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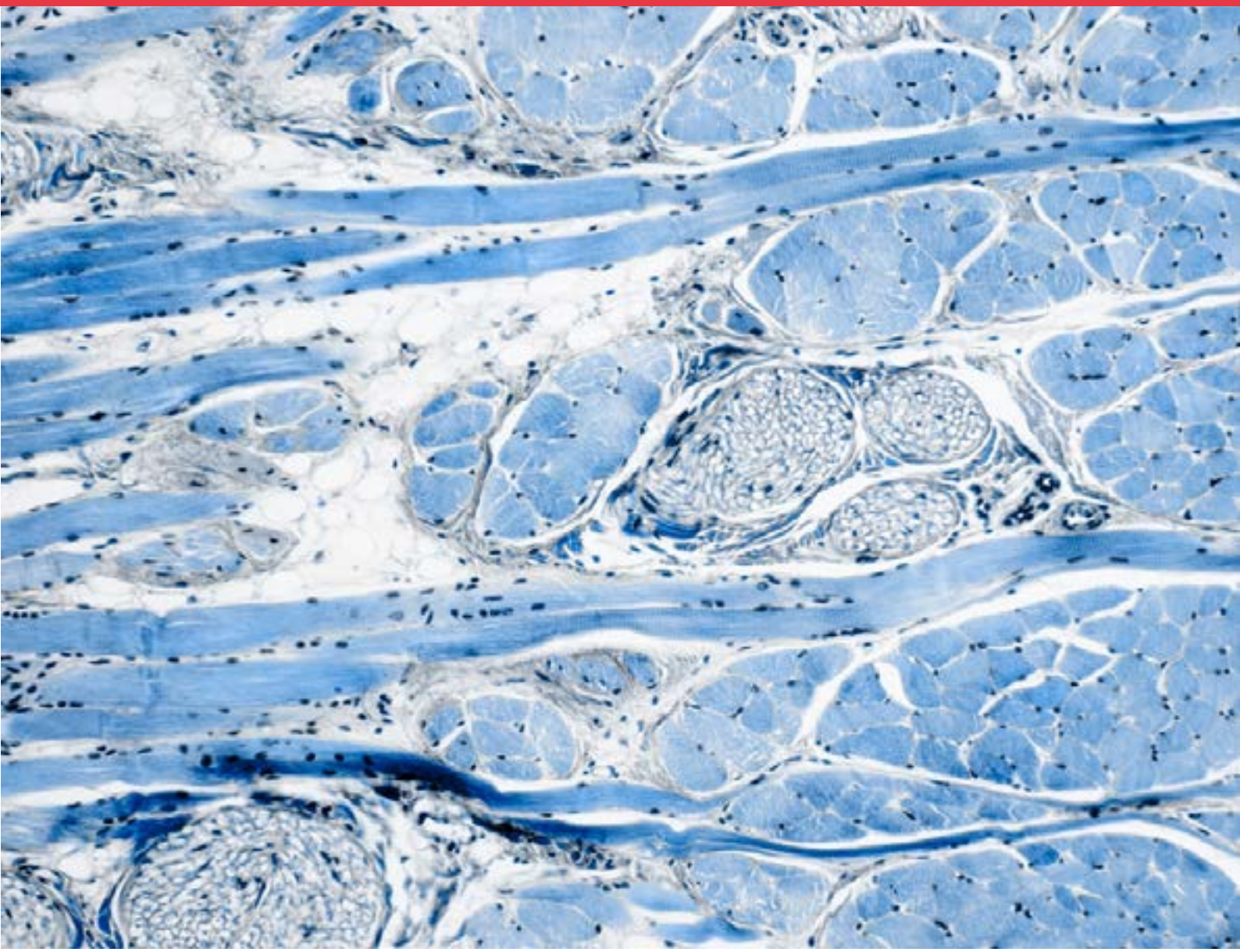

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CARDIAC T-TUBULE BIOGENESIS AND REMODELING

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Abstract
Cardiomyocyte T-tubules are crucial for cardiac contraction, and any disruption in T-tubule biogenesis, structure, or patterns can induce cardiomyopathies. These structures are not just sarcolemma invaginations but rather they exhibit microfolds, crucial for maintaining differences in ionic concentrations between the extracellular and intracellular environments, enabling proper contraction. Despite the importance of T-tubules for cardiac function, relatively little is understood about the molecular pathways that govern their formation and maintenance. In this review, we discuss some of the most studied proteins related to the formation of T-tubules and their relation to cardiac function, such as Junctophilin-2, Bridging Integrator 1, and Caveolin-3. We also highlight some promising proteins for understanding the pathways that regulate T-tubule structure, such as Dynamin-2. Understanding the biogenesis and regulation of T-tubule structure is crucial for comprehending at least part of the development of different cardiomyopathies.
Keywords: Cardiac T-tubule, BIN1, Junctophilin-2, Caveolin-3

Resumen
Los túbulos-T cardiacos son cruciales para la función de contracción cardiaca y cualquier cambio en su biogénesis, estructura o patrón de presentación puede estar relacionada al desarrollo de cardiomiopatías. Estas estructuras no son sólo invaginaciones del sarcolema, sino que presentan microplegamientos críticos para mantener las concentraciones iónicas en el lado extracelular e intracelular, posibilitando así una correcta contracción. A pesar de la importancia de los túbulos-T en la función cardiaca, relativamente poco es conocido acerca de las vías moleculares que regulan su formación y mantención. En esta revisión discutimos sobre algunas de las proteínas más estudiadas relacionadas con la formación de los túbulos-T, así como su relación con la mantención de la función cardiaca; Junctofilina-2, Bridging Integrator 1 y Caveolina-3. También comentamos sobre algunas prometedoras proteínas que podrían regular las vías relacionadas con la mantención de la estructura de los túbulos-T, tales como Dinamina-2. La comprensión de la biogénesis y la regulación de la estructura de los túbulos-T es crucial para comprender, por lo menos en parte, el desarrollo de diferentes cardiomiopatías.
Palabras claves: Túbulos-T cardiacos, BIN1, Junctofilina-2, Caveolina-3

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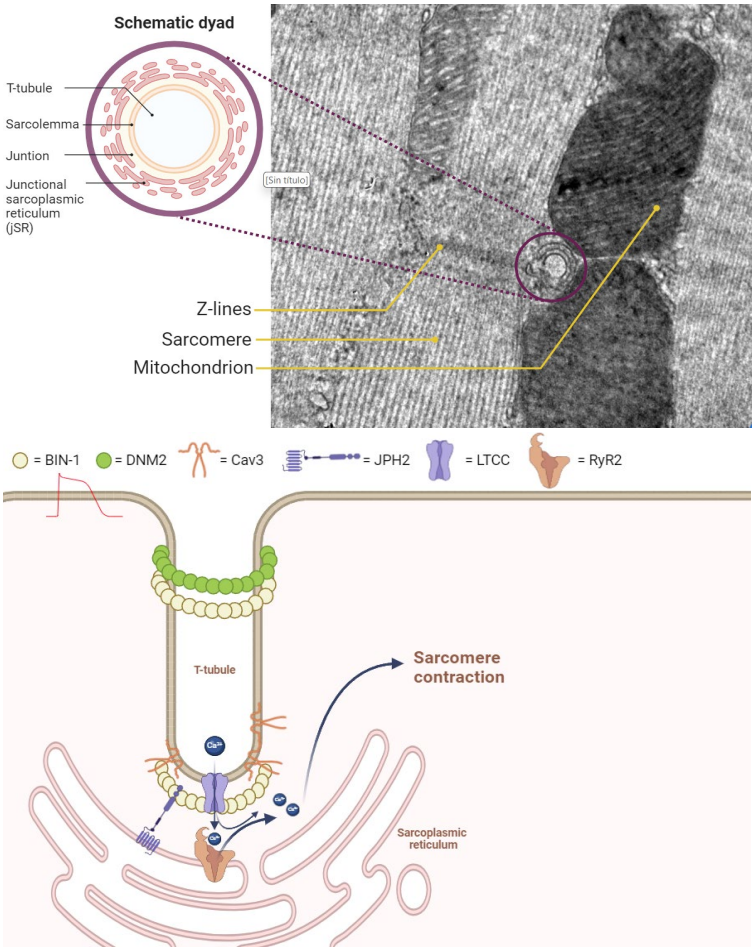
Introduction

Transverse tubules (T-tubules) are sarcolemmal invaginations first described in ventricular cardiomyocytes in 1957 [1]. The network of cardiomyocyte T-tubules is composed of transverse and perpendicular tubules that are interconnected and arranged along the Z-lines at the ends of each sarcomere. These tubules feature specific subdomains formed by sarcolemmal microfoldings, which are crucial for recruiting various specific channels and receptors involved in extracellular ion diffusion, excitation-contraction coupling (ECC), and contractility in cardiomyocytes. Additionally, they play a role in regulating several signaling pathways involved in cardiomyocyte metabolism [1]. Although the crucial relevance of cardiomyocyte T-tubules in cardiac function is well known, the cellular mechanisms of T-tubule biogenesis and maintenance are not. Understanding the mechanisms involved in cardiomyocyte tubulogenesis is essential to comprehending the physiological function of cardiac tissue. Here, we will discuss the most relevant proteins related to cardiac tubulogenesis.

T-tubule during cardiac development

In small mammals, ventricular cardiomyocyte T-tubules are rudimentary at birth, with biogenesis beginning after the postnatal period and extending until the third week [2]. Conversely, evidence demonstrates that cardiomyocyte T-tubules in larger mammals, such as sheep and humans, start to develop during fetal life, with T-tubule maturation occurring after birth [3,4]. Initially, this developing T-tubule network appears disorganized and is largely oriented along the longitudinal axis of the cell [2]. During maturation, T-tubule density increases, and the network becomes primarily organized transversely along the Z-line, continuing into adulthood [2].

The molecular mechanisms involved in T-tubule biogenesis are currently unclear. However, it has recently been described that increased fetal workload (systolic load) induces T-tubule growth [4], suggesting that, as in adult cardiomyocytes, mechanical load could be a crucial signal regulating cardiac T-tubule structures.



Despite the lack of clarity regarding the mechanisms of T-tubule biogenesis and maintenance, different adapter proteins have been associated with tubulogenesis. The most studied proteins include Junctophilin-2 (JPH2), Bridging Integrator 1 (BIN1), and caveolin 3, among others.

Figure 1. Scheme of the cardiac dyad and proteins involve in regulation of T-tubule biogenesis and its structure maintaining. T-tubule. Figure obtained from Díaz-Vesga et al [5].

Junctophilin-2 (JPH2)

The Junctophilin protein family is a junctional membrane complex (JMC)-associated protein family, with JPH2 expressed specifically in cardiac tissue. JPH2 contains 696 amino acids, with 92% similarity between humans and rats [6], and functions as a structural protein crucial for the maintenance of T-tubule integrity.

JPH2 anchors the sarcolemma to the sarcoplasmic reticulum (SR), inducing dyad formations through its C-terminal transmembrane segment that spans the SR membrane and a repetition of conserved motifs in the N-terminal region (MORN), which interact with the plasma membrane [6,7]. This allows the interaction of L-type Ca2+ channels (LTCC), caveolin-3, and Ryanodine receptor 2 (RyR2) to regulate Ca2+-induced Ca2+ release (CICR) [7].

PH2 plays a key role in the development of T-tubules and dyads, both pre- and postnatally [3,4,8,9]. Some studies have reported that decreased levels of JPH2 in mice hearts induce T-tubule remodeling, leading to loss or degeneration into an immature longitudinal configuration [9]. Furthermore, Poulet et al. observed loss of T-tubules in rat ventricular myocytes kept in culture for 4 days, but overexpression of JPH2 via an adenovirus prevented the loss and disorganization of these structures. Interestingly, they also described that cholesterol participates in the binding of JPH2 to T-tubules as well as in the modulation of LTCC activity [10]. Additionally, Zhang et al. found a reduction in JPH2 in samples of the left ventricular wall of explanted human hearts with end-stage heart failure from heart transplant recipients, as well as a lower density of JMCs [11]. These findings and others demonstrate the relevance of JPH2 in maintaining T-tubule structure, the physiological function of the heart, and the association between decreased expression of JPH2 and the development of cardiomyopathies in both animal preclinical models and humans [12].

As mentioned above, the vast majority of studies associate JPH2 with T-tubule structure maintenance. However, its role in tubulogenesis appears to be less significant or, at least, not as clear, and more studies are required to clarify this issue.

Bridging integrator 1 (BIN1)

BIN1, also known as Amphiphysin 2, belongs to the BAR (Bin-Amphiphysin-Rvs) domain-containing protein superfamily [13]. BIN1 has been reported as one of the main regulators of the formation and maintenance of T-tubules and their associated proteins, such as LTCC [13], as it is involved in both the trafficking and clustering of these channels and the organization of cell membrane microdomains [14]. BIN1 is encoded by a gene with 20 exons that are selectively spliced to produce various isoforms expressed in different tissues. All BIN1 isoforms contain a conserved lipid-binding BAR domain at the N-terminus (exons 1-9), a coiled-coil region of alternative splicing (exons 13-16), a MYC binding domain encoded by exon 17, a constitutive exon 18, and exons 19-20 in the conserved C-terminus (SH3 homology domain), which allows interaction with the cytoskeleton and other intracellular proteins [15]. Four different isoforms are expressed in mouse cardiac tissue: BIN1+12 and BIN1+17, which are ubiquitous, and two cardiac alternative splicing variants, BIN1+13 and BIN1+13+17 [13,15].

T-tubule formation requires membrane insertion of BIN1 dimers through its N-terminal domain to initiate T-tubule invagination [15,16]. In the mouse heart, BIN1+13 is the most abundant isoform, but although BIN1+13+17 is less abundant, it plays a fundamental role in the formation, quantity, and functionality of T-tubules [13]. Regarding the key role of BIN1 in the formation and maintenance of dyads, it has been described that complete genetic deletion is embryonically lethal, and cardiomyocyte-specific deletion promotes dilated cardiomyopathy [17].

In cardiac BIN1 knockout (KO) mice, which develop dilated cardiomyopathy, restoration of BIN1+13+17 expression rescues T-tubule and cardiac function [17]. In both animal and human models, levels of BIN1 decrease during heart failure (HF) [5,18]. Furthermore, BIN1 directs the assembly and maintenance of cardiac dyads. It has been shown that cardiac isoforms of BIN1 are responsible for the formation and maintenance of the ultrastructure of T-tubules (microfoldings), which are membrane microdomains that help maintain ionic concentration homeostasis, primarily Ca2+, in cardiac dyads,

thus being vital for the contractile function of the heart [13,15]. Guo et al. identified five BIN1 splice variants in heart samples from healthy human donors: isoforms 6, 8, 9, 10, and 13, with isoform 6 being the most prominent human BIN1 isoform, followed by isoform 9 [19]. In this study, they used adult rat ventricular myocytes to investigate regeneration after the loss and maintenance of ECC, as well as studying the improvement of ECC in hiPS-CM, through the overexpression of human BIN1 variants. Findings suggest that five splice variants of human BIN1 induced de novo generation of T-tubules in both cell types [19]. Additionally, a study in human embryonic stem cell-derived cardiomyocytes (hESC-CMs) transduced with BIN1 found structures similar to T-tubules radiating towards the center of the cell, where BIN1 was located [16].

On the other hand, a study by Hong et al. found that overexpression of exogenous cBIN1 (cardiac BIN1) is protective in mice hearts subjected to high-dose isoproterenol (ISO) infusion and severe pressure overload induced by aortic constriction (TAC) [20]. In both heart failure models, expression of the specific exogenous cBIN1 isoform improves cardiac inotropy and lusitropy, thus limiting the development of pathological hypertrophy of the left ventricle (LV) [20]. These results highlight that BIN1 is a key protein for the maintenance, regeneration, and de novo generation of functional T-tubules.

Caveolin-3

Caveolins (Cav) are small integral membrane proteins that oligomerize within the endoplasmic reticulum before being trafficked to the plasma membrane, becoming crucial components of caveolae formation [21]. Ubiquitous Cav1 and muscle-specific Cav3 are essential for caveolae formation in non-muscle and muscle cells, respectively [21]. Caveolae are involved in the biogenesis of skeletal muscle T-tubules in various animals such as chickens, rats, and mice [22]. Recently, Lemerle et al. reported that T-tubules grow from sub-membrane rings composed of caveolae and BIN1 in mammalian skeletal muscle cells [23]. Furthermore, Cav3 knockdown led to a significant decrease in BIN1-induced tubes, supporting that Cav3-positive caveolae are required for efficient membrane tubulation in mouse and human myotubes [23].

In cardiac ventricular myocytes, Cav3 has been involved in T-tubule formation and the regulation of myocyte function. Notably, in cardiac hypertrophy and heart failure, a decrease in Cav3 expression has been reported, causing T-tubule disorganization, loss of LTCC localization in the T-tubule membrane, and diminished Ca2+ current density [24]. The same changes have been reproduced in Cav3 knockout mice [25]. In contrast, Cav3 overexpression in mice exposed to pressure overload showed cardioprotective effects, linked to maintained T-tubular Ca2+ current and prevention of tubular network loss in cardiomyocytes [26]. While the undeniable role of Cav3 in maintaining T-tubule organization in cardiomyocytes is acknowledged, further studies are required to demonstrate its potential importance in their biogenesis.

Dynamin-2 (DNM2)

Dynamins are large GTPases that facilitate membrane fission in clathrin-mediated endocytosis and regulate cytoskeletal reorganization [27]. Dynamins have five domains: an N-terminal GTPase domain, followed by the middle and pleckstrin homology (PH) domains, the GTPase effector domain (GED), and the C-terminal proline/arginine-rich domain (PRD). Mammals express three Dynamin genes: DNM1, DNM2, and DNM3. DNM1 and DNM3 are mainly expressed in the nervous system, whereas DNM2 is ubiquitously expressed [28].

Several studies have demonstrated that excess DNM2 activity disrupts the T-tubule membrane network and is related to centronuclear myopathy (CNM) in skeletal muscle [29]. Increased BIN1 expression improved the T-tubule defect in mice carrying a CNM-associated DNM2 mutation [30], demonstrating that BIN1 regulates DNM2 activity. Moreover, it appears that basal levels of DNM2 are necessary for the formation and maintenance of skeletal muscle T-tubules [31], and that DNM2 basal activity may contribute to the organization of the T-tubule, since the presence of DNM2 promotes BIN1-induced liposome tubulation in vitro [32]. This suggests a delicate balance between DNM2 content and its activity to regulate T-tubule maintenance in skeletal muscle.

The role of DNM2 in tubulogenesis of cardiac myocytes has been less studied. However, it has recently been described that a decrease in DNM2, together with an increase in BIN1 expression, is associated with the formation of T-tubules. Moreover, high levels of DNM2 induce a reduction in the density and growth of T-tubules in HL-1 cells and hiPSC-CMs [33], while an increase in the expression of DNM2 was associated with heart failure development [33]. Despite the apparent relevance of DNM2 in tubulogenesis regulation associated with BIN1, there are currently few studies that have explored this potential role in cardiac tissue, as well as its role in the development of cardiomyopathies.

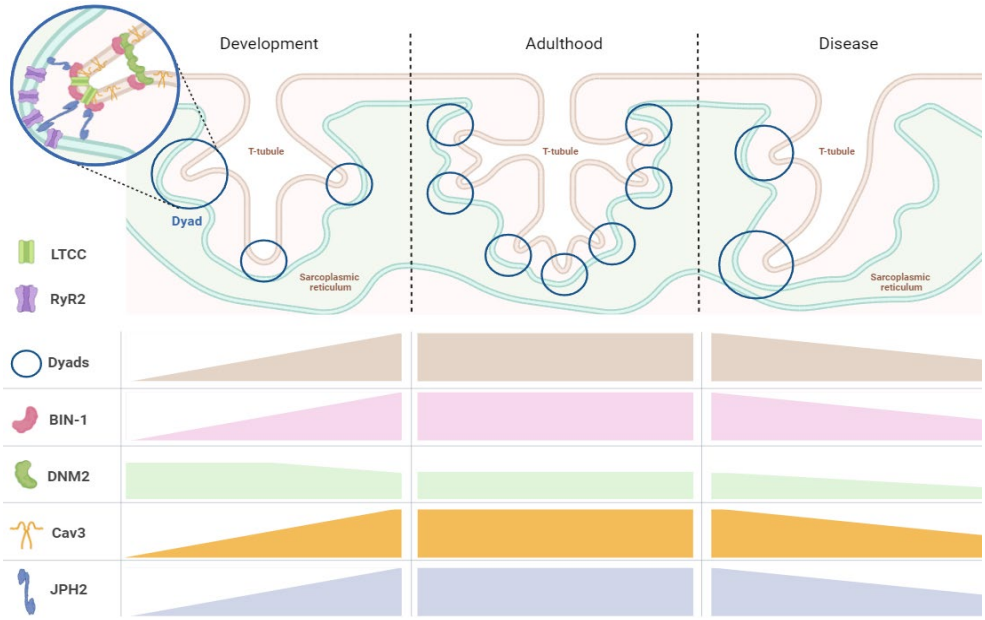


Figure 2. Changes in the number of dyads and expression of the proteins involved in the regulation of T-tubule biogenesis and structure maintenance during development, adulthood, and cardiac disease. Adapted from Setterberg et al. [1]

Future directions

T-tubules of cardiac myocytes are crucial for physiological heart contractility. However, our current knowledge regarding the biogenesis and maintenance of T-tubule structure is still scarce and at times contradictory. More research is required to understand the proteins and signaling pathways involved. It has recently been described that the tyrosine phosphatase, nonreceptor type 23 (Ptpn23) protein plays an important role in both the formation and maintenance of cardiac T-tubules running alongside Z-discs. Moreover, it was also demonstrated that decreased Ptpn23 expression is associated with the development of dilated cardiomyopathy [34]. Whether Ptpn23 induces membrane deformation through interactions or regulates BIN1, JPH2, or other proteins associated with T-tubule biogenesis is still unknown.

An interesting line of research is the role of insulin signaling in the regulation of cardiac physiology. Cardiomyocytes highly express insulin receptors in the sarcolemma and altered insulin signaling has been linked to cardiac remodeling and heart failure development. Interestingly, it was also described that insulin signaling is important in attenuating DNM2 activation, maintaining its inhibition through interaction with BIN1, and thereby maintaining T-tubule structure in skeletal muscle [35]. DNM2 has barely been studied in cardiac tissue. However, it could represent a crucial protein to understand T-tubule dynamics and its association with cardiac dysfunction and the development of cardiomyopathies, such as diabetic cardiomyopathy.

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