TRIC Channel and Hypertension

Hiroshi Takeshima

Graduate School of Pharmaceutical Sciences, Kyoto University

Summary

Ca$^{2+}$ release from the endo/sarcoplasmic reticulum (ER/SR) regulates important cellular functions. Ryanodine receptors (RyRs) expressed in excitable cells and inositol 1,4,5-trisphosphate receptors (IP$_3$Rs) distributed in almost all types of cells comprise a unique family of Ca$^{2+}$ release channels that are structurally and functionally distinct from other known ion channels. To regulate separate cellular functions, RyRs and IP$_3$Rs are activated by different mechanisms and often generate distinct spatiotemporal profiles of Ca$^{2+}$ signals. For example, in vascular smooth muscle cells (VSMCs), agonist-induced IP$_3$R activation evokes global Ca$^{2+}$ transients, which frequently accompany Ca$^{2+}$ waves and oscillations, inducing contraction, while spontaneous RyR opening generates local Ca$^{2+}$ sparks and activates cell-surface Ca$^{2+}$-dependent K$^+$ channels leading to hyperpolarization. When Ca$^{2+}$ is released from intracellular stores, a negative potential probably arises in the lumen that would disturb subsequent Ca$^{2+}$ release. Therefore, physiological Ca$^{2+}$ release may require counter-ion movements to balance ER/SR membrane potential. We have identified TRIC (trimeric intracellular cation) channel subtypes, which form bullet-shaped homo-trimers to function as monovalent cation channels. Recent studies in embryonic cardiomyocytes, alveolar epithelial cells and skeletal muscle from knockout mice indicate that TRIC channels act as counter-ion channels facilitating physiological Ca$^{2+}$ release from the ER/SR.

Tric-a-knockout mice grew normally, but developed hypertension during daytime. Resistance arteries from the knockout mice exhibited enhanced myogenic tone. TRIC-A channel deficiency inhibited RyR-mediated hyperpolarization signaling to stimulate voltage-dependent Ca$^{2+}$ influx, and adversely enhanced IP$_3$R-mediated Ca$^{2+}$ transients by producing Ca$^{2+}$-overloaded stores in VSMCs. Moreover, association analysis identified single nucleotide polymorphisms around the human TRIC-A gene, that increase hypertension risk and restrict the efficiency of antihypertensive drugs. Therefore, the TRIC-A channel contributes to maintaining vascular tonus, while its genetic polymorphisms could provide useful markers for constitutional diagnosis and personalized medical treatment of essential hypertension.