Mechanisms of muscle damage in muscular dystrophy

G.S. Lynch, Department of Physiology, The University of Melbourne, Victoria 3010, Australia.

Muscular dystrophies are a group of neuromuscular disorders characterised by progressive and extensive muscle wasting and weakness. Patients with Duchenne muscular dystrophy (DMD) have mutations in the gene for the subsarcolemmal protein dystrophin. The muscles of the *mdx* mouse, an animal model for DMD, also lack dystrophin. Although *mdx* mice exhibit a relatively benign phenotype, the lack of dystrophin renders their limb muscles more susceptible to contraction-induced injury (Brooks 1998; DelloRusso *et al.*, 2002). Due to its role in linking the cytoskeleton to the extracellular matrix, dystrophin is postulated to have a mechanical function, namely the stabilisation of the muscle fibre membrane integrity in both quiescent and contracting muscles (Lynch *et al.*, 2000). Support for this hypothesis has been demonstrated by the sarcolemmal fragility of fibres from *mdx* mice which have a greater susceptibility to rupture following osmotic shock and active muscle lengthening, although the findings remain controversial (Brooks, 1998). In many cases, the severity of the contraction protocols used, make it difficult to discern genuine differences between the injury susceptibility of normal and dystrophin-deficient skeletal muscle.

More recently, contraction protocols have been devised that might more accurately test the hypothesis that dystrophin deficiency increases the likelihood of contraction-mediated damage. These protocols are important for testing whether muscles from transgenic *mdx* mice, expressing different truncated dystrophins are protected against damage caused by muscle activity. In fact, injection of adeno-associated viruses carrying micro-dystrophins into dystrophic muscles of immunocompetent *mdx* mice results in a significant reversal of the histopathological features of the disease, and protection from contraction injury, highlighting the clinical potential of these therapeutic approaches (Harper *et al.*, 2002).

It is generally accepted that damage to membranes in dystrophic muscle represents a component of the initial mechanism of injury that does not occur in normal muscles. Membrane disruption could allow influx of calcium that triggers the cellular pathways of destruction, leading to necrosis. However, the lack of dystrophin may not be the sole reason for the greater susceptibility of dystrophic muscles to contraction-mediated damage. Other studies have suggested that the appearance of significant numbers of abnormally branched fibres in dystrophic muscles might also contribute to the aetiology of damage. Branched fibres and their specific branching points may render them inherently weaker than non-branched fibres and this may help explain why regeneration ultimately fails (Schmalbruch, 1984).

Traditionally, it was thought that larger calibre fibres were more susceptible to contraction-mediated damage than small calibre muscle fibres, and that increasing the size of dystrophic muscle fibres following treatment with anabolic agents may actually increase injury susceptibility. Instead, recent work by Bogdanovich and colleagues (2002) suggests that making muscle fibres larger may ameliorate the symptoms of the disease, as advocated previously (Lynch, 2001). Although these results are encouraging from a clinical perspective, it is still possible that these hypertrophied dystrophic muscles remain vulnerable to extreme stress (Zammit & Partridge, 2002).

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