Computational models predict the effect of anti-fibrotic therapies in Duchenne muscular dystrophy

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Duchenne muscular dystrophy is a devastating neuromuscular disease caused by the lack of the dystrophin protein. The lack of dystrophin renders the muscle more susceptible to contraction-induced damage resulting in chronic damage and muscle degeneration. Despite extensive experimental research, there remains no cure for this disease. Therapies to replace the missing dystrophin protein show promise; however they have yet to show clinical benefit. We believe the failure to translate successful therapies from animal models to the clinic occurs because DMD is a complex disease driven by multiple mechanisms, including inflammation, fibrosis, altered satellite stem cell (SSC) dynamics, and an increased susceptibility to damage. In order to develop successful therapies, we must understand how these mechanisms drive disease progression and how interventions should be timed to elicit maximal benefit.

To address this challenge, we developed a multiscale computational modeling framework that includes agent-based (ABM) and finite element (FE) models of skeletal muscle degeneration and regeneration. The FE model simulates an eccentric-contraction in dystrophic muscle and predicts the amount of damage in the muscle. This damage is then used as the input boundary condition to the ABM. The ABM simulates the regenerative response of inflammatory cells, fibroblasts, and satellite stem cells (SSCs) to repair the muscle. The modeled cell behaviors are governed by over 40 rules curated from over 100 literature sources. The goals of this work were to (i) tune our model to capture experimental results in the literature, such as the impaired regeneration from low levels of fibroblasts or SSC depletion, and (ii) use the model to predict the potential effect of anti-fibrotic therapies.

To achieve this, we developed computational models of DMD phenotypes to test the effect of anti-fibrotic drugs at two stages of disease: early (e.g., no fibrosis, extensive inflammation) and late (e.g., fibrosis, attenuated inflammation). The simulations revealed a temporally dependent effect of therapies. At the early stages of disease there was no effect with the anti-fibrotic therapy. At the late stages we predicted increased damage in the muscle for the first 15 days, since elimination of fibrosis was predicted to increase the contraction-induced damage. However, this reduced fibrosis also allowed for a more robust regenerative response and we predicted better regeneration at 28 days. These simulations revealed the critical importance of understanding the temporal effects of therapies, to determine when therapies would be most effective, and how to design experiments to capture their true effect.