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TRIC Channel and Hypertension

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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_3Rs) 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_3Rs 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_3R 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_3R-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.