Human Calmodulin Mutations

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Calmodulin (CaM) is a key sensor of local and global changes in cellular Ca^{2+} concentration, where this archetypical Ca^{2+} binding protein relay Ca^{2+} signals to numerous intracellular interaction partners. The critical role of accurate Ca^{2+} signal sensing on cellular function is underscored by the fact that there are three independent CaM genes (*CALM1-3*) in the human genome encoding the exact same CaM protein. Moreover, the CaM amino acid sequence is completely conserved across all vertebrate species. It was therefore a big surprise when we identified the first CaM missense mutations in humans in 2012. Today, more than 25 human CaM mutations have been described in patients with severe cardiac arrhythmias, constituting the cardiac calmodulinopathies. This presentation will focus on how biochemical, biophysical and structural studies collectively have enabled plausible molecular mechanisms for the cardiac calmodulinopathies. CaM mutations demonstrate vastly differential effects on protein structure, Ca^{2+} and target binding affinity. Further, regulation of key cardiac ion channels, including the voltage-gated calcium channel ($Ca_V1.2$) and the sarcoplasmic reticulum Ca^{2+} release channel (RyR2), is differentially impaired by individual CaM mutations, suggesting a mechanism for their distinct phenotypes.