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Commentary

# IL-6 Blockade as a Therapeutic Approach for Duchenne Muscular Dystrophy

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Duchenne muscular dystrophy (DMD) is a recessive X-linked form of genetic muscle disease affecting approximately 1 in 3500 males (Flanigan, 2014). Boys with DMD carry mutations in the dystrophin gene resulting in defective or absent dystrophin protein. Both skeletal and cardiac muscles undergo progressive damage in this disease, with most boys confined to wheelchairs by age 12. There is currently no cure for DMD and affected patients die from respiratory failure, cardiomyopathy, or other complications at an average age of 25 years. In this issue of *EBioMedicine*, Pelosi and colleagues present evidence that blockade of interleukin-6 (IL-6) ameliorates muscle destruction and weakness in a mouse model of DMD and suggest that this may represent a novel therapeutic approach in humans.

In DMD, dystrophin deficiency disrupts the dystrophin–glycoprotein complex, leading to muscle fiber necrosis as well as a prominent inflammatory response. Although the inflammatory response may play a role in muscle repair, accumulating evidence suggests that it also contributes to muscle damage (Spencer and Tidball, 2001). In the 1970s, recognition of this inflammatory response prompted Drachman and colleagues to treat DMD patients with glucocorticoids (Drachman et al., 1974). The improvements these investigators noted in some DMD patients in an open-label trial have subsequently been confirmed in randomized, placebo-controlled clinical trials (Manzur et al., 2008). However, glucocorticoids, which remain the only available treatment for DMD, have relatively modest effect on the course of this fatal disease. Furthermore, these drugs have significant side effects including weight gain, osteoporosis, and increased risk of infection. Clearly, more effective and safer treatments for DMD are desperately needed.

In an article in this issue of *EBioMedicine*, Pelosi and colleagues observe that the inflammatory cytokine IL-6 is expressed at high levels in the serum of boys with DMD as well as in inflammatory cells infiltrating their muscle tissue. Moreover, serum IL-6 levels were increased in untreated DMD patients compared to those receiving treatment with glucocorticoids. Taken together, these observations suggested that IL-6 might play a role in mediating muscle damage through the inflammatory response.

In order to further study the possible role of IL-6 in mediating muscle damage, these investigators utilized the mdx mouse model of DMD. These mice lack functional dystrophin and, like boys with DMD, develop a progressive muscular dystrophy that includes a prominent inflammatory response. As in boys with DMD, Pelosi and colleagues demonstrated that circulating levels of IL-6 are increased and cells expressing high levels of IL-6 infiltrate the diaphragm muscles of mdx mice. To test whether blockade of IL-6 would ameliorate the dystrophic process in mdx mice, these mice were treated with an antibody recognizing the IL-6 receptor. Compared to untreated mdx mice, mice treated with the neutralizing antibody had decreased myofiber necrosis, improved functional performance after exercise on a treadmill, and evidence of a decreased inflammatory response in their muscle tissue.

Based on their findings, Pelosi and colleagues suggest that IL-6 inhibitors, which are already approved for children with systemic juvenile idiopathic arthritis, should be considered for use in boys with DMD. However, optimism about their potential effectiveness is tempered by at least five considerations. First, another recent study by Kostek et al. showed that IL-6 blockade increased muscle inflammation and did not significantly improve muscle function in mdx mice (Kostek et al., 2012). These conflicting results may be due to differences in the dosing regimens used in each study. If that's the case, it remains unclear what the appropriate dosing regimen would be for DMD patients. Second, boys with DMD frequently die as a result of cardiomyopathy and the effect of IL-6 on cardiac muscle has not been studied. Third, in addition to promoting a potentially harmful inflammatory milieu, IL-6 has also been reported to play a role in muscle regeneration by promoting myoblast differentiation (Serrano et al., 2008); any therapeutic intervention aimed at blocking IL-6 in humans should consider this dual role of IL-6. Fourth, although mdx mice have been used extensively to understand the pathophysiology of DMD, they have limitations as a model for testing the effectiveness of therapeutic interventions (Partridge, 2013). Indeed, the literature includes numerous examples of drugs that improved outcomes in mouse models but did not have a similar effect in humans. And finally, any therapy for DMD that does not involve repletion of dystrophin is unlikely to cure this fatal disease. Despite these caveats, IL-6 blockade certainly warrants further study as a potential treatment modality for patients with DMD.

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## Conflict of interest statement

The authors declare no conflict of interest.

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