Department of Biological Chemistry

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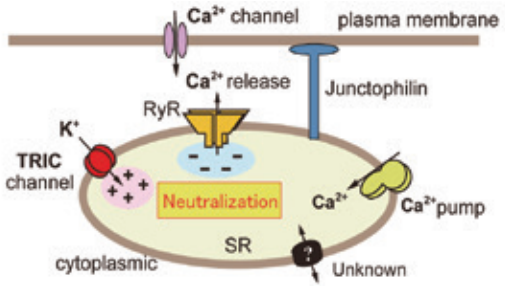
Research Projects:

In living organism, biomacromolecules physically and functionally interact with each other and induce chemical reactions to establish flexible life processes. We are dealing with biochemical and gene-handling studies on membrane proteins toward unlocking the molecular basis of life. Our efforts contribute to not only the global progress of basic biology, but also the healthcare field, for example, identifying reliable target proteins for pharmaceutical development and locating mutations in human genetic diseases. Our current research projects are listed below.

1) Ca^{2+} signaling from intracellular stores: Intracellular Ca^{2+} signaling is triggered by Ca^{2+} influx and Ca^{2+} release for the physiological regulation of a wide variety of cellular functions. In excitable cells, machinery for Ca^{2+} release from the endo/sarcoplasmic reticulum (ER/SR) is well organized and is essential for regulating muscle contraction and neural excitability. We are focusing on the Ca^{2+} release mechanism and molecular architecture of the ER/SR as intracellular stores. Our current aims are to clarify physiological roles of Ca^{2+} release mediated by ryanodine receptors, sets of ryanodine-sensitive intracellular Ca^{2+} release channels, to define functions of junctophilin contributing to junctional membrane complexes between the plasma membrane and the ER/SR, and to identify novel protein ER/SR components essential for Ca^{2+} store functions. The figure below shows major components in the juctional membrane complex for cardiac excitation-contraction coupling. Our previous studies demonstrated that cardiac Ca^{2+} signaling absolutely requires Ca^{2+} channel, TRIC channel, RyR and JP. Knockout mice lacking the components exhibit heart failure at early embryonic stages. Genetic mutations in Ca^{2+} channel and RyR cause familial cardiac myopathy and arrhythmia, respectively. Moreover, our biochemical analysis identified several membrane proteins with unknown functions in the ER/SR.

2) Novel signaling in central nervous system: Information processing and cellular organization in the central nervous system (CNS) is in mystery. Uncharacterized protein components from the brain indicates the existence of unknown intercellular and intracellular signaling in CNS. Our group identified several receptor-like membrane proteins specifically expressing in the brain, including DNER (delta-notch-type EGF repeat containing protein) and BSRPs (brain-specific receptor-like proteins), and started to survey their roles in brain development and function. Interestingly, both knockout mice lacking DNER and BSPRs show motorcoordination defects and probably share cerebellar dysfunction.

3) Structure and function of muscle membrane systems: There are many strange membrane structures in striated muscle cells, for example the transverse tubule, Z-tubule, triad and diad, junctional SR and longitudinal SR (see textbook for histology). Because molecular mechanisms for such membrane structures are almost unknown, we would like to identify proteins contributing to these membrane structures. Our previous screening identified a series of muscle membrane proteins with unknown functions, namely the "mitsugumin" family. Recent studies found that mitsugumin 29 partially restricts the ultrastructure of the transverse tubule and is involved in physiological and histological defects during muscle aging. Moreover, mitsugumin 53 is involved in repair of membrane damage in striated muscle. Therefore, it is thought that mitsugumin 53 is a responsible gene of muscular dystrophy.



Components for Ca^{2+}-induced Ca^{2+} release (CICR) in cardiac muscle cells. Ca^{2+} influx mediated by Ca^{2+} channels induces channel opening of ryanodine receptors (RyR) and triggers Ca^{2+} release from the sarcoplasmic reticulum (SR). This CICR requires the colocalization of Ca^{2+} channel and junctophilin within junctional membrane complex supported by junctophilin because the loss of the close association between Ca^{2+} channels and RyR disconnects Ca^{2+} effects. TRIC channels are likely to act as counter-ion channels that function in synchronization with Ca^{2+} release from intracellular stores and maintain an efficient Ca^{2+} release. Moreover, unidentified SR protein components might have important roles as channels and Ca^{2+} binding proteins. Our findings are expected as not only development of biochemistry but also the clinical application.

Recent publications

- Qian N et al. TRPM7 channels mediate spontaneous Ca^{2+} fluctuations in growth plate chondrocytes that promote bone development. ***Sci Signal***. Apr 9;12(576). pii: eaaw4847. 2019.
- Zhao C et al. Mice lacking the intracellular cation channel TRIC-B have compromised collagen production and impaired bone mineralization. ***Sci Signal***. May 17;9(428):ra49. 2016.
- Kakizawa S. et al. Nitric oxide-induced calcium release via ryanodine receptors regulates neuronal function. ***EMBO J***. 31, 417-428, 2012.