MUSCULAR DYSTROPHY

Fixing the leak

Duchenne muscular dystrophy (DMD), a genetic disorder characterized by rapidly progressing muscle weakness and early death, remains without a cure and has only limited supportive therapies. Now, writing in *Nature Medicine*, Bellinger and colleagues reveal that defective skeletal muscle ryanodine receptor (RYR1) may contribute to the deregulated Ca^{2+} homeostasis and muscle damage typical of this disease, thereby suggesting a new therapeutic target.

DMD is the most common muscular dystrophy, which is caused by an absence of the protein dystrophin. The consequential disruption of the sarcolemmal dystrophin–glycoprotein complex (DGC), which ordinarily forms a crucial link between the cytoskeleton and the extracellular matrix, disturbs cytoplasmic Ca^{2+} homeostasis, which leads to muscle cell damage. Previous studies have indicated the occurrence of an intracellular Ca^{2+} leak within dystrophic muscle. RYR1 is a skeletal muscle sarcoplasmic reticulum Ca^{2+} channel that releases stored Ca^{2+}, which mediates muscle contraction when required. Given this knowledge, Bellinger and colleagues hypothesized that faulty RYR1 may contribute to the abnormal intracellular Ca^{2+} levels and the subsequent deleterious effects in DMD.

To explore their theory, the authors first analyzed the RYR1 complex in the extensor digitorum longus hindlimb muscle of the X-chromosome-linked muscular dystrophy (mdx) mouse, which lack dystrophin and so provide a model of DMD. In 35-day-old mice, in which muscular dystrophy is histologically evident, *S*-nitrosylation of cysteine residues in RYR1 was significantly higher than in control mice, probably owing to increased levels of inducible nitric oxide synthase. This effect correlated with depletion of the Ca^{2+} channel-stabilizing protein calstabin 1 (also known as FKBP12) from the complex, causing a Ca^{2+} leak from RYR1 channels.

Next, they determined whether restoration of RYR1 function has beneficial effects in mdx mice. Subcutaneous administration of the RYR Ca^{2+} release channel stabilizer, the 1,4-benzothiazepine derivative S107, for 2 weeks to 4–5-week-old mdx mice, prevented depletion of calstabin 1 from *S*-nitrosylated RYR1. Muscle damage was probably decreased, as suggested by a decreased serum creatine kinase concentration (a marker of muscle necrosis) and reduced activation of calpains (which cause muscle damage). Positive effects on muscle function were also observed: forelimb grip strength improved and downhill run rate was higher. Importantly, continuation of treatment up to 4 weeks improved muscle histological hallmarks of dystrophy.

To further assess the potential improvements in muscle function, mdx mice were exposed to S107 in their drinking water for 7–10 days. A deficit in force production observed in mdx mice during eccentric contraction was restored, in conjunction with a reduced frequency of spontaneous Ca^{2+} release events. In addition, treated mice spent more time on a wheel, achieving 50% higher maximal velocities, than untreated mice. Finally, *in situ* force measurements of the extensor digitorum longus muscle revealed that S107 increased specific force as well as resistance to fatigue.


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Together, these studies indicate that inhibition of RYR1 Ca^{2+} leak may protect DMD muscle from damage and improve function. This points to a possible new strategy for the treatment of DMD, with the potential for considerably faster effects than current gene therapy approaches may provide.

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ORIGINAL RESEARCH PAPER Bellinger, A. *et al.* Hypernitrosylated ryanodine receptor calcium release channels are leaky in dystrophic muscle. *Nature Med.* **15**, 325–330 (2009)
FURTHER READING Khurana, T. & Davies, K. Pharmacological strategies for muscular dystrophy. *Nature Rev. Drug Discov.* **2**, 379–390 (2003)