

Speed and endurance: you can have it all

Se-Jin Lee

Department of Molecular Biology and Genetics, Johns Hopkins University School of Medicine, Baltimore, Maryland

SKELETAL MUSCLE COMPRISES multiple fiber types that vary in their contractile and metabolic properties. Muscle fibers are classified primarily on the basis of the specific myosin heavy chain isoform that they express. Slow twitch or type I fibers are rich in mitochondria, rely principally on oxidative metabolism, and have a high resistance to fatigue. Fast-twitch or type II fibers are more susceptible to fatigue and come in several subtypes (IIa, IIx, and IIb); these subtypes can be distinguished not only in terms of their contractile protein isoforms, but also with respect to their metabolic properties, which range from mixed oxidative/glycolytic to predominantly glycolytic. The relative proportions of different fiber types in a given muscle are believed to affect its overall functional properties, such as power, speed, and endurance, and dysfunction of specific fiber types can accompany a variety of disease processes, including type II diabetes and age-related muscle loss or sarcopenia. As a result, there is considerable interest in developing strategies and agents capable of enhancing the functions of specific types of myofibers.

One major focus of efforts to develop drugs capable of promoting muscle growth for clinical applications is the signaling pathway regulated by myostatin (MSTN), which is a transforming growth factor- β (TGF- β) family member that normally acts to limit skeletal muscle mass (12). Genetic loss of *MSTN* has been shown to result in dramatic increases in muscle mass in multiple species, including humans, and inhibition of myostatin activity in adult mice has been shown to induce significant increases in muscle growth and muscle strength (for review, see Ref. 8). These and other studies have demonstrated that myostatin normally plays two roles in limiting muscle mass. One role is to regulate the number of muscle fibers that are formed during development, and several studies have shown that the increases in fiber number seen in *Mstn* null mice result mostly from increases in the numbers of type IIx and IIb fibers (2, 4, 6, 11). A second role of myostatin is to regulate postnatal growth of muscle fibers, and hypertrophy of type II fibers has been well documented in adult mice treated with myostatin inhibitors. The combination of increased numbers and sizes of type II fibers has been interpreted to be largely responsible for one of the striking examples of the functional consequences of myostatin loss, namely the superior racing performance of whippets that are heterozygous for a *MSTN* loss-of-function mutation (14). Although the major effects of blocking myostatin activity seem to be on inducing type II fiber hypertrophy, effects on type I fibers have also been reported following viral delivery of an expression construct for the myostatin propeptide, which is an inhibitor of myostatin signaling (5, 10). In this issue of the *Journal of Applied Physiology*, Cadena et al. (3) use a pharmacological approach to examine the role of this signaling pathway in regulating growth

of different fiber types. The authors provide additional evidence that this pathway seems to function in adult mice to regulate growth of not only type II fibers, but also type I fibers.

To block myostatin activity, Cadena et al. (3) utilized a biologic called ACE-031, which is Acceleron's version of a soluble form of the activin type IIB receptor (ACVR2B or ActRIIB). Previous studies have demonstrated that myostatin signals initially by binding to activin type II receptors and that systemic administration of a soluble form of ACVR2B, consisting of its ligand binding portion fused to an Fc domain, can cause dramatic muscle fiber hypertrophy (9). Cadena et al. (3) carried out a detailed examination of the effects of systemic administration of ACE-031 at the level of the muscle fiber. Analysis of the soleus muscle, which contains a mixture of type I and type II fibers, revealed that the total numbers of muscle fibers, as well as the total numbers of each of the individual fiber types, were similar in ACE-031-treated and control mice. The fact that overall fiber number was unchanged implied that all of the increased muscle growth induced by ACE-031 resulted from muscle fiber hypertrophy, and, consistent with previous reports, the authors found significantly increased muscle fiber sizes in mice treated with ACE-031. The new finding was that these increases in fiber sizes were seen both in type II and in type I fibers.

An important issue raised by these findings that warrants further investigation is the identity of the ligand being targeted by ACE-031 to induce its effect on type I fibers. Previous studies have shown that muscle growth is regulated by multiple TGF- β -related ligands that signal through activin type II receptors and that one of the reasons for the dramatic effects seen with the soluble ACVR2B receptor in terms of inducing muscle growth is that this agent is capable of blocking more than just myostatin, as demonstrated by the ability of this inhibitor to induce muscle growth even in *Mstn* null mice (9). Given that there is considerable debate as to whether the best pharmacological agents for clinical use will be ones that are highly specific for myostatin or ones with a broader range of ligand specificity, it will be important to determine whether these effects of ACE-031 in inducing type I fiber hypertrophy reflect inhibition of myostatin activity or that of another ligand that also signals through activin type II receptors to regulate muscle growth. An intriguing possibility is that different TGF- β -related ligands may be responsible for regulating the growth and function of different fiber types, although previous studies have demonstrated effects on type I fibers by overexpressing the myostatin propeptide (5, 10), which seems to be capable of blocking only myostatin and the highly related ligand, GDF-11.

From the perspective of muscle as a contractile organ, the findings reported by Cadena et al. (3) are significant in that they further support the possibility that blocking this signaling pathway could lead to enhancement of not only functional parameters like strength and speed, but perhaps also those related to muscle fatigue and endurance. Moreover, these findings have potential implications for the use of myostatin inhibitors in disease settings in which type II fibers are lost,

Address for reprint requests and other correspondence: S.-J. Lee, Dept. of Molecular Biology and Genetics, Johns Hopkins Univ. School of Medicine, 725 North Wolfe St., PCTB 803, Baltimore, MD 21205 (e-mail: sjlee@jhmi.edu).

such as in age-related sarcopenia, which seems to affect type IIb fibers preferentially. In particular, the new findings suggest that myostatin inhibition may be beneficial not only for providing an anabolic stimulus to the residual type II fibers, but perhaps also for promoting the function of the type I fibers that are relatively spared in aged muscle.

From the perspective of muscle as a metabolic tissue, these findings raise additional questions regarding the metabolic effects seen when this signaling system is manipulated. Early studies showed that genetic loss of *Mstn* can reduce fat accumulation and improve glucose metabolism in mouse models of obesity and type II diabetes (13), and several follow-up studies have documented similar metabolic effects using pharmacological methods to block myostatin activity (1, 7). Assuming that some, if not all, of these metabolic effects result from loss of direct myostatin signaling to muscle, it will be important to understand the extent to which altered signaling in different fiber types contributed to these overall physiological effects. A major question in this regard is whether the effects of ACE-031 in inducing type I fiber hypertrophy are accompanied by corresponding effects on type I fiber metabolic activity.

From both perspectives, the findings reported by Cadena et al. (3) expand the spectrum of beneficial effects that can be seen by blocking this signaling pathway and will likely continue to fuel the optimism surrounding the targeting of this pathway for clinical applications. In this respect, at least four biotechnology and pharmaceutical companies, including Acceleron, have entered clinical trials with myostatin inhibitors in a variety of disease states. Given the wide range of clinical settings characterized by debilitating loss of muscle function, scientists, physicians, and patients will all be eagerly awaiting the results of these trials.

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DISCLOSURES

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