Functional study of the ryanodine receptor type 1 using cryo-electron microscopy

A. des Georges[1,2,3*], O.B. Clarke[2*], R. Zalk[4*], K.J. Condon[2,3], R.A. Grassucci[3], W.A. Hendrickson[2,4], A.R. Marks[4,5,6], J. Frank[2,3,7]

[1]Advanced Science Research Center, City University of New York, [2]Department of Biochemistry and Molecular Biophysics, [3]Howard Hughes Medical Institute, [4]Department of Physiology and Cellular Biophysics, [4]Department of Medicine, [6]Wu Center for Molecular Cardiology, College of Physicians and Surgeons, [7]Department of Biological Sciences, Columbia University, New York, NY, USA. *Contributed equall,. **amedee.desgeorges@asrc.cuny.edu**

Cryo-electron microscopy (cryo-EM) is revolutionizing the structural biology of membrane proteins. It has allowed the structural study of long sought after targets, such as the type 1 ryanodine receptor (RyR1). But another very important advantage is that it allows to study the complex dynamics associated with membrane protein function.

The type-1 ryanodine receptor (RyR1) is an intracellular calcium (Ca2+) release channel required for skeletal muscle contraction. We used single-particle cryo-EM to study the dynamics of RyR1 in multiple functional states, revealing the conformational changes key to channel gating and ligand-dependent activation (1). The binding sites for the channel activators Ca2+, ATP and caffeine were identified and the conformational changes associated with their binding observed independently. They induce by themselves a priming of the cytoplasmic assembly without pore dilation. In contrast, in the presence of all three activating ligands, open and closed states of the pore were obtained from the same sample, enabling analysis of conformational changes associated with gating. The analysis of multiple functional states was greatly facilitated by the use of holey-gold grids, which allowed cryo-EM reconstructions to reach high resolution with much fewer number of particles than with conventional holey carbon grids.

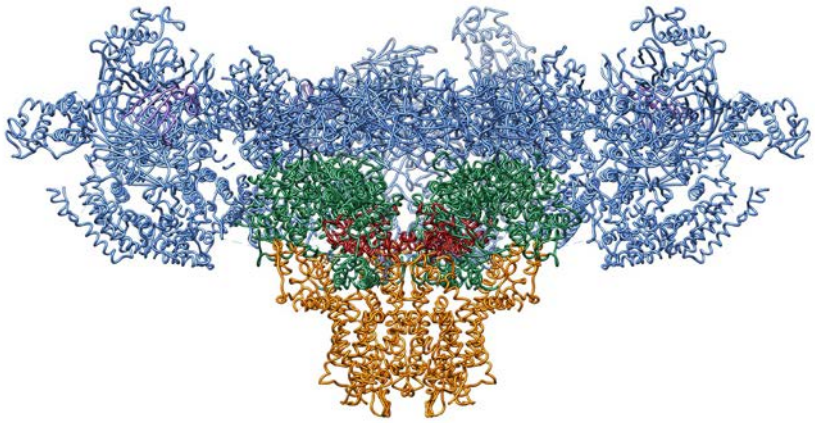

Figure 1: Architecture of the ryanodine receptor

References

[1] - A. des Georges, O.B. Clarke, R. Zalk, Q. Yuan, K.J. Condon, R.A. Grassucci, W.A. Hendrickson, A.R. Marks, J. Frank, Structural basis for gating and activation of RyR1. Cell. **167**, 145 (2016).