Structural studies of the phosphorylation domain of cardiac myosin binding protein-C

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Cardiac myosin binding protein–C (cMyBPC) is a large regulatory protein within the sarcomere, although the molecular mechanism underlying regulation is poorly understood. cMyBPC phosphorylation increases systolic tension, and dissociates the N-terminal region of cMyBPC from the S2 neck region of myosin. cMyBPC mutations are associated with familial hypertrophic cardiomyopathy (FHC), which is one of the most common forms of congenital heart disease. The N-terminal region of cMyBP-C that is phosphorylated and interacts with myosin S2 is the "linker" region between immunoglobulin (IgI) motifs C1 and C2 (C1-linker-C2). Unfortunately, the structure of C1-linker-C2 is unknown. *Ab initio* modeling of this fragment suggested the presence of alpha-helix. We hypothesize that the helix is located within the phosphorylatable linker region. Thus, we have cloned, expressed and purified several fragments of the N-terminal region of cMyBPC and performed structural analysis using circular dichroism (CD) spectroscopy. Our CD data obtained using smaller fragments of C1C2, namely, C1-linker and linker-C2, have confirmed the presence of a similar quantity of α-helix in both C1-linker and linker-C2. We therefore conclude that the α-helix is present in the linker region. Furthermore, we conclude that the folding of the α-helices within the linker region is likely to be independent of the adjacent IgI motifs, C1 and C2.