Novel regeneration in nemaline myopathy

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Nemaline myopathy (NM) is the most common of the congenital myopathies, presenting at birth or in early childhood as hypotonia and muscle weakness. A defining feature of this condition is the presence of electron dense rod-shaped structures in the sarcomeres termed nemaline rods. So far six genes with NM-causing mutations in humans have been identified. These genes code for proteins that form the thin filament of the sarcomere (α-skeletal actin, β-tropomyosin, α-tropomyosin$_{slow}$, nebulin, troponin T slow and cofilin-2).

Recent gene profiling studies on nemaline patients and the α-Tm$_{slow}$(Met9Arg) transgenic mouse model have shown that focal muscle repair and altered regeneration are previously unrecognised features of NM. Affymetric oligonucleotide array analysis of muscle from a heterogeneous group (i.e., various mutations) of patients with NM showed increased expression of genes associated with proliferating myoblasts and satellite cells (*NCAM1* and *CDK4*). This was confirmed immunohistochemically using a satellite-specific marker, Pax7, where there was a 10-fold increase in satellite cell abundance in the nemaline patient samples compared to normal healthy muscle. This is consistent with data from the mouse model where markers of satellite cell number, activated satellite cells and immature fibers (M-Cadherin, MyoD, desmin, Pax7 and Myf6) were elevated by Western-blot and immunohistochemical analysis. This study showed direct evidence of focal muscle repair in a number of muscles from the nemaline mouse (segmental regeneration with centrally-located nuclei) by electron microscopy. In keeping with ongoing repair, there was an increase in the number of fibres with centralised nuclei compared to wild-type mice. The number of central nucleated fibres was rather low (7-12%) compared to diseases characterized by overt regeneration (e.g. muscular dystrophies), which may explain why this feature had not been reported previously for NM. A novel regenerative process was also observed in a previous study on this mouse model, regeneration with a relative lack of centralised nuclei in response to chronic over-stretch.

Taken together, these studies suggest that there is a process of ongoing focal repair in nemaline muscle. This repair is distinct from the classical form of muscle regeneration as occurs in the muscular dystrophies where there is myonecrosis and extensive numbers of regenerating myofibers with centralized nuclei. The focal repair in nemaline myopathy maybe specific to diseases of the sarcomeric thin filament and are distinct from sarcolemmal repair in muscular dystrophy.