Saying NO to muscular dystrophy

According to the prevailing model for Duchenne muscular dystrophy (DMD) pathogenesis, a lack of dystrophin protein makes muscle cells susceptible to mechanical damage, leading to muscle breakdown. On page 123, Wehling et al. suggest that the major damage in DMD may actually be caused by a secondary consequence of dystrophin loss: destruction of muscle tissue by a patient’s own macrophages. Dystrophin forms a complex with several other proteins, including nitric oxide synthase (NOS). In dystrophin-deficient muscles, such as those of the mdx mouse, a model for DMD, NOS expression is decreased. Reasoning that the loss of nitric oxide’s anti-inflammatory activity might exacerbate muscle breakdown, the authors introduced a transgene to produce normal levels of NOS in the muscles of mdx mice. The transgene reduced the concentrations of macrophages in the muscles and prevented the majority of muscle membrane injury in the mdx mouse. Antibody depletion of macrophages from mdx mice similarly reduced muscle membrane injury. The results suggest that dystrophin loss acts as a triggering event in DMD, rather than the main pathogenic mechanism. A lack of dystrophin decreases NOS levels in muscle, leading to cytolytic macrophage infiltration and muscle breakdown. The authors are now introducing NOS transgenes into other mouse models of DMD, and have initiated a clinical trial to test the efficacy of anti-inflammatory drugs in patients with DMD.

Muscle cells experience a nuclear buildup

In response to stimulation, muscle fibers can switch between two types: fast-twitch, used for quick movement; and slow-twitch, which are more resistant to fatigue. On page 27, Liu et al. find that the nuclear localization of a transcription factor may be the key to this switch. Liu et al. applied electrical pulses to isolated adult murine muscle fibers, thus simulating fast-twitch and slow-twitch muscle stimulation in vitro. They then looked at the localization of the transcription factor NFATc, which has been implicated in muscle- and T-cell transcriptional regulation. NFATc is cytoplasmic in unstimulated fast-twitch muscle fibers, but translocates to distinct nuclear foci when the fibers are exposed to kinase inhibitors or trains of electrical pulses at 10 Hz, simulating slow-twitch stimulation. Two conditions do not cause NFATc nuclear-translocation: simulated fast-twitch stimulation, and continuous 1 Hz stimulation, which provides the same number of electrical jolts per minute as the 10 Hz pulses without mimicking any natural stimulation pattern. The nuclear NFATc localizes to distinct intranuclear foci. Liu et al. report that the foci are similar in size and shape to the Cajal bodies that are believed to be involved in splicing in certain cells, but the two structures may not be the same. The authors are now trying to identify additional components of the NFATc-containing foci, and hope to use their in vitro system to determine whether NFATc translocation alone is sufficient to initiate the conversion of fast-twitch muscle fibers into slow-twitch fibers.

Bone breakage

Many growth factors that promote the formation of bone-forming cells called osteoblasts are thought to act through a transcription factor called core binding factor α1 (Cbfa1). Mice lacking Cbfa1 fail to form any mature osteoblasts or bones, and experiments with a dominant negative form of Cbfa1 have suggested that the protein is important in regulating osteoblast functions such as matrix formation and mineralization. Now, Liu et al. (page 157) find that mice overexpressing Cbfa1 in their osteoblasts have weak bones and multiple fractures within a few weeks after birth. Immature osteoblasts accumulate, suggesting that the excess Cbfa1 inhibits a late stage of osteoblast maturation. Thus, Cbfa1 is essential early in maturation but must then be downregulated to allow final maturation.