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Minireview

Cell–cell junction remodeling in the heart: Possible role in cardiac conduction system function and arrhythmias?

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ABSTRACT

Anchoring cell–cell junctions (desmosomes, *fascia adherens*) play crucial roles in maintaining mechanical integrity of cardiac muscle cells and tissue. Genetic mutations and/or loss of critical components in these macromolecular structures are increasingly being associated with arrhythmogenic cardiomyopathies; however, their specific roles have been primarily attributed to effects within the working (ventricular) cardiac muscle. Growing evidence also points to a key role for anchoring cell–cell junction components in cardiac muscle cells of the cardiac conduction system. This is not only evidenced by the molecular and ultra-structural presence of anchoring cell junctions in specific compartments/structures of the cardiac conduction system (sinoatrial node, atrioventricular node, His-Purkinje system), but also because conduction system-related arrhythmias can be found in humans and mouse models of cardiomyopathies harboring defects and/or mutations in key anchoring cell–cell junction proteins. These studies emphasize the clinical need to understand the molecular and cellular role(s) for anchoring cell–cell junctions in cardiac conduction system function and arrhythmias. This review will focus on (i) experimental findings that underline an important role for anchoring cell–cell junctions in the cardiac conduction system, (ii) insights regarding involvement of these structures in age-related cardiac remodeling of the conduction system, (iii) summarizing available genetic mouse models that can target cardiac conduction system structures and (iv) implications of these findings on future therapies for arrhythmogenic heart diseases.

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Contents

Introduction

The contractile and synchronous nature of the heartbeat requires robust mechanical and electrical coupling to maintain the physical and functional integrity of the heart. For tissues that undergo constant mechanical stress, like the heart, anchoring cell–cell junctions

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are particularly relevant since they provide stability to cardiac muscle cells in the face of severe stress by mechanically 'anchoring' cells to one another while the heart expands and contracts. In adult ventricular and atrial cardiac muscle cells, these cell–cell junctions are classically localized at the longitudinal end and in a step-wise fashion at lateral ends, in a structure known as the intercalated disc (Shimada et al., 2004). Intercalated discs can be readily visualized through light microscopy as an eosinophilic band following hematoxilin/eosin staining of heart tissue sections. At the molecular level, the intercalated disc appears as a highly organized triad of junctions between cardiac muscle cells, which includes both adhesive as well as communicating structural complexes containing anchoring (e.g. desmosomes and adherens junctions) and communicating junctions (e.g. gap junctions), respectively (Sheikh et al., 2009). Considerable attention has focused on the importance of anchoring cell junctions within cardiac muscle cells of the working (especially ventricular) myocardium, mainly because human and mouse genetic studies show that loss/mutations of key components within these complexes are associated with and can recapitulate human right and left ventricular cardiomyopathies, such as arrhythmogenic right ventricular dysplasia/cardiomyopathy and dilated cardiomyopathy, respectively (Garcia-Gras et al., 2006; Kostetskii et al., 2005; Li et al., 2005; Pilichou et al., 2006). For this reason, anchoring cell junctions have become the subject of a great deal of attention in both basic and clinical cardiac research fields.

Growing evidence also suggests potential key roles for anchoring cell junctions within specialized cardiac muscle cell subpopulations that form structures of the cardiac conduction system (sinoatrial node, atrioventricular node, His-Purkinje system). These cell populations are critical for generating and propagating electrical signals across the heart, giving rise to normal heart rhythm. It has become increasingly clear that a more thorough understanding of these structures in cardiac conduction system cells is of clinical necessity. Arrhythmias are a key feature of cardiomyopathies associated with genetic defects and/or loss of anchoring cell junction components (Asimaki et al., 2009; Delmar and McKenna, 2010), yet there is limited information on their origin, triggers, and specific underlying mechanisms. Furthermore, this cardiomyocyte subpopulation is especially relevant in the aging population. Cardiac conduction system cells are particularly prone to age related structural and functional remodeling, increasing the likelihood of arrhythmias (Haqqani and Kalman, 2007; Yanni et al., 2009) and the requirement for pacemaker implantation (Mond et al., 2008) in the growing aging population. This review will provide an up-to-date overview of the anchoring cell junction complexes currently identified within the cardiac conduction system and discuss evidence regarding cross-talk between proteins of these junctions and electro-generating, propagating and coupling channels (e.g., connexins and ion channels) to highlight how defects in the anchoring cell junction protein complexes may play a pivotal and specific role in cardiac conduction system related arrhythmias.

Anchoring cell–cell junction biology in cardiac muscle

The heart contains a number of cell types that contain a wide variety of cell–cell junction complexes. These may be broadly classified according to function as anchoring and communicating junctions. Anchoring junctions bind one cell to another through direct association with cytoskeletal components of both cells and include the adherens junctions and desmosomes. Adherens junctions are mainly composed of *fascia adhaerentes/fascia adherens* junctions (Franke et al., 2009) which, in cardiac tissue, are formed by membrane spanning cadherins (N-cadherin) linking the actin microfilaments at the cytoplasmic end with cadherins from the neighboring cell at the extracellular end. The molecular components of *fascia adherens* junctions in cardiac muscle include the (i) main transmembrane protein N-cadherin (~88 kDa), as well as other more recently identified transmembrane and catenin-binding proteins: Coxsackievirus and adenovirus receptor (CAR; ~40 kDa) and lysosomal integral membrane protein 2 (LIMP-2; ~54 kDa) (Lim et al., 2008; Schroen et al., 2007), (ii) the catenins/armadillo proteins, α, β and γ (plakoglobin)-catenin (~102, ~88 and ~82 kDa respectively) as well as (iii) the cytoskeletal actin-binding proteins, vinculin/metavinculin (~117/124 kDa), zonula occludens-1 (ZO-1; ~220 kDa), Xin repeat containing protein, mXinα (~155 kDa) and α-actinin (~110 kDa) (Borrmann et al., 2006; Choi et al., 2007; Franke, 2009; Gutstein et al., 2003; Itoh et al., 1997; Sheikh et al., 2006). Desmosomes (*maculae adhaerentes*) are considered the strongest anchoring junctions and are formed by specialized cadherins (desmocollin-2 ~100 kDa and desmoglein-2 ~122 kDa in the heart) of neighboring cells that bind to one another at the extracellular end (Franke, 2009). From the intracellular side, the desmosomal cadherins are anchored to the catenins/armadillo proteins, β and γ-catenin (plakoglobin), as well as plakophilin-2 (~97 kDa) which are in turn bound to the central cytoplasmic component, desmoplakin (~ 250 kDa, large isoform; ~210 kDa small isoform), that anchor directly to the intermediate filament network of cardiac muscle via desmin (55 kDa) (Sheikh et al., 2009) (Fig. 1). Recent studies also show that the localization of molecular components of desmosomes and *fascia adherens* junctions is not as distinct as previously thought and can overlap in a structure known as the '*area composita*', which is a hybrid junction combining components from both complexes and suggesting cross-talk between desmosomes and *fascia adherens* junction (Pieperhoff et al., 2010). Communicating junctions (gap junctions or *nexus*), are channels that allow passage of small molecules and ions between two cells and are formed by the connexin family of proteins. These tetraspan membrane proteins form hexamers ("connexons") at each cell membrane and give rise to a pore between two neighboring cells. A detailed review of specific connexins in the cardiac conduction system is summarized in Severs et al. (2008). The recent identification of ZO-1, and its presence at *fascia adherens junctions* have been proposed to actively target connexins to the gap junction (Barker et al., 2002; Toyofuku et al., 1998, 2001). However, there are more complex functions of ZO-1 in relation to gap junction biology since Rhett et al. (2011) have also proposed that ZO-1, which is present at the perinexus (surrounding the gap junction), might prevent connexon recruitment to the communicating *nexus*. Furthermore, Shaw et al. (2007) propose a model for adherens junction mediated targeting of connexin 43 (Cx43) to gap junctions, suggesting that proper gap junction positioning at the ends of cardiomyocytes depends on the presence and interaction of adherens junction proteins and the cellular trafficking machinery. A schematic representation of the major molecules that form the anchoring cell–cell junctions in cardiac muscle alongside electro-propagating, generating and coupling channels (e.g., connexins, ion channels) is shown in Fig. 1.

Cardiac conduction system: Evidence of anchoring cell junction structures and molecular components

The generation and propagation of spontaneous action potentials by the cardiac conduction system (CCS) have stimulated decades of exciting research concerning the role of electrical channels (e.g., connexins and ion channels) in CCS structures. An additional level of complexity is brought to the CCS when increasing evidence suggests that anchoring cell–cell junctions, thought to purely serve a mechanical scaffolding role, may also be involved in maintaining the stability and function of electro-generating, propagating and coupling channels. Therefore, understanding how CCS cells are anchored to one another may provide important insights on how anchoring structures may play an intimate role in the maintenance of electrical channels and a healthy CCS. The main components of the CCS include the sinoatrial node (SAN), atrioventricular node (AVN) and the His-Purkinje system (Boyett, 2009). These structures are classically formed by specialized cardiac cells that possess a rudimentary contractile apparatus