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**POSTER ABSTRACT PRESENTATIONS**

**SESSION TITLE: STRUCTURE OF MEMBRANE PROTEINS**

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**Abstract P-12: Structure of RyR1 in Native Membranes**

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**Background:** Ryanodine receptor 1 (RyR1) mediates excitation-contraction coupling by releasing Ca<sup>2+</sup> from the lumen of sarcoplasmic reticulum (SR) to the cytoplasm of skeletal muscle cells. RyR1 activity regulation is complicated and modulated by numerous molecules, including several regulatory proteins from both the cytoplasmic and luminal sides of the SR, and cation ions such as Ca<sup>2+</sup> and Mg<sup>2+</sup>, and chemicals such as caffeine and ryanodine. The activity regulation mechanism of RyR1 is not fully elucidated, though high resolution structures of purified RyR1 in detergent solved by single particle cryo-EM have been reported.

**Methods:** We isolated the SR from rabbit skeletal muscle and imaged RyR1 in native SR membrane with cryo-electron tomography. The structures of RyR1 in closed and open states were solved by sub-tomogram averaging, respectively.

**Results:** Compared to the reported structures of purified RyR1, our structure reveals the occupied competitive binding site of the regulatory proteins calmodulin and S100A1 on RyR1, helix-like densities traversing the bilayer approximately 5 nm from the RyR1 which are speculated to be triadin or junctin, and sarcoplasmic extensions linking RyR1 to the putative calsequestrin network. We document the major conformation of RyR1 *in situ* and its structural variations. Activation of RyR1 leads to significant changes of membrane curvature and sarcoplasmic extensions movement.

**Conclusion:** Our structures of RyR1 *in situ* show novel densities in cytoplasmic region and transmembrane region and SR lumen, respectively. Activation of RyR1 *in situ* reveals new conformational changes in the SR membrane and SR lumen. The results provide structural insights for mechanistic understanding of RyR1 in native environment.

**Key Words:** ryanodine receptor • sarcoplasmic reticulum • *in situ* • sub-tomogram averaging

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