Does skeletal muscle fiber branching play a role in the inability of old EDL dystrophic muscle to resist large passive stretches?

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TO THE EDITOR: Hakim et al. (3) examined the passive mechanical properties of fast-twitch extensor digitorum longus (EDL) muscles from young and old mdx dystrophic mice. They elegantly showed that by increasing passive strain on the dystrophic muscle from 110% of optimal length (Lo) to 160% of Lo, the muscle physically ruptured in a manner that got progressively worse with age. At the oldest age points tested, 14 and 20 mo, the dystrophic muscles pulled apart. Importantly, in age matched dystrophin positive controls, this pulling apart of the muscle did not occur. The authors (3) propose that one reason for this dramatic tearing of the dystrophic muscle with age is due to increased fibrosis and muscle stiffness. Undoubtedly, increasing stiffness with age would play a role in dystrophic damage. However, I suggest that the widely reported age-related increase in the number of branched skeletal muscle fibers present within the dystrophic muscle will also make a significant contribution (1, 2, 4–6). It is not the absence of dystrophin, in itself, that is weakening the muscle; as it is absent from both young and old mdx muscles. There must be some additional age-related factor or factors at play. The paper by Hakim et al. (3) demonstrates that ageing in itself is not one of these factors. To further interpret the findings of Hakim et al. (3), I propose that the production of branched fibers in ageing dystrophic muscle contributes to the increase susceptibility to damage (1). As the dystrophic disease progresses, one of the most striking features of the skeletal muscle pathology in the dystrophinopathies is the appearance of abnormal, branched, skeletal muscle fibers (6). These branched fibers have been widely reported in humans with Duchenne muscular dystrophy, where the number of branched fibers has been correlated with the severity of the disease (5). Earlier work from my laboratory has shown that there is a strong correlation between the appearance of branched fibers in the mdx mouse and the susceptibility of EDL muscle to eccentric damage (2). In this work we showed a mild eccentric contraction produced no damage in EDL muscle from young mdx mice with very few branched fibers and a 60% force deficit in old EDL mdx muscles, where over 90% of fibers show some degree of branching. Further evidence that it was the fiber branching itself and not the absence of dystrophin that resulted in muscle weakness and breakage was obtained using the skinned fiber technique. When a single isolated mdx muscle fiber was tied up with a branch between the points of attachment it broke, then when the same muscle fiber was reattached with no branch point between the attachments, it could sustain maximal isometric force without breaking (4). This is evidence that the breakage is a result of branching and not some other intrinsic weakness. In the study by Hakim et al. (3), by 14–20 mo nearly 100% of mdx EDL fibers would have extensive branching and I would suggest this makes a significant contribution to the muscle tearing, in addition to the increase in stiffness mechanism proposed by the authors (3).

DISCLOSURES

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AUTHOR CONTRIBUTIONS

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