X-ray fiber diffraction as a tool to study Nemaline Myopathy, a debilitating muscle disease

T Irving[1]
[1]Biology, Illinois Inst of Technology, Chicago, IL
irving@iit.edu

Nemaline myopathy (NM) is one of the most common congenital non-dystrophic human muscle diseases and is characterized by severe muscle weakness and the presence of nemaline bodies (rods) in skeletal muscle biopsies. In this talk I will highlight two recent X-ray diffraction studies done at the BioCAT Beamline 18ID at the Advanced Photon Source ANL that have yielded new insights into the pathogenic mechanisms in these debilitating diseases. Both of these studies showed that the muscle dysfunction has its basis in changes in the structure of the actin containing thin filaments. One form of nemaline myopathy is caused by mutations in the KBTBD13 (NEM6) gene. The role of KBTBD13 in muscle is unknown. An international team of investigators recently reported In de Winter J et al. 2020 (J Clin Invest. 130(2):754-767 how a combination of transcranial magnetic stimulation-induced muscle relaxation, muscle fiber- and sarcomere-contractility assays, super-resolution microscopy, and low angle X-ray diffraction revealed that the impaired muscle relaxation kinetics in NEM6 patients are caused by structural changes in the thin filament that are the fundamental cause of muscle weakness. Other forms of NM are due to mutations in nebulin , a giant protein that winds around the actin filaments in the sarcomeres of skeletal muscle. The authors of a second study in Nature Communications (Lindquist et al., Nat Commun. 2020 Jun 1;11(1):2699.) created a mouse model that mimics the typical nebulin-based NM patient with compound-heterozygous mutations. Functional, structural, and biochemical studies revealed altered thin filament structure, increased myofilament lattice spacing, a reduced myofibrillar fractional area, and reduced force production. In particular, X-ray diffraction studies revealed that the actin filament is twisted with a larger radius, that tropomyosin and troponin behavior is altered, and that the myofilament spacing is increased, again showing that the muscle weakness in nemaline myopathy is caused by changes in thin filament structure. These results will be discussed in the context of technical advances at that BioCAT that enabled these studies along with some future directions.