Phosphorylation of tropomyosin – response to sarcomeric stress?

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Tropomyosin (TM) is a key actin-binding protein of the muscle sarcomere. It associates with the troponin complex to regulate calcium dependent actin-myosin cross bridging during muscle contraction. Mutations in the three TM genes cause congenital myopathies (mutations in TPM2 and TPM3) and cardiomyopathies (mutations in TPM1). TM is phosphorylated at a far N-terminal residue (serine 283). Current evidence indicates this modification enhances force generation during muscle contraction by increasing cooperative activation of myosin. Reduced levels of phosphorylation have been linked to reduced cardiac function and lower sarcomeric calcium sensitivity in a mouse model for dilated cardiomyopathy. Although evidence suggests that TM phosphorylation is of biological significance, the processes that regulate TM phosphorylation and the roles it has in adaptation to physiological stress and disease are unclear.

We characterized TM phosphorylation in human skeletal muscle by Western blot and immunohistochemistry using an antibody specific for tropomyosin phosphorylated at serine 283. We assessed phosphorylation status in healthy individuals as well as in patients with a range of genetically defined skeletal muscle diseases to investigate the role of TM phosphorylation in human skeletal muscle.

In healthy individuals tropomyosin is highly phosphorylated during early development and levels decrease during childhood. Immunohistochemistry of stretched longitudinal muscle sections showed that phosphorylated TM is not evenly distributed along the thin filaments, but is concentrated close to the Z-band, a region that interacts with intermediate filament networks and various signalling molecules. Interestingly, contrary to previous studies which found that cardiac pathology was associated with decreased TM phosphorylation, we observed high levels of phosphorylation in adult patients with various types of skeletal muscle disease including tropomyosin-related myopathy, limb-girdle muscular dystrophy 2B and Becker muscular dystrophy.

The localisation of phosphorylated TM adjacent to Z-disks suggests it has other roles in addition to increasing muscle contractility, such as signalling or interaction with intermediate filament proteins. Our finding that tropomyosin phosphorylation is commonly up-regulated in many muscle diseases suggests it is part of a stress response that can be activated by a range of disease processes. Modification of sarcomeric proteins in response to muscle disease is an area that has been largely unexplored and that may contain many worthwhile therapeutic opportunities.