OptoRyR

Light-induced opening of Ryanodine receptors

Invention

The ryanodine receptor (RyR) Ca2+ release channel resides in the largest membrane organelle, the sarco-/endoplasmic reticulum (SR/ER), where it plays an important role in Ca2+-induced Ca2+ release (CICR). CICR is an essential signaling process for all excitable cells, particularly neurons and cardiomyocytes to maintain physiological functions without which life is not possible. Importantly, abnormally increased RyR channel activity, for example during the resting phase of cardiomyocytes, contributes to a "leak" flux of Ca2+ ions from the SR/ER organelle to the cytosol which may induce intracellular Ca2+ overload. Consequently, increased metabolic stress can lead to cell injury and for example neurological disorders like seizures and dementia. Likewise in the heart, abnormal RyR Ca2+ leak in cardiomyocytes for example due to inherited RyR2 mutations or pathologically increased RyR2 phosphorylation in patients with acquired heart failure can cause lethal arrhythmias and cardiac degeneration.

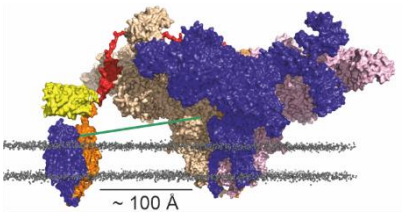

Figure 1: OptoRyR2 structure, predicted with MODELLER, restraining known structures of ChR2 monomer (orange, blue, PDB: 3UG9), EYFP (yellow, PDB: 1EMA), CRP1 linker (red, PDB: 1B8T) and RyR2 (protomers visible blue, grey, violet, PDB: 5GOA).

Giving the vital importance of normal RyR channel function, a growing number of common as well as rare genetic organotypic diseases were associated with ER/SR Ca2+ leak. Accordingly, there is a growing need for reproducible and scalable screening systems, ideally based on human cell types, to identify and optimize therapeutically active RyR channel modifying substances.

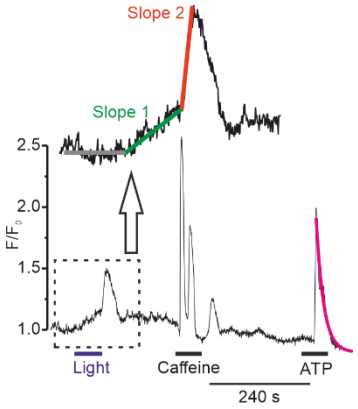

Figure 2: Ca2+ imaging (X-Rhod-1) with light (blue bar), caffeine (10 mM) and ATP (1 mM) induced Ca2+ releases. Note the biphasic effect of light (upper insert: slope 1 (green) and slope 2 (red) analyzed by linear fits).

The present invention provides such a scalable screening system, which is a genetically engineered protein composed of the light-gated Channelrhodopsin-2 of Chlamydomonas reinhardtii, which was fused by linker with the human RyR2 channel protein, which is the most abundant form in the brain and heart. (OptoRyR2; Figure 1).

This novel optogenetic tool is able to release Ca2+ from the ER/SR upon light activation in close vicinity to the cytosolic Ca2+ sensor of RyR2, and subsequently triggers physiological RyR2 activation through CICR (Figure 2). By analyzing the shape and height of light-induced Ca2+ release, substances can be screened for RyR2 modifying effects.

Commercial Opportunities

Cell lines stably transfected with the OptoRyR expression construct are available ready to use. Screening projects can be advised by scientists which have invented OptoRyR.

Current Status

A European patent application is pending.

An invention of University of Bonn.

Competitive Advantages

- Scalable drug screening system
- Ready to use

Technology Readiness Level

1 2 3 4 5 6 7 8 9

System complete and qualified

Industries

- Cardiology Pharma
- Neurology Pharma

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