Point:Counterpoint: IGF is/is not the major physiological regulator of muscle mass

**POINT: IGF IS THE MAJOR PHYSIOLOGICAL REGULATOR OF MUSCLE MASS**

The insulin-like growth factors (IGFs)-I and -II are homologous peptides that are structurally related to insulin. However, IGFs retain the C-peptide, enabling binding to their main signaling receptor, the IGF type 1 receptor (IGF1R). IGF-II, however, can also bind to and signal via the A isoform of the insulin receptor; it additionally binds the IGF2R, which has an important role in IGF-II degradation rather than signaling. Unlike insulin, the IGFs are not stored in vesicles but are secreted immediately as they are synthesized; their potency is such that their activity is tightly regulated by a family of six binding proteins (IGFBPs 1–6).

Myogenesis is the developmental process by which muscle precursor cells proliferate, migrate to sites of muscle formation, differentiate and fuse to form postmitotic multinucleated myotubes. Muscle formation is orchestrated by a highly regulated series of events in the embryo (reviewed in Ref. 2), comprising primary and secondary myogenesis, which largely define muscle fiber number by birth. Subsequently, all muscle growth and repair occur by activation of “adult” muscle stem cells, termed satellite cells; these proliferate and fuse with (or replace in severe damage) existing myofibers, resulting in fiber hypertrophy (7). Although the precursor populations that define embryonic and postnatal myogenesis are different, the cellular mechanisms controlling myoblast differentiation have many common elements. Critically since fiber number at birth will determine the extent of muscle mass in later life, the regulators of prenatal myogenesis ultimately limit the compensatory hypertrophy elicited as a consequence of growth and exercise; therefore for any growth to occur in later life we need to acknowledge the key role of the IGFs in muscle physiology during development.

*IGFs in muscle development and growth.* A fundamental role for IGF signaling in embryonic muscle development was suggested from the lethal neonatal phenotype of *Igf1r*-null mice, which display severe growth retardation and muscle hypoplasia and whose death is thought to occur via respiratory muscle weakness (9). IGF-II is highly expressed in developing embryonic somites (23) with its importance in myogenesis first being identified by Florini and colleagues (4); here, antisense oligodeoxyribonucleotides complementary to the first five codons of IGF-II, reduced IGF expression, inhibited myogenic differentiation, and the expression of the myoblast regulatory transcription factor myogenin. In support of these observations, inhibition of IGF activity in vivo, by overexpression of IGFBP-5, which is highly expressed in muscle, also inhibits muscle development (16). In several additional compelling studies, (e.g., see Ref. 1), overexpression of IGFs in muscle increases its mass via fiber hypertrophy. Although IGF-I and -II have largely overlapping functions via the IGF1R in myogenesis, the normal development of mice that are null for both the *Igf1r* and *Igf2r* [and therefore have “excess” IGF-II (10)] demonstrate that IGF-II signaling via the insulin receptor could support muscle growth, illustrating the plasticity of the IGF network. Together, these in vivo studies support a central role for the IGFs in embryonic and therefore ultimately postnatal muscle development and growth. Furthermore, numerous studies in vitro, using either cell lines or primary isolated satellite cells, suggest an obligatory function for IGFs in the regulation of muscle mass, e.g., (25).

Although most cell types express IGFs, hepatic expression usually exceeds that of other tissues by approximately tenfold, with liver-derived IGFs generally responsible for determining systemic IGF concentrations. Therefore, whether the growth of individual tissues is orchestrated by endocrine or local autocrine/paracrine IGF synthesis is the focus of ongoing debate. Normal muscle development of liver-specific *Igf1* knockout mice, which have a 75% reduction in circulating IGF-I, (26) suggests that locally derived IGF-I is sufficient to support myogenesis. Whether there is a threshold of circulating IGF-I, below which muscle development would be compromised, as occurs for bone growth (27), is not unequivocally established. The outcome of reciprocal studies, in which *Igf* null mice are crossed with transgenic mice that overexpress IGF-I in the liver (i.e., synthesize endocrine but not muscle autocrine/paracrine IGF-I), are awaited. In the meantime, recent studies by Ma-theny et al. using the liver IGF-I-deficient (LID) mouse model demonstrated that 16 wk of resistance training in 12- to 13-mo-old male LID and control mice resulted in equal strength gains in both, with elevated IGF-I mRNA in the LID mouse muscle and enhanced tyrosine phosphorylation of the IGF-IR, compared with controls (11). Overall, these findings therefore suggest that the upregulation of local IGF-I may be involved in the compensatory growth of muscle that occurs in response to resistance training and increasing the mechanical load.

*IGFs in postnatal muscle adaptation.* The maintenance of adult muscle mass depends on satellite cell activation, proliferation, survival, and differentiation (8, 24), processes also central to myogenesis during development. Hence it is not only critical that satellite cell numbers are retained throughout life, but also that their ability to respond to activating cues, such as muscle damage (23) is facilitated. Well-established studies in vitro using satellite cell lines and isolated primary adult satellite stem cells have demonstrated key roles for IGFs in satellite cell proliferation, differentiation (reviewed in Ref. 19), survival (22), fiber hypertrophy via satellite cell recruitment (7), and myofibrillar protein accretion in myotubes (14), again underscoring the essential role these peptides play in muscle physiology.

IGF-I expression and hypertrophy are also induced during injury, e.g., following stretch-induced hypertrophy (28). In vivo models of muscle specific IGF overexpression demonstrate that IGFs accelerate recovery following muscle injury (18). This occurs via multiple mechanisms not only including its established actions in satellite cell activation, but also by improving recruitment of cells from non-myogenic lineages into the myoblast lineage (15), and by modulation of inflammatory cytokine activity (13). Indeed, overexpression of IGF-I can counteract angiotensin-II-induced muscle wasting (21). In terms of myogenic signaling, IGFs not only activate “anabolic"
pathways (e.g., PI3 kinase/Akt; discussed in Ref. 5), but also inhibit catabolic pathways involved in the pathogenesis of muscle atrophy (17). This is particularly relevant in studies of muscular dystrophy, where transgenic overexpression of IGF-I within muscle of the mdx mouse reduces the necrotic phenotype of dystrophic myofibers (discussed in Ref. 6). During aging, muscle mass decreases, partially as a consequence of reduced satellite cell number (20); however, this decline is attenuated in mice overexpressing IGF-I in skeletal muscle (12). Recent studies have determined that the ability of satellite cells derived from aged muscle to respond to activating stimuli is not impaired, implying that the lesion in satellite cell function in ‘aged’ muscle is due to the soluble cellular environment, rather than intrinsic activity of muscle stem cells (3); changes in IGF concentrations may well contribute to this.

IGFs therefore are essential to our muscle mass and consequently to our function throughout life. They are central to determining the future potential of our lean body mass. After all, if individuals are born with small muscles as a consequence of reduced IGF in utero, they will only be able to hypertrophy that muscle which is already present and then only in the face of adequate IGF stimulation.

REFERENCES


C. E. Stewart1

J. M. Pell2

1Institute for Biomedical Research into Human Movement and Health

Manchester, UK

e-mail: c.stewart@mmu.ac.uk

2The Babraham Institute

Babraham Research Campus

Babraham, Cambridge, UK

COUNTERPOINT: IGF IS NOT THE MAJOR PHYSIOLOGICAL REGULATOR OF MUSCLE MASS

Insulin-like growth factor I (somatomedin C or mature IGF-I) is an anabolic factor and its overexpression in skeletal muscle promotes muscle mass. Today, a paracrine loop of IGF-mediated cell signaling is seen as the default mechanism for control of muscle mass (14, 34). Concern on this view is presented by the recent demonstration that load-induced muscle growth does not depend on IGF receptor signaling (8, 20,