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Regulation of muscle size in humans: Role of myostatin?

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Significant advances over the past few years have led to an improved understanding of the cellular and molecular processes regulating muscle mass and myofiber size. Much like bone, skeletal muscle is a highly plastic tissue exquisitely responsive to environmental cues including mechanical load, endocrine factors, neural activity, and autocrine/paracrine factors in the muscle microenvironment. As described by Dr. Esser, mechanical overload drives growth signaling in skeletal muscle. Conversely, a reduction in the nominal daily loading pattern or specific alterations in the muscle microenvironment can activate mechanisms leading to skeletal muscle atrophy as described by Dr. Kandarian. Many of the findings from animal model systems regarding muscle mass regulation have now been translated to adult humans. Through studies of muscle growth or regeneration, it has become increasingly apparent that key events driving developmental myogenesis recapitulate in adult myofibers in response to injury or increased mechanical load, and that successful myogenesis is dependent upon a complex array of co-ordinated activities regulating both net muscle protein synthesis and muscle stem (satellite) cell recruitment.

Autocrine/paracrine as well as endocrine factors (e.g., IGF-I) are important modulators of these processes. Myostatin, a member of the transforming growth factor β superfamily, is perhaps the single most powerful negative regulator of developmental myogenesis as demonstrated by marked muscle hypertrophy in homozygous mutant mice[1], cattle[2], and a single known human case[3]. This potent peptide "anti-growth" factor inhibits proliferation[4,5] and differentiation[6,7] of myoblasts during development and evidence suggests it may also impair satellite cell function in differentiated adult muscle undergoing regeneration/growth[8]. Myostatin mRNA expression appears to be sensitive to mechanical load and other hypertrophy or atrophy stimuli. Its expression increases during multiple models of muscle atrophy[9-14] and, in fact, the magnitude of myostatin mRNA elevation is significantly related to the magnitude of type II myofiber atrophy consequent to disuse[12]. On the other hand, long-term resistance training[15,16], as well as a single bout of resistance loading[17,18] markedly inhibit myostatin mRNA expression. While a physiologic consequence of altering myostatin mRNA in adult muscle has not been clearly demonstrated, the findings have sparked numerous efforts to suppress or block myostatin as a treatment for muscles suffering atrophy due to disuse, aging, or primary muscle myopathy[19-22]. It is abundantly clear that myostatin plays a dominant, negative role during mammalian muscle development but its role and importance in normal, healthy adult muscle remains poorly understood.

In this session, the speaker will overview some of the key metabolic and molecular processes regulating muscle size in adult humans with a focus on mechanisms driving skeletal muscle protein synthesis and muscle satellite cell recruitment. In the context of the latter, the state of the current literature on myostatin will be discussed including a recent application of K-means cluster analysis by the speaker's laboratory[23].

Learning objectives

The information presented in this seminar should enable you to better: (1) Understand the key metabolic and molecular processes regulating muscle size in humans; (2) Understand the biological actions of myostatin in skeletal muscle; (3) Appreciate the remarkable effects of myostatin inhibition in animal models; and (4) Compare and contrast the current evidence regarding the influence of myostatin in developing vs. adult muscle.

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