Yulia Einav, J Bioanal Biomed 2019, Volume 11
DOI: 10.4172/1948-593X-C1-047

The novel suppression of function mutation in the cardiac RyR2 channel presents an allosteric dose-dependent effect mechanism

Yulia Einav
Holon Institute of Technology, Israel

The cardiac ryanodine receptor RyR2 is a calcium release channel present in the sarcoplasmic reticulum, which plays a major role in regulation of Ca^{2+} homeostasis in the heart. We discovered a novel RyR2 missense mutation, G3118R, with recessive co-segregation, in a large family presenting with cardiac arrest and ventricular fibrillation phenotype. Interestingly, and unlike the other clinically relevant mutations in this gene, which are dominantly inherited, the clinically affected individuals in this family are homozygous for the mutation, whereas the heterozygous family members are almost unaffected. Moreover, the mechanism by which this mutation determines this unusual clinical phenotype is unknown. The aims of this study were to perform functional and structural analysis of G3118R RyR2 in order to investigate the mechanism of this mutation's pathogenicity. We inserted the mutation into HEK293 cells and performed functional studies, including measurements of changes in intracellular Ca^{2+} levels and the monitoring of the endoplasmic reticulum Ca^{2+} dynamics. G3118R causes suppression of function of the channel, which is by far less described mechanism caused by most RyR2 mutations. Next, we used a computational model to study the changes in the stability and the flexibility of RyR2 protein. We found that G3118R, a peripheral mutation located in a region, whose function is unknown, causes a major allosteric effect on the channel pore region of two out of the four RyR2 monomers, and that this effect accumulates in a dose-dependent manner.

Biography

Yulia Einav has completed her PhD in Tel Aviv University. She works at Holon Institute of Technology (Israel). Currently she has published about 25 papers and book chapters in reputed journals and textbooks. In addition, she serves as Dean of Students of her institution.

yulia_e@hit.ac.il

Notes: