Insights into and therapies for nemaline myopathy

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Nemaline myopathy, the most common congenital myopathy, is caused by mutations in genes encoding thin filament and thin filament-associated proteins in skeletal muscles. Severely affected patients fail to survive beyond the first year of life due to severe muscle weakness. Currently, there are no specific therapies for this disease, but we have generated the first mouse model for severe nemaline myopathy in order to trial therapies. This mouse model carries a mutated form of the skeletal actin gene - *Acta1*(H40Y). It has severe muscle weakness that manifests as shortened lifespan, significant forearm and isolated muscle weakness and decreased mobility. Muscle pathologies characteristic of human patients carrying this mutation are present in the mouse (*e.g.* nemaline rods, fibre atrophy and an increase in slow fibres). A previous study by us using a mouse model for a mild form of the disease revealed that fibre hypertrophy may lessen muscle weakness. We tested the impact of hypertrophy by mating the *Acta1*(H40Y) mouse with 3 mouse hypertrophy models. Hypertrophy caused by overexpression of four and a half LIM domains protein 1 and insulin-like growth factor-1 increased forearm strength and mobility, and decreased nemaline pathologies. Dietary L-tyrosine supplements also alleviated the mobility deficit and decreased the chronic repair and nemaline rod pathologies. These results suggest that L-tyrosine may be an effective treatment for muscle weakness and immobility in nemaline myopathy. The positive response to L-tyrosine may provide additional insights into the mechanism of muscle weakness in this disease and other myopathies.