Functional significance of interaction of unconventional myosin VI with the AKAP9-PKA complex: Potential novel regulatory mechanism of muscle contraction and myogenic cell differentiation

DESCRIPTION FOR THE GENERAL PUBLIC

Despite enormous work on muscle contraction, mechanisms involved in regulation of muscle function and myogenic cell differentiation still remain to be elucidated. One of yet uncovered mechanisms is involvement of unconventional myosins [i.e. such that do not resemble typical muscle myosins and not form filaments] in muscle function and myogenesis. The data we gathered so far during our pursuit of the function of unconventional myosin VI (MVI) in skeletal muscle and myogenic cells provided evidence that MVI could play important role in muscle, possibly by its involvement in PKA pathway. We showed that this unique myosin motor not only interacted with AKAP9 (A Kinase Anchoring Protein 9), a regulator of PKA kinase activity but it was also phosphorylated by the kinase. Noticeably, both AKAP9 and PKA play important roles for muscle function. Moreover, we observed elevated amount of MVI in patients with muscle atrophy. Therefore the question arises as of what is a role of involvement of MVI in PKA signaling and of functional significance of this novel interaction for skeletal muscle contraction and myogenic cell differentiation. We would also like to reveal whether MVI acts as a substrate for the kinase or whether it is involved in regulation of PKA activity, or may be both mechanisms could be engaged dependent on molecular/physiological context. Response to the following questions should elucidate the nature of this interaction. First, does MVI phosphorylation by PKA affect MVI function and interaction of MVI and PKA with AKAP9? Secondly; does MVI function as a motor targeting AKAP9-PKA complex to the desired muscle fiber localization thus contributing to the AKAP9-dependent regulation of the kinase activity that may affect muscle contraction and myoblast differentiation? And thirdly, is MVI, known to function also in the nuclei of skeletal muscle, involved in PKA function in the nucleus and thus activation of CREB, transcription factor activated by PKA with a role in muscle gene expression?

The studies will be performed on molecular, cellular and tissue levels with the use of muscle of Snell's waltzer mice (SV) that do not synthesize MVI. Modern biochemical, molecular and cellular biology as well as physiological methods and techniques will be employed with special emphasis on contemporary visualization techniques including confocal and electron microscopy, and laser scanning cytometry. We are also going to evaluate the contractile parameters of muscle and single myofibers with the use of the *in vitro* system.

We expect that the obtained results will contribute to better understanding the mechanism(s) regulating/modulating muscle contraction, especially engagement of MVI in muscle function and pathology, and myoblast differentiation. Also, the data will broaden general knowledge on the role of unconventional myosins in muscle contraction and regeneration as well as will bring new insights into the molecular mechanisms leading to myopathies. Thus the outcome of proposed research by understanding mechanisms of muscular disorders could also have potential translational implications.