Editorial

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Ca^{2+} Homeostasis in Normal and Diseased Heart

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Editorial

The heart's ability to contract greatly depends on a mechanism termed excitation-contraction coupling (E-C coupling). In each heartbeat, the open of voltage gated L-type Ca^{2+} channel (LTCC) due to membrane depolarization results in the influx of a small amount of Ca^{2+}, which in turn triggers massive Ca^{2+} release from sarcoplasmic reticulum (SR) [1]. The binding of cytosolic Ca^{2+} with troponin C of myofilaments induces shortening of myofilament, so the excitatory membrane depolarization is converted into cell contraction. After contraction, 99% of Ca^{2+} is either recycled back to SR through SR Ca^{2+}-ATPase (SERCA), or extruded out of the cell through Na^{+}-Ca^{2+} exchanger (NCX). During this process, ryanodine receptor (RyR), the Ca^{2+} channel inserted in SR membrane, serves as the SR Ca^{2+} release conduits. The communication between LTCC and RyR determines the amplitude of Ca^{2+} release through SR, and thus the force of contraction [2]. As Ca^{2+} plays a crucial role in E-C coupling and serves as a second messenger in signaling pathways, the tuning of Ca^{2+} release is precisely regulated by varieties of proteins, kinases, and ions. In fact, any mutation in LTCC, RyR, or other Ca^{2+} related protein may lead to ventricular arrhythmia, impaired contractility, or cardiomyopathy.

Catecholaminergic Polymorphism Ventricular Tachycardia (CPVT) is an inherited heart disorder, which is triggered due to cytosolic Ca^{2+} dysregulation. Patients have normal heart structure and function in resting state, but burst severe ventricular tachycardia morphologies when under acute emotional stress or after exercise [3]. More than 70 mutations of RyR, which are distributed in three hotspots in amino acid sequence, are known to be associated with CPVT. With gain-of-function mutations, RyRs have increased open probabilities, even when the cardiomyocyte is in resting condition during diastole. The stochastic, unsynchronized SR Ca^{2+} release during diastole overloads NCX to extrude Ca^{2+} out of the cell. The stoichiometry of 3 Na^{+} (in) to 1 Ca^{2+} (out) generates a net inward current, which depolarizes membrane potential and triggers a delayed-afterdepolarization after a normal action potential. In this situation, paroxysmal tachycardia and arrhythmia can be triggered, even the focal Ca^{2+} turbulence only happens in a few cardiomyocytes. While most RyR mutations lead to gain-of-function of the channel, a loss-of-function mutation (A4860G) is found in recent study, which also results in arrhythmia. Cardiomyocyte with decreased RyR activity has decreased Ca^{2+} transient in each beating, gradually overloading SR Ca^{2+}. Once SR Ca^{2+} reaches threshold, a prolonged Ca^{2+} release is induced, activating NCX to trigger an early-afterdepolarization in cardiomyocyte [4].

In summary, good heart performance depends on proper Ca^{2+} homeostasis. Although RyR dysfunction in CPVT has been elucidated, how to rescue the phenotype remains to be investigated. As RyR acts as a scaffold for other proteins, the potential regulatory proteins, and co-factors of RyR should be studied to regulate RyR function, thus propose novel treatments for heart diseases (Figure 1).

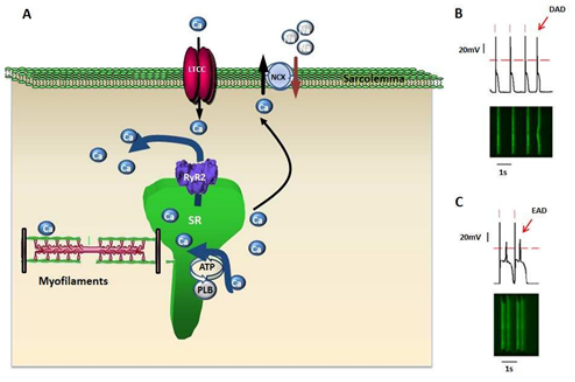

Figure 1 Ca^{2+} homeostasis in cardiomyocytes.

(A) Excitation-contraction coupling in cardiomyocytes. LTCC: L-type Ca^{2+} channel, RyR2: ryanodine receptor type 2, NCX: Na^{+}-Ca^{2+} exchanger, SR: sarcoplasmic reticulum, PLB: phospholamban.

(B) Spontaneous Ca^{2+} release triggers delayed-afterdepolarization (DAD) in cardiomyocyte. Upper panel: action potential; bottom panel: fluorescence labeled Ca^{2+} transient. Red bars label normal beatings of cardiomyocyte (same in figure C).

(C) Early-afterdepolarization (EAD) in cardiomyocyte.

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