## AT THE HEART OF THE MATTER

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Hypertrophic cardiomyopathy (HCM) is an autosomal dominantly inherited primary cardiac disease which is considered to be a model for studying the pathophysiology of cardiac hypertrophy. HCM is caused by numerous mutations in many sarcomeric protein-encoding genes, of which mutations in cardiac myosin binding protein C (cMyBPC) is the second most prevalent cause of HCM worldwide. As different HCM-causing mutations have diverse effects on fibre contractility, a unifying theory for HCM pathophysiology has been sought. Evidence suggests that the mechanism by which mutations in most sarcomeric protein-encoding genes cause HCM involves energy imbalance. However, as the functions and quaternary structure of cMyBPC are largely unknown, the mechanisms through which mutations in cMyBPC cause HCM have remained elusive.

We used yeast two-hybrid screening of cardiac cDNA libraries to identify ligands of cMyBPC domains in which HCM-associated variants have been found, and assessed the effect of these variants on bait:ligand interaction by surface plasmon resonance and/or co-immunoprecipitation.

Novel interactions between C-terminal domains of cMyBPC as well as interactions with titin were identified, and, integrated with previously known biochemical particulars on cMyBPC, allowed development of a model of MyBPC quaternary structure within the sarcomere in which a tight MyBPC trimer-collar surrounds the thick filament backbone[1]. HCM-associated variants in C-terminal domains significantly reduce the affinity of these domains for their respective ligands and destabilise the tight cMyBPC collar. This would promote formation of the loose thick filament structure which has been associated with increased cross-bridge cycling[2].

Our results indicate that the pathophysiology of cMyBPC-associated HCM follows the energy paradigm and supports this mechanism as the unifying pathomechanism underlying HCM.

1. Moolman-Smook et al. Multiple Structures of Thick Filaments in Resting Cardiac Muscle and Their Influence on Cross-Bridge Interactions. Circ Res 2002; 91(8):704-11.

2. Levine R et al. Multiple Structures of Thick Filaments in Resting Cardiac Muscle and Their Influence on Cross-Bridge Interactions. Biophys J 2001; 81:1070-1082.