AN MBG FOCUS TALK

hosted by Section for Structural Biology
Dept. Molecular Biology & Genetics, Aarhus University


Focus talks in Molecular Biology at MBG

Tuesday 13 January 2015 at 11:15-12:00

The conference room (3130-303), 3. floor, Gustav Wieds Vej 10C, Aarhus

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The ryanodine receptor store-sensing gate controls Ca^{2+} waves and Ca^{2+}-triggered arrhythmias

Spontaneous Ca^{2+} release from intracellular stores is important for various physiological and pathological processes. In cardiac muscle cells, spontaneous store overload -induced Ca^{2+} release (SOICR) can result in Ca^{2+} waves, a major cause of ventricular tachyarrhythmias (VTs) and sudden death. The molecular mechanism underlying SOICR has been a mystery for decades. Here we show that a point mutation, E4872A, in the helix bundle crossing region (the proposed gate) of the cardiac ryanodine receptor (RyR2) completely abolishes luminal, but not cytosolic, Ca^{2+} activation of RyR2. The introduction of metal-binding histidines at this site converts RyR2 into a luminal Ni^{2+}-gated channel. Mouse hearts harboring a heterozygous RyR2 mutation at this site (E4872Q) are resistant to SOICR and are completely protected against Ca^{2+}-triggered VTs. These data show that the RyR2 gate directly senses luminal (store) Ca^{2+}, explaining the regulation of RyR2 by luminal Ca^{2+}, the initiation of Ca^{2+} waves and Ca^{2+}-triggered arrhythmias. This newly identified store-sensing gate structure is conserved in all RyR and inositol 1,4,5-trisphosphate receptor isoforms.

Link to the article *The ryanodine receptor store-sensing gate controls Ca^{2+} waves and Ca^{2+}-triggered arrhythmias* (Chen et al. 2014):
http://www.nature.com/nm/journal/v20/n2/full/nm.3440.html

Link to Wayne Chen's group website:
https://www.ucalgary.ca/pp/profiles/s-r-wayne-chen

Host:
Claus Olesen, Section for Structural Biology
Dept. Molecular Biology & Genetics, Aarhus University

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