Revertant fiber studies in Duchenne muscular dystrophy

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ORAL Discovery

Duchenne Muscular Dystrophy (DMD) is a genetic disorder caused by mutations in the dystrophin gene. DMD patients progressively lose muscle function due to lack of dystrophin, a protein required for muscle stability. However, sporadic dystrophin-positive revertant fibers (RFs) are observed in dystrophic muscles of DMD patients and murine models such as mdx. RFs clonally expand with age during frequent regeneration of necrotic fibers, and are believed to arise from muscle precursor cells that undergo spontaneous exon skipping of the mutation during translation. Mdx (nonsense mutation in exon 23), a DMD mouse model, is found to have lower regenerative capacity with a DBA/2 genetic background (mdx-DBA/2) than a C57BL/6 genetic background (mdx-C57BL/6). We hypothesize that RF expansion depends on the regenerative capacity of dystrophic muscles. To test our hypothesis, we employed haematoxylin and eosin (H&E) staining and immunostaining of tibialis anterior (TA) and gastrocnemius (GC) muscles in mdx-DBA/2 mice for 2, 6, 12 and 18 months of age. We compared our results to our recently published data, which examined the RF expansion and regenerative capacity in mdx-C57BL/6 mice (Echigoya et al., 2013). We found, via H&E staining, that the number of centrally nucleated fibers (indicative of regenerating muscle fibers) in mdx-DBA/2 is lower than mdx-C57BL/6 mice in TA and GC muscles for all age groups. Our immunostaining results show that mdx-DBA mice have lower RF expansion than mdx-C57BL/6 in all age groups. Taken together, our results show that lower RF expansion is attributable to reduced regenerative capacity of muscle precursor cells.

Reference: