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


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.