

Sizing up muscular dystrophy

In Duchenne muscular dystrophy, functional muscle fibers enlarge to compensate for damaged fibers. A new treatment in a mouse model makes muscles even larger and ameliorates symptoms of the disease.

How often does the glare of the self-evident blind us to the obvious? Enthusiasm for gene therapy to rectify primary genetic defects has tended to divert attention from combating the processes that actually cause disablement. For example, in Duchenne muscular dystrophy (DMD), the commonest lethal X-linked recessive disorder¹, the therapeutic goal has largely been correction or compensation of the genetic defect in the dystrophin gene. This has occurred to the relative neglect of seeking ways to combat the loss of muscle structure, bulk and strength. This progressive, unrelenting muscle impairment confines the patient to a wheelchair by 12 years of age and leads to death, usually from respiratory or cardiac failure, by his early 20s. In the November 29 issue of *Nature*, Bogdanovich *et al.*² demonstrate the therapeutic potential for tackling this muscle impairment rather than the primary biochemical defect. Myostatin (CDF8), a member of the transforming growth factor (TGF- β) superfamily, is a major regulator of muscle growth whose absence in mice results in a marked increase in muscle mass³. Bogdanovich *et al.* explore the straightforward approach of compensating muscular weakness in a mouse model of DMD (the *mdx* mouse) by blocking the action of myostatin, and they find a surprising degree of functional improvement.

The dystrophin gene is a major chal-

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lenge for gene therapy. Not only is it the largest and most complex gene thus far described⁴, but any effective gene therapy would have to be delivered to both the

delivery of a small drug designed to act predominantly on muscle tissue. Such thinking lies, for example, behind the search for agents that may activate expression of utrophin, a homolog of dystrophin, which is able to substitute for dystrophin function⁵. This strategy aims to ameliorate the primary biochemical dysfunction in DMD, but there are other potential therapeutic targets in the chronic pathology deriving from this genetic defect. One such target is the satellite cell, the resident muscle stem cell⁶ whose activity in the early stages of DMD counteracts the loss of muscle fibers by efficient regeneration and repair. Augmentation of satellite-cell activity—for example, by insulin-like growth factor 1 (IGF-1)—produces larger muscle fibers and improves dystrophic phenotypes^{7,8}.

Bogdanovich *et al.* used the more targeted pharmacological approach of treatment with a myostatin-neutralizing antibody on the rationale that blockade of myo-

statin relieves inhibition of satellite cell-mediated muscle growth. Weekly intraperitoneal injections of the antibody into *mdx* mice made their hypertrophic muscle fibers even bigger. Moreover, the muscles of treated mice demonstrated both improved physical performance and force generation. However, they remained vulnerable to a type of stress that provokes a characteristic loss of strength in dystrophic muscle, 'eccentric work' (max-

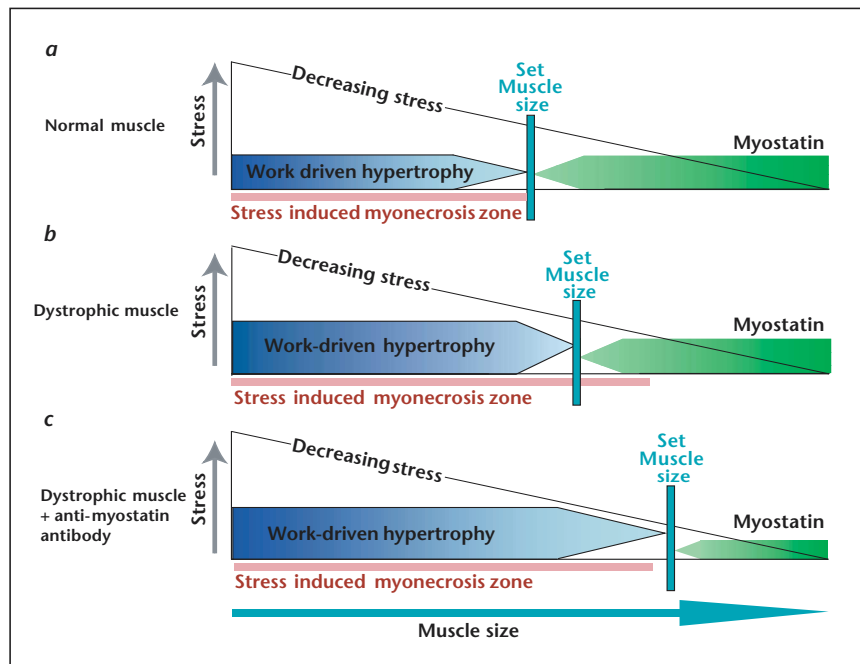


Fig. 1 Simplified model of the relationship between muscle fiber size (horizontal axis) and susceptibility to work-induced damage (vertical axis). Muscle size is set by the balance between work-induced hypertrophy (blue) and counteracting signals from myostatin (green). **a**, In normal muscle, the balance between these stimuli sets the muscle size at the upper edge of the zone of damage caused by everyday work (pink). **b**, In dystrophic muscle, the extra workload imposed on the fewer functional muscle fibers drives hypertrophy, but due to the lack of dystrophin, they remain susceptible to stress-induced damage (pink). **c**, Blockade of myostatin permits hypertrophic stimuli to drive the muscle size above the range in which everyday stress causes damage to dystrophic muscle. Such muscle may still be vulnerable to some types of extreme stress. This model does not take into account changes in contractile-protein profiles that occur during muscle growth and regeneration.

large mass of skeletal muscle distributed throughout the body and the heart. The combined need for widely dispersed and accurate, or at least efficient, delivery of any reparatory or supplementary construct has so far eluded all proposals for gene therapy, cell therapy or even stem-cell therapy, despite tangible advances in all of these disciplines.

There is therefore great appeal in a pharmacological approach for systemic

imal contraction combined with simultaneous stretching of the muscle). This vulnerability implies that enlargement of muscle without replacement of dystrophin did not protect against severe physical stress. Thus, all the more surprising was the observation that leakage of muscle creatine kinase into the serum (a sensitive indicator of muscle damage) dropped to near wild-type levels in the anti-myostatin-treated *mdx* mice. This indicates that suppression of myostatin had rendered most dystrophin-deficient muscle resistant to necrosis during normal activity.

Why should fiber integrity be preserved by a treatment whose main effect is presumed to be on satellite cells? The observation that large muscle fibers are resistant to necrosis in anti-myostatin-treated *mdx* mice contravenes the observation that small fibers survive better than large in dystrophin-deficient muscle⁹. Nor does it fit well with the common view of dystrophin—that it functions predominantly as a mechanical linkage to transmit forces across the surface membrane of the fiber between the internal contractile apparatus and the overlying basement membrane¹⁰. This model would predict that in the absence of efficient dystrophin-mediated linkage, the higher force generated by large muscle fibers would then have to be transmitted across their relatively smaller surface area, which would make them more susceptible to damage than small fibers.

How then could blocking myostatin help to stabilize muscle fibers? Muscle size can be visualized as a balance between hypertrophic signals arising, in part, from workload and inhibitory signals such as

that from myostatin (Fig. 1). In young DMD boys and *mdx* mice, the extra stress placed on muscles by the degeneration of a proportion of fibers is thought to drive a net hypertrophy but may also damage dystrophin-deficient muscle fibers. Blocking myostatin may permit hypertrophic signals to drive muscle growth above the point where it is compromised by normal workloads, thus lifting dystrophic muscle above damaging levels of stress. A similar explanation has been proposed for the observed beneficial effect of IGF-1-induced hypertrophy in *mdx* mice⁸. This sparing of large muscle fibers is an unexpected benefit, in that the associated reduction in inflammation should also alleviate the progressive fibro-fatty replacement, which is thought both to impair muscle function and to obstruct regeneration.

These are encouraging findings. They suggest that relatively simple strategies for increasing muscle size and strength have potential to at least slow the progression of DMD. Moreover, the approach is relevant to human patients as it works on muscles already in a cycle of degeneration and regeneration. It is important to stress, however, that these are very preliminary studies conducted on a model that only partly simulates the pathology of DMD. Human studies of this strategy should be preceded by a thorough investigation of the mechanisms involved and of the long-term consequences of blocking myostatin, absence of which has been shown to modify fat accumulation and metabolism¹¹. We also need a more comprehensive understanding of the factors that regulate muscle size and strength so that we may intervene more delicately in their control.

Extension of the potential benefits to aging muscle and muscle-wasting conditions would stimulate the industrial interest required to drive this strategy forward.

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