Anti-inflammatory drugs, or increased IGF-1 expression, reduce necrosis of dystrophic muscle

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Dystrophic myofibres with defective dystroglycan complexes are susceptible to sarcolemma damage. Little is known about the balance between the repair of minor damage and the necrotic death of these myofibres. Inflammatory cytokines and cells can exacerbate initial damage, and we have shown reduced necrosis of dystrophic mdx muscle following a range of *in vivo* anti-inflammatory interventions including; silencing TNF-α using antibodies (human Remicade/Infliximab and mouse cV1q) or the soluble receptor (Enteracept/Enbrel), the depletion of neutrophils, the blocking of mast cell degranulation (Cromolyn), the blocking of complement C5a, and exposure to the corticosteroid prednisolone. The protective effect of these treatments on myofibre necrosis was tested in the mdx mouse model of Duchenne Muscular Dystrophy (DMD) using both adult mdx mice where the relatively low level of muscle damage is increased in reponse to voluntary exercise, and young mice at the time of acute onset of necrosis. These data support an important role for inflammation in exacerbation of muscular dystrophy and suggest new drug interventions to reduce the clinical severity of DMD. Conversly, we have shown that over-expression of IGF-1 specifically within dystrophic myofibres of MLC.IGF-1:Ea/mdx also reduces necrosis. As TNF-α can block IGF-1 signalling, the mechanisms of action of both TNF-α and IGF-1 combined with interactions between these signalling pathways is a central focus of our ongoing research.

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