Revertant fiber studies in Duchenne muscular dystrophy

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ORAL Discovery

Duchenne Muscular Dystrophy (DMD) is 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) straining 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:

Echigoya Y*, Lee J*, Rodrigues M* (*equally contributed), Nagata T, Tanihata J, Nozohourmehrabad

A, Panesar D, Miskew B, Aoki Y, Yokota T (2013) Mutation Types and Aging Differently Affect

Revertant Fiber Expansion in Dystrophic Mdx and Mdx52 Mice. PLoS One. 8(7):e69194.