Circular dichroic spectra of the N-terminal region of cardiac myosin binding protein – C

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Myosin binding protein – C (MyBPC) is a multi-domain protein whose role in the sarcomere is complex and not yet fully understood. Three isoforms of human MyBPC have been identified; fast skeletal, slow skeletal and cardiac. The cardiac isoform has been of particular interest because of its link to the heart disease familial hypertrophic cardiomyopathy (FHC). FHC is caused by the expression of abnormal contractile proteins in the heart muscle including numerous mutations in MyBPC. The core structure of cardiac MyBPC consists of eight immunoglobulin (IgI) and three fibronectin (FnIII) domains, numbered 0 – 10 from the N-terminus.

MyBPC is phosphorylated up to 3 times near the N-terminus and this is associated with increased contractile force. The binding of MyBPC to myosin S2 in a phosphorylatable-dependent manner is well established, although the role of the extent of phosphorylation is unknown. The location of phosphorylation is a linker of about 100 amino acids between IgI domains 1 and 2. The focus of this work is the effect of phosphorylation and FHC mutations on the structure of the linker or the IgI domains that flank it.

The N-terminal IgI motifs, C1C2, have been cloned, expressed, purified and circular dichroic (CD) spectra for (i) the wild type, (ii) the "permanently" phosphorylated mutants (Ser to Asp) and (iii) 9 FHC mutants collected. The spectra indicate that a proportion of the protein is alpha-helix. Modelling of the C1C2 construct also suggested an alpha-helical content and indicated that it is likely to be part of the phosphorylation linker region. Changes in the CD spectra of the FHC mutants indicate a change in secondary structure and may explain the pathogenesis of these mutations. Similarly, a change in spectra due to pseudo-phosphorylation may provide an insight into the functional role of MyBPC in the sarcomere.