【Biological Sciences（Biology）】

Structure and dynamics of actin filament complex: mechanism of calcium regulation of muscle contraction

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【Outline of survey】

The actin filament complex, consisting of actin, tropomyosin and troponin, plays the major roles in muscle contraction and its regulation. Transient increase of intracellular Ca^{2+} concentration induces the Ca^{2+} binding to troponin, whose signal is transferred through tropomyosin to polymerized actin, initiating the force generation (the Ca^{2+} regulation). We have so far elucidated for the first time the atomic structures of constituting proteins, troponin and tropomyosin. In this project, the atomic structure of the entire actin filament complex, as well as the structural dynamics should be elucidated, in order to elucidate the mechanism of the Ca^{2+} regulation. What are challenging in this project are, that the structure of the complex as large as 1MDa should be elucidated, and that the path should be found and established to go from the atomic structure to the structural dynamics, then further to our understanding the mechanism. Particularly, using troponin with cardiomyopathy-causing mutations, the relationship between the abnormalities of structural dynamics and the functional aberrations should be elucidated. This must be the path leading to our understanding the mechanism of calcium regulation.

【Expected results】

In this project, we are going to take innovative approaches which may be generally applicable in the biological study. First, we should construct not-naturally-occurring mini-actin filament complex of a uniform length. This is our effort to know the nature by analyzing objects which are artificially constructed, conferring the first step towards “engineering life”. Second, our project also includes developing novel procedures of analyzing structures of elongated protein complexes, which has remained under-developed in the structural biology. Third, we should establish what to measure for our understanding the structural dynamics, and find the path from the structural dynamics to our understanding the mechanism. Finally, we should shed lights on the cause of disease, based on our knowledge on the structural dynamics of the mutated protein. This may lead us to propose novel concept of structural dynamics-based drug design.

【References by the principal investigator】

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【Term of project】 FY2008－2012	【Budget allocation】 **158,200,000 yen** (direct cost)

【Homepage address】 None