Mouse model of Duchenne muscular dystropy identifies potential new approaches to therapy

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Genetic ablation of P2RX7 can improve muscle function and partially correct cognitive impairment and bone loss in a mouse model of Duchenne muscular dystrophy (DMD), according to a study published this week in *PLOS Medicine*. The study, conducted by Dariusz Gorecki of the School of Pharmacy and Biomedical Sciences, University of Portsmouth, UK and colleagues, additionally suggests that P2RX7 antagonists can reduce certain DMD phenotypes in these mice.

Duchenne muscular dystrophy comprises muscle waste with chronic inflammation, cognitive and behavioral impairments and low bone density. DMD is caused by mutations in dystrophin, a membrane scaffold protein with a role in protecting muscle fibers from damage during muscle contraction. The function of P2RX7, a purinoceptor that senses ATP released from damaged cells and activates the innate immune response, is altered in dystrophic cells to mediate cell death in the mdx mouse model of DMD and in human DMD. In this study, the researchers investigate whether genetic ablation of P2RX7 can attenuate the DMD symptoms of the mdx mouse model. The researchers found that double mutant mice that make no functional dystrophin or P2RX7 showed improved muscle structure and strength, decreased inflammation, and decreased fibrosis compared to mdx mice. P2RX7 ablation also reduced blood levels of creatinine kinase, cognitive impairment, and bone structure alterations. Finally, aspects of the dystrophic pathology in mdx mice could also be reduced by treatment

with P2RX7 antagonists.

The findings show that, in mdx mice, P2RX7 ablation affects multiple disease phenotypes analogous to those of human DMD. However, data from animal models always require validation in human studies. Nonetheless, should the findings translate to human pathology, these results may identify new options for DMD therapies. The authors state, "Given that specific P2RX7 antagonists have been in human trials for other conditions, these could be readily repurposed for treatment of this lethal disease."

More information: Sinadinos A, Young CNJ, Al-Khalidi R, Teti A, Kalinski P, Mohamad S, et al. (2015) P2RX7 Purinoceptor: A Therapeutic Target for Ameliorating the Symptoms of Duchenne Muscular Dystrophy. *PLoS Med* 12(10): e1001888. DOI: 10.1371/journal.pmed.1001888