Mechanisms leading to muscle weakness in Nemaline myopathy

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Nemaline myopathy (NM) is a heterogeneous congenital non-dystrophic myopathy, characterized by generalized muscular weakness and the presence of nemaline rods in the skeletal muscle. Despite the improvement in the genetic diagnosis of NM, the mechanisms underlying muscle weakness are still not fully understood and no cure is currently available. The aim of this thesis is to identify mechanisms leading to muscle weakness in order to develop treatment strategies which could improve patients’ quality of life.

Permeabilized muscle fibers, from NM patients or animal model, were dissected and mounted between a force transducer and length motor and activated by exposure to solutions containing saturating [Ca$^{2+}$]. Maximal tension, cross bridge cycling kinetics ($k_{tr}$), calcium-sensitivity of force ($pC_{a50}$), Hill coefficient ($nH$), and the active stiffness were determined. Furthermore, maximal tension was determined at incremental sarcomere lengths (range 2.0–3.5 µm) to obtain the force-sarcomere length relationship.

Our results highlight a number of mechanisms leading to muscle weakness in NM patients and NM animal models including thin filament length dysregulation, abnormal calcium sensitivity and altered cross-bridge cycling kinetic. We showed that the cause of muscle weakness is largely dependent on which gene is affected and on the specific mutation present in the patient. The existence of multiple disease-causing genes and the large variety of mutations involved in NM do not allow the development of a unique treatment, but require mutation-specific therapies.