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BIN1 regulates dynamic t-tubule membrane☆

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ABSTRACT

Cardiac transverse tubules (t-tubules) are specific membrane organelles critical in calcium signaling and excitation–contraction coupling required for beat-to-beat heart contraction. T-tubules are highly branched and form an interconnected network that penetrates the myocyte interior to form junctions with the sarcoplasmic reticulum. T-tubules are selectively enriched with specific ion channels and proteins crucial in calcium transient development necessary in excitation–contraction coupling, thus t-tubules are a key component of cardiac myocyte function. In this review, we focus primarily on two proteins concentrated within the t-tubular network, the L-type calcium channel (LTCC) and associated membrane anchor protein, bridging integrator 1 (BIN1). Here, we provide an overview of current knowledge in t-tubule morphology, composition, microdomains, as well as the dynamics of the t-tubule network. Secondly, we highlight multiple aspects of BIN1-dependent t-tubule function, which includes forward trafficking of LTCCs to t-tubules, LTCC clustering at t-tubule surface, microdomain organization and regulation at t-tubule membrane, and the formation of a slow diffusion barrier within t-tubules. Lastly, we describe progress in characterizing how acquired human heart failure can be attributed to abnormal BIN1 transcription and associated t-tubule remodeling. Understanding BIN1-regulated cardiac t-tubule biology in human heart failure management has the dual benefit of promoting progress in both biomarker development and therapeutic target identification. This article is part of a Special Issue entitled: Cardiomyocyte Biology: Integration of Developmental and Environmental Cues in the Heart edited by Marcus Schaub and Hughes Abriel.

1. Introduction

Each beat-to-beat heart contraction is a result of the synchronous contraction of millions of cardiac muscle cells initiated by a single action potential. To generate a coordinated and effective contraction of the heart chambers, a rapid and efficient intracellular conversion of the electrical signal to mechanical contractile force is required at the individual myocyte level. This process is known as cardiac excitation–contraction (EC) coupling, which involves a sequence of intracellular signaling events [1]. Efficient cardiac EC coupling requires development of normal calcium transients for healthy heart activity. In contrast, a weakened calcium transient and the resultant impaired EC coupling are the key pathological conditions of human heart failure, an end stage cardiac syndrome affecting more than 40 millions of people worldwide.

In mammalian ventricular cardiomyocytes, the functional unit of the working myocardium, the production of a healthy calcium transient relies on a well-developed complex membrane network of transverse tubules (t-tubules). Specific to striated muscle cells, t-tubules are sarcolemmal invaginations penetrating into the intracellular space of myocytes, allowing fast propagation of action potentials into the cell interior. Cardiac t-tubules are enriched in L-type calcium channels (LTCC), which mediate the initial action potential-triggered calcium entry into myocytes. A rise in local calcium concentration subsequently activates nearby ryanodine receptors (RyR), located at the sarcoplasmic reticulum (SR), resulting in a large release of calcium from SR stores to the cytoplasm. By concentrating LTCCs and bringing them in proximity to RyRs at the SR membrane, t-tubules serve as the structural foundation for healthy calcium transient production necessary for efficient EC coupling. The essential function of t-tubules is highlighted by dynamic changes in their structure during disease progression, whereby t-tubules undergo substantial remodeling. For instance, t-tubule remodeling in heart failure not only causes impaired contractile function, but also alters local electrophysiological properties and increases ventricular arrhythmia susceptibility.

In this review, we will first explore the current views of how t-tubules organize, function, and turnover in normal and diseased hearts, with a focus on mechanisms related to calcium signaling. Second, we will address in detail a crucial cardiac t-tubule membrane adaptor protein, bridging integrator 1 (BIN1, alternatively known as amphiphysin 2), which facilitates microtubule-dependent LTCC trafficking and clustering, as well as formation of t-tubule microdomains.

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Only within the past five years has BIN1 emerged as an essential multifunctional regulator of calcium signaling at cardiac t-tubules. Finally, we will discuss a role of BIN1 and t-tubule regulation in heart failure.

2. Cardiac t-tubules

Cardiac t-tubules are critical in controlling the calcium transient and EC coupling, which ultimately determines the strength of each heartbeat. As a membrane organelle, t-tubules also serve as a signaling hub by selectively compartmentalizing membrane proteins and signaling molecules. In this section, we will address the nature of t-tubule morphology and composition, followed by a discussion of t-tubule dyad microdomains and dynamic changes in cardiac t-tubule structure.

2.1. T-tubule morphology and composition

T-tubules are continuous membrane invaginations extended from sarcolemmal membrane. Originally discovered by Dr. Lindner, the primary element of cardiac t-tubules runs transverse to the long axis of myocytes [2]. However, the longitudinal element and branched tubular component can comprise up to 40% of t-tubule volume [3], thereby forming a complex tubular network. This tubular network significantly expands onto the sarcolemmal surface area and is estimated to constitute approximately 21% to 64% [3–6] of the total membrane. This type of complex network allows extracellular signals such as an action potential to propagate rapidly and simultaneously to activate all myofilaments [7–9]. Extracellular ions and circulating hormones can also reach deep inside of cardiomyocytes through t-tubules and activate receptors and transporters to initiate various cellular processes.

Present in mature ventricular cardiomyocytes across all mammalian species studied [10], cardiac t-tubules have unique characteristics distinct from skeletal muscle t-tubules that allow for precise cardiac EC coupling. In cardiomyocytes, t-tubules occur periodically at ~1.8 μm intervals along the longitudinal axis coinciding with the Z-disc (see Fig. 1 for schematic illustration). Along a Z-line, t-tubule invaginations are spaced out at an interval of ~1.2 μm [11]. The diameters of cardiac t-tubules are much more heterogeneous compared to those of skeletal muscle. For example, within a single rat cardiomyocyte, t-tubule diameter can range from 20 nm to 450 nm, with an overall average of 200–300 nm [3], which is almost ten times wider than that of skeletal muscle [12,13]. The size and density of cardiac t-tubules also vary across mammalian species and correlates to their respective heart rate. Small murine like rodents [3,14] with higher heart rates that require fast action potential penetration into the cell interior have t-tubules that are much deeper and denser. In contrast, large mammals [15] and humans [16,17] with heart rates less than 100 beats per minute have larger and more scarce t-tubules.

T-tubules are lipid bilayers embedded with specific transmembrane and lipid-associated proteins [18]. The protein components of t-tubules include: regulatory membrane scaffolding proteins, structural proteins, transmembrane ion channels, ion handling proteins, and signaling molecules. Specific membrane scaffolding proteins and cytoskeletal structural proteins are necessary for the organization and regulation of the t-tubule network and structure. Membrane scaffolding proteins caveolin-3 [19,20], junctophilin-2 [21], and BIN1 [22–24] have been suggested to be important in the maintenance of t-tubule morphology. Moreover, caveolin-3 [25], ankyrin-B [26], and BIN1 [23] are critical in the organization and regulation of distinct subdomains at the t-tubule membrane. Ion channels and transporters, which are important in regulation of EC coupling and membrane excitability, have been well characterized in the cardiac t-tubule system (see reviews in [10,27]). Important signaling molecules such as G-protein coupled β-adrenergic receptors (β-ARs) are also found to be present [28] or enriched [29] in t-tubules. Recent studies further suggest that the β2 subtype of the β-AR family is mainly localized within t-tubules [30], and redistribution of β2-ARs out of t-tubules is a pathophysiological phenomenon of heart failure [30,31]. By differentially compartmentalizing proteins involved in ion handling and signaling, t-tubules serve as a signaling hub-like organelle to regulate myocyte function. The following subsections will focus on some critical subdomains within t-tubule membrane including dyads.

2.2. Dyad and L-type calcium channels

The primary function of a cardiac t-tubule is its role in initiating calcium transients for efficient EC coupling. The current accepted model of intracellular calcium transient development is calcium-induced-calcium-release (CICR) [32]. In response to action potential-triggered inward sodium current, sarcolemmal membrane depolarization activates voltage-gated LTCCs. This initial calcium influx subsequently induces a massive calcium release from SR stores. After its original proposal in early 1980s, the CICR model was supplemented by the identification of the calcium release channels on the SR membrane, the ryanodine receptors [33,34]. In 1993, the Lederer lab further identified and described calcium sparks from the SR as the "elementary units" of the calcium transient [35]. The complexes consisting of t-tubule LTCCs together with junctional SR membrane RyRs (approximately 1:4 ratio) are known as dyads [36,37]. Optimal CICR requires close physical association of RyRs, the calcium sensing and releasing channel, at junctional SR membrane with sarcolemma LTCCs [32–35], which is achieved by LTCC localization in t-tubules [1,38]. Upon membrane depolarization, the initial calcium influx through LTCCs and the close association between LTCCs and RyRs (~15 nm) at dyads permit efficient CICR and subsequent sarcomeric contraction [39].

LTCCs, which initiate the calcium transient, are formed by a large pore-forming α subunit, together with auxiliary β, α2δ1, and γ subunits. The auxiliary subunits are critical in regulating the trafficking and gating properties of the pore-forming α subunit [40]. The splice variant of the LTCC α-subunit expressed in the heart is $Ca_V1.2$ [41], which is critical in cardiac development and function [42]. Global deletion of $Ca_V1.2$ induces abnormal cardiac morphogenesis with embryonic lethality [42], whereas cardiac specific deletion in adult mice causes reduced contractility and increased susceptibility to stress-induced heart failure [43]. As the t-tubule component of dyads, LTCCs need to be enriched at t-tubules for normal intracellular calcium transient development. Immunocytochemistry and electrophysiological data indicate that 80% of the sarcolemma LTCCs are concentrated to the t-tubule surface [18]. The precise t-tubule localization of LTCCs requires the membrane scaffolding protein BIN1. Previously, we have shown that BIN1 facilitates microtubule-dependent targeted delivery of $Ca_V1.2$ channels to t-tubules [44], as discussed later in Section 3.2. More recently, we demonstrated that BIN1 also creates microfolds within t-tubules [23] (details in Section 3.3), which may serve as the structural base of dyad microdomains anchoring $Ca_V1.2$ channels at t-tubules.

2.3. Other microdomains in t-tubules

In addition to dyad subdomains, the most well studied membrane microdomain is caveolae. Caveolae are flask-shaped structures enriched with cholesterol and sphingolipids formed by the cholesterol-binding scaffolding protein Caveolin-3. Biochemical fractionation and electron microscopy studies have identified a subpopulation of many ion channels at caveolae, and loss of caveolae is associated with arrhythmogenesis [25]. Caveolae exist in both t-tubule and lateral sarcolemma of ventricular cardiomyocytes [5,45]. Within t-tubules, caveolae are often found at sub-sarcolemmal areas connecting t-tubules to extracellular space [46]. The mechanism of caveolae localization and regulation at t-tubules remains unclear, although a recent study indicates BIN1 may play a role in caveolae distribution within t-tubules [47]. Furthermore, studies show that a subset of $Ca_V1.2$ channels are localized within caveolae and are perhaps involved in regulating