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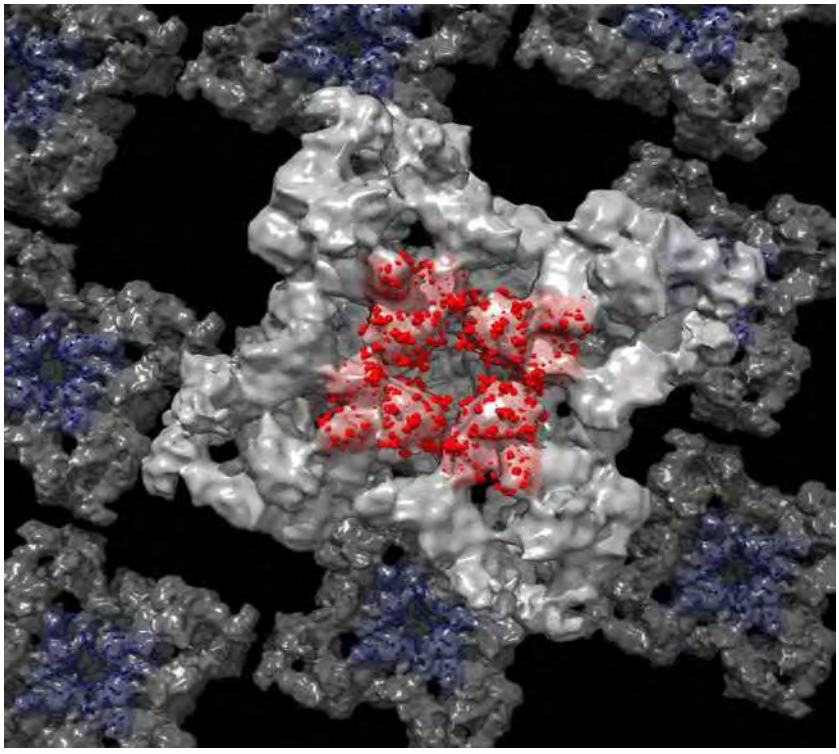
The Ryanodine Receptor: Arrhythmias and Muscle Disorders at High Resolution

F. Van Petegem[1]

[1]*University of British Columbia, Department of Biochemistry, Vancouver, Canada*

Calcium ions play crucial roles in our bodies, acting as second messengers in multiple signaling pathways. The resting calcium levels in the cytosol are very low, but can increase rapidly and transiently by influx from the extracellular space, or by release from intracellular stores. The Endoplasmic and Sarcoplasmic Reticulum (ER/SR) form major intracellular calcium stores. The 'Ryanodine Receptor' (RyR) is a protein that dictates calcium release from the ER/SR. It forms a huge ion channel with a molecular weight exceeding 2 MegaDalton. RyRs are expressed in multiple cell types, but are particularly abundant in cardiac and skeletal muscle, where they are directly involved in excitation-contraction coupling. Three RyR isoforms exist in mammalian species (RyR1, RyR2, RyR3). Mutations in RyR1 and RyR2 have been linked to a number of devastating genetic disorders, including stress-induced cardiac arrhythmias (CPVT), malignant hyperthermia, and central core disease. In the past 5 years we have been solving crystal structures of several RyR domains. Cryo-electron microscopy structures have helped us to build pseudo-atomic models, allowing us to locate these domains in full-length RyRs. Over 80 disease mutations are scattered throughout the structures. The bulk of these affect domain-domain interactions. By comparing the RyR in the open and closed state, we find that some of these interactions are labile: they are disrupted during channel opening. Many disease mutations weaken these interactions, leading to facilitated channel opening, resulting in premature or prolonged release of calcium. In addition, many other disease mutations affect the same labile interactions allosterically. Stabilizing the closed-state domain-domain interactions may therefore be of therapeutic value.

[1] *Tung, C., Lobo, P.A., Kimlicka, L., Van Petegem, F. (2010) Nature, 468, 585-588,* ***[2]*** *Kimlicka, L., Lau, K., Tung, C., Van Petegem, F. (2013) Nat. Comm., 4:1506.,* ***[3]*** *Yuchi, M., Lau.,K., Van Petegem, F. (2012) Structure, 20,1201-1211*



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