pathways and to share common intracellular signaling components with these cytokines. Sensitivity of the muscle IGF-I system to proinflammatory cytokines may contribute to the catabolic effects of these cytokines on skeletal muscle.

Figure 5. Satellite cells and myofiber hypertrophy is shown. Similar to the processes involved with myofiber repair and regeneration, IGF-I may stimulate the contribution of satellite cells to compensatory hypertrophy responses. Incapacitation of the mitotic capabilities of satellite cells prevents muscle regeneration and muscle hypertrophy. Blocking IGF-I signaling also blocks hypertrophy.
lorate this process.\(^4\) In addition, glucocorticoids (methylprednisolone, triamcinolone) are known to modulate IGF-I abundance and IGF-I effects in muscle whereas HMGCoA reductase inhibitors (Pravastatin, Simvastatin) may interfere with PI3K signaling.\(^6\) Therefore, numerous commonly prescribed drugs may unwittingly impair the IGF-I system in muscles.

The proper functioning of skeletal muscle is important for positive outcomes in the setting of orthopaedic medicine and in a broader quality of life context. It appears that the IGF-I system may function in an autocrine and/or paracrine mode as an intrinsic mediator of muscle repair and adaptation. As such, awareness of this system may provide useful insights in patient care settings.

**References**

28. Haddad F, Adams GR: Acute cellular and molecular...


