Sarcomere function in nemaline myopathy

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Nemaline Myopathy (NM) is the most common hereditary, non-dystrophic, congenital myopathy. It occurs worldwide with an estimated incidence of 1 per 50,000 live births. Patients with NM are characterized by the presence of nemaline rods in their muscle fibres and by muscle weakness. Historically, this weakness has been ascribed to the nemaline rods impairing muscle cell function. However, patients display weakness before rods occur, indicating that the presence of rods is likely not causative. Thus, the mechanisms leading to muscle weakness in NM are obscure, which hampers the development of therapy.

Seven mutated genes have been observed in NM. Strikingly, all code for proteins of the sarcomeric thin filament, a microstructure crucial for muscle function. Whether the functioning of the thin filament is affected by the genetic defects remains to be studied in detail, and many important questions have yet to be answered. The two most pressing ones are: How is thin filament function affected in NM, and does this explain muscle weakness?

Our research program aims to address these questions by studying thin filament structure and function in NM patients with well characterized genetic mutations. We focus mainly on NM caused by mutations in nebulin - a major constituent of the thin filament - as this represents the main form of NM.

Our findings so far suggest that the nature of muscle weakness in NM strongly depends on which of the seven genes is involved. A better understanding of such genotype-phenotype correlations is important, as it allows to develop genotype-targeted treatment strategies.