

Structural insight of Ca^{2+} induced Ca^{2+} release mechanism revealed by cryo-EM

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Ryanodine receptor (RyR) is a Ca^{2+} release channel in the sarcoplasmic reticulum of skeletal and cardiac muscles and plays a key role in excitation-contraction coupling. It is widely known that the cardiac specific isoform of the receptor (RyR2) mediates Ca^{2+} induced Ca^{2+} release (CICR) that opens the channel by binding of Ca^{2+} to the RyR2. Although number of structures of the RyR1 and RyR2 have already been determined by cryo-EM with near atomic resolution, there is no reported open structure just with bound Ca^{2+} , and most structures in the open state were created by adding extra molecules such as caffeine and ATP in addition to Ca^{2+} . Therefore, the mechanism of CICR is still largely unknown. Here, we have successfully obtained high-resolution cryo-EM structure of recombinant RyR2 in the open state just with bound Ca^{2+} . By comparing with structure in the closed state, we are finally able to discuss the mechanism of CICR clearly. The results of functional studies with numerous mutant RyR2 channels strongly support our mechanism.