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МАТЕРИАЛЫ КОНФЕРЕНЦИИ И ШКОЛЫ

MOLECULAR MECHANISMS OF SKELETAL MUSCLE DYSFUNCTION IN THE EARLY STAGES OF HUMAN CONGENITAL MYOPATHY

© 2020 г. O. E. Karpicheva[1,*] and Y. S. Borovikov[1]

[1] *Institute of Cytology of the Russian Academy of Science, Saint Petersburg, Russia*

**e-mail: olexiya6@ya.ru*

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A large number of mutations in the genes of muscle fibre proteins were identified to date. These mutations are causes of severe congenital diseases of the skeletal muscles – myopathies, characterized by muscle weakness and hypotension. The early differential diagnosis of myopathies is extremely difficult due to heterogeneity and insufficient criteria. The molecular mechanisms that lead to muscle weakness due to a variety of genetic disorders are still unknown. The incompleteness of scientific knowledge in this area is the reason for the lack of effective therapy of skeletal myopathies. The purpose of our research is to identify the hallmarks of the contractile system functioning in the presence of different amino acid substitutions and deletions in tropomyosin associated with the development of several variants of skeletal myopathies. We focus on the mechanisms of nemaline myopathy, cap myopathy, congenital fibre type disproportion and distal arthrogryposis, as well as variants not yet described. The main technique is polarized microfluorimetry in single muscle fibres with a reconstructed regulatory system of thin filaments. The specific modification of actin, myosin and tropomyosin with fluorescent probes allows us to obtain priority data on the conformational rearrangements of actin and myosin, which underlie muscle contraction, and on the distinctive features of actin-myosin work regulation by the mutant forms of tropomyosin. It has been shown that muscle weakness and hypotension in skeletal myopathies can be caused by an abnormal change in the position of tropomyosin on thin filaments and in the number of myosin cross-bridges in the conformation of strong binding to actin in the ATPase cycle in response to a change in the concentration of calcium ions in the sarcoplasm of the muscle fibre. Possible ways for the rehabilitation of contractile function of muscle tissue are proposed.

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