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Mechanisms of disturbance of the contractile function of slow skeletal muscles induced by myopathic mutations in the tropomyosin TPM3 gene

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Abstract

Several congenital myopathies of slow skeletal muscles are associated with mutations in the tropomyosin (Tpm) TPM3 gene. Tropomyosin is an actin-binding protein that plays a crucial role in the regulation of muscle contraction. Two Tpm isoforms, γ (Tpm3.12) and β (Tpm2.2) are expressed in human slow skeletal muscles forming γγ-homodimers and γβ-heterodimers of Tpm molecules. We applied various methods to investigate how myopathy-causing mutations M9R, E151A, and K169E in the Tpm γ-chain modify the structure-functional properties of Tpm dimers, and how this affects the muscle functioning. The results show that the features of γγ-Tpm and γβ-Tpm with substitutions in the Tpm γ-chain vary significantly. The characteristics of the γγ-Tpm depend on whether these mutations located in only one or both γ-chains. The mechanism of the development of nemaline myopathy associated with the M9R mutation was revealed. At the molecular level, a cause-and-effect relationship has been established for the development of myopathy by the K169E mutation. Also, we described the structure-functional properties of the Tpm dimers with the E151A mutation, which explain muscle weakness linked to this substitution. The results demonstrate a diversity of the molecular mechanisms of myopathy pathogenesis induced by studied Tpm mutations.

Keywords: Ca2+-regulation of muscle contraction; actin-myosin interaction; in vitro motility assay; myopathic mutations; slow skeletal muscles; tropomyosin.