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REVIEW

At the heart of inter- and intracellular signaling: the intercalated disc

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Abstract

Proper cardiac function requires the synchronous mechanical and electrical coupling of individual cardiomyocytes. The intercalated disc (ID) mediates coupling of neighboring myocytes through intercellular signaling. Intercellular communication is highly regulated via intracellular signaling, and signaling pathways originating from the ID control cardiomyocyte remodeling and function. Herein, we present an overview of the inter- and intracellular signaling that occurs at and originates from the intercalated disc in normal physiology and pathophysiology. This review highlights the importance of the intercalated disc as an integrator of signaling events regulating homeostasis and stress responses in the heart and the center of several pathophysiological processes mediating the development of cardiomyopathies.

Keywords Intercalated disc · Intercalated disc · Heart · Cardiomyocyte · Cardiomyopathy

Introduction

The intercalated disc was first described over a hundred years ago as "compression strips" or "cementing material" at the ends of cardiomyocytes (Saphir and Karsner 1924). In the mid 1950s, transmission electron microscopy was used to identify an extension of the sarcolemma found at the transverse ends of cells that separates neighboring myocytes, which became known as the intercalated disc (ID) (Muir 1957; Sjostrand and Andersson 1954; Van Breemen 1953). The ID is a highly organized structure that is arranged both transversely and longitudinally in a staircase-like fashion with "steps" and "risers" (Hoyt et al. 1989; Shimada et al. 2004; Tandler et al. 2006) (Fig. 1). The "steps" are transverse or plicate segments of the membrane that run in a zigzag arrangement with three-dimensional finger-like micro projections. Longitudinal or interplicate segments form the "risers." The ID's extensive three-dimensional structure with many folds and projections increases the surface area of connected neighboring myocytes, providing superior communication between cells.

IDs are composed of three main junctional complexes: gap junctions, adherens junctions, and desmosomal junctions, along with their associated proteins. Gap junctions and desmosomal junctions are often found within the interplicate regions of the ID, while adherens junctions localize mainly to plicate regions (Fig. 1).

Gap junctions directly couple the cytosol of neighboring myocytes and enable the propagation of electrical stimuli through low resistance pores (Rohr 2004). A single gap junction is composed of 12 connexin proteins, 6 from each neighboring myocyte. Six connexin molecules form a hemi-channel and are trafficked to the ID membrane as a single unit (Shaw et al. 2007; Sohl and Willecke 2004). Once at the ID, two hemichannels from opposing myocytes couple to form a gap junction. An assembly of 5–500 gap junctions constitutes a gap junction plaque and facilitates electrical coupling between myocytes. In the mammalian ventricular myocyte, connexin-43 is the most prominent connexin (Beyer et al. 1987; Vozzi et al. 1999) (Fig. 2).

Adherens junctions directly couple the membrane to the contractile apparatus of cardiomyocytes and facilitate the transmission of contractile force from one myocyte to the next (Tepass et al. 2000). The adherens junction protein complex

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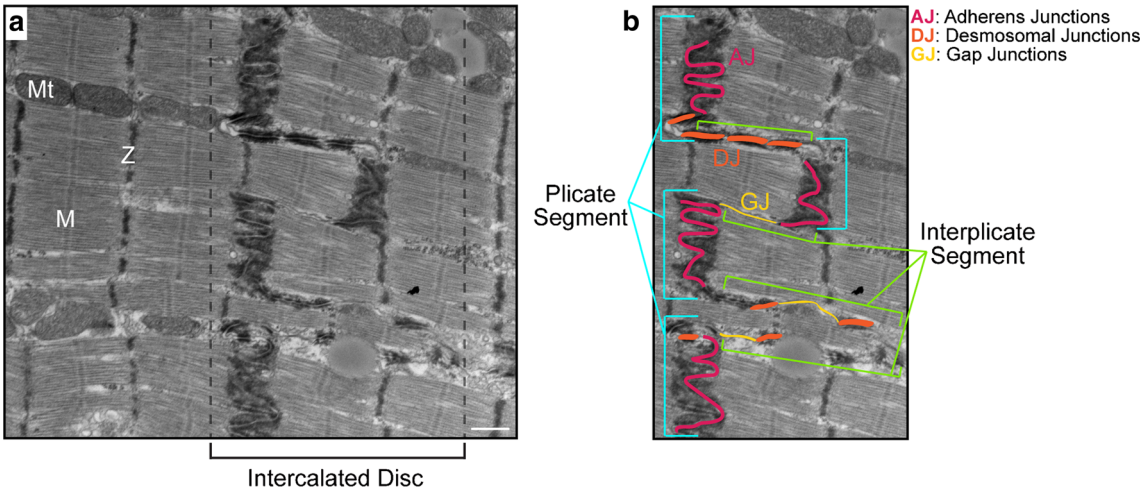

Fig. 1 Intercalated disc ultrastructure in human myocardium. A non-failing donor heart was obtained in collaboration with Lifeline of Ohio and Dr. Paul Janssen at the Ohio State University. Freshly isolated heart tissue was prepped for transmission electron microscopy (TEM) according to our previously published methods (Ackermann et al. 2017b). **a** Representative TEM of the human heart myocardium is used to illustrate the canonical ID structure. Mitochondria, Z-lines, and M-bands are denoted by the Mt, Z, and M, respectively. Scale bar = 500 nm. **b** A focused region of the ID, dotted box from (**a**), highlighting specific ID structures

is composed of transmembrane cadherins and cytosolic catenins (Niessen 2007) (Fig. 2). Through its extracellular domain, N-cadherin anchors to a neighboring myocyte by the formation of a calcium-dependent homodimer (Niessen 2007). Various members of the catenin family (α-, β-, γ-, and p120), present on the cytosolic side of the ID, link the intracellular portion of N-cadherin with the actin cytoskeleton (Bass-Zubek et al. 2009).

Desmosomal junctions provide robust structural support by linking neighboring cardiomyocytes, which is necessary for myocytes to withstand strong contractile stress during cycles of systole and diastole (Delmar 2004). The desmosomal complex is similar to adherens junctions as they are composed of desmosomal cadherins (desmocollin and desmoglein), which link neighboring myocytes through heterodimers (Green and Simpson 2007; Rayns et al. 1969) (Fig. 2). On the intracellular side, proteins of the armadillo/catenin (plakoglobin and plakophilin) and plakin (desmoplakin) families stabilize the desmosomal structure by linking membrane components with the intermediate filament desmin (Bass-Zubek et al. 2009).

Classically, these three structures were identified as distinct assemblies of proteins; however, it has been recognized that components of gap, adherens, and desmosomal junctions form

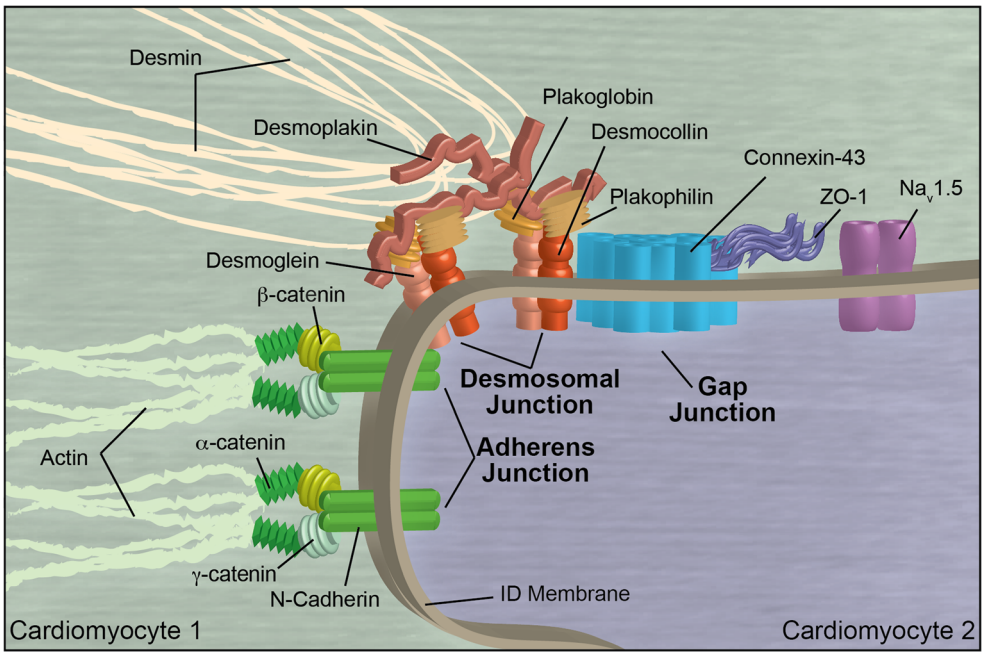

Fig. 2 Schematic representation of major proteins at the intercalated disc. Cardiomyocytes 1 and 2 are shown with green and blue backgrounds respectively

the basis of a highly integrated model that work together to incorporate the electrical and mechanical functions of the ID (Vermij et al. 2017). Consistent with this, components of desmosomal and adherens junctions are intimately associated within the "area composita" and work together to facilitate mechanical coupling (Borrmann et al. 2006; Franke et al. 2006, 2007; Pieperhoff and Franke 2007) (Fig. 2). Similarly, the direct association of proteins of desmosomal junctions with gap junctions provides structural stability to the electrical coupling at the ID (Delmar 2004). To this end, desmocollin directly interacts with connexin-43 to provide additional support for gap junctions (Gehmlich et al. 2011) (Fig. 2).

To facilitate this integrated model, over 200 additional proteins reside at the ID, including but not limited to ion channels, i.e., $Na_v1.5$, scaffolding proteins, i.e., vinculin, spectrins, ankyrins, zona occludens (ZO)-1, and obscurins, and signaling molecules, i.e., CaMKII, PKCα, and TGFβ (Ackermann et al. 2017a, b; Bennett et al. 2006; Dowling et al. 2008; Estigoy et al. 2009; Geisler et al. 2007; Jung-Ching Lin et al. 2005; Kargacin et al. 2006; Lange et al. 2016; Satomi-Kobayashi et al. 2009; Schroen et al. 2007; Seeger et al. 2010; Vermij et al. 2017). Together, these highly organized proteins along with the convoluted nature of the ID membrane allow for the formation of a single functional unit facilitating complex inter- and intracellular signals. Herein, we provide an overview of the inter- and intracellular signaling originating from the ID.

Intercellular electrical communication

Cardiac conduction is characterized by the propagation of electrical stimuli throughout the heart and is responsible for the synchronous contraction of individual cardiomyocytes. At the ID, two types of electrical coupling allow for a mixed mode of intercellular signaling across neighboring myocytes: (1) direct coupling through gap junctions and (2) ephaptic coupling involving ion channel complexes. Canonically, the process of direct coupling was shown to occur via the flow of ions from one myocyte to the next, through gap junctions (Agullo-Pascual and Delmar 2012; Evans and Martin 2002; Rohr 2004). More recently, experimental and modeling evidence suggest another form of gap junction-independent coupling at the ID. Ephaptic coupling is the process by which cardiac ion currents, specifically the cardiac sodium current (I_{Na}), respond to local changes in membrane potential via a local depletion of ions within small clefts between neighboring membranes and drive electrical excitation (Lin and Keener 2010). This is mediated through the cardiac voltage-gated sodium channel, $Na_v1.5$ (Kleber and Saffitz 2014).

Electrical coupling is modulated by multiple mechanisms, including transcriptional regulation and post-translational modifications. This affects functionality and proper localization of key electrical couplers, such as connexin-43 and $Na_v1.5$ (Evans and Martin 2002). For the remainder of this subsection, we will focus on the regulatory mechanisms of the main proteins involved in direct and ephaptic coupling.

Regulation of electrical coupling Cardiomyocytes have multiple ways to regulate both direct and ephaptic coupling in order to maintain homeostasis, as well as adapt to stress. Mechanisms allowing electrical coupling regulation include modulating the expression, localization, and functionality of the proteins involved in this process. These regulatory mechanisms are described below.

Transcriptional regulation of electrical coupling The expression levels of both connexin-43 and $Na_v1.5$ are regulated by signaling through the Wnt/β-catenin pathway (Ai et al. 2000; Wang et al. 2016). Specifically, activation of this pathway increases connexin-43 expression, leading to increased cardiomyocyte coupling through gap junctions (Ai et al. 2000). On the contrary, Wnt/β-catenin signaling can also inhibit $Na_v1.5$ transcription (Wang et al. 2016). Together, this suggests a tight regulation of the balance between direct and ephaptic coupling within the myocyte.

Trafficking and localization of electrical coupling components Proper trafficking and localization of connexin-43 and $Na_v1.5$ to the ID are necessary for normal electrical coupling. Connexin-43 is trafficked to the ID via the filamentous highways throughout cardiomyocytes. Connexin-43 delivery to the membrane is facilitated by microtubules and is dependent on the plus-end microtubule-binding protein EB1 and its interaction with desmoplakin, a desmosomal protein (Shaw et al. 2007). In addition, it has been recently demonstrated that actin is essential for connexin-43 trafficking to the plasma membrane by serving as a rest stop during the transport process (Smyth et al. 2012). Maintenance of the proper localization of connexin-43 at the ID and the formation of gap junctions is largely dependent on its interaction with zona occludens (ZO)-1. ZO-1 functions to restrict the size of gap junction plaques by regulating the accrual of connexin-43 in membranes adjacent to gap junctions (Laing et al. 2007; Toyofuku et al. 1998). The interaction of ZO-1 with connexin-43 negatively regulates the formation of gap junctions, and therefore a loss of connexin-43/ZO-1 binding results in increased available connexin-43 and a subsequently augmented gap junction size and conduction velocity (Laing et al. 2007; Toyofuku et al. 1998). $Na_v1.5$ trafficking to the ID is still not clearly understood. It is suggested that its delivery to the ID via microtubules is also reliant on EB1, but with ankyrin-G as a necessary membrane anchor (Eichel et al. 2016; Herfst et al. 2004; Mohler et al. 2004). At the ID, $Na_v1.5$ complexes with several structural proteins, including β_{IV}-spectrin, α_2-spectrin, and ankyrin-G, and several signaling molecules including CaMKII (Makara et al. 2014). The

interaction between $Na_v1.5$ and ankyrin-G is specifically important to maintain proper localization of the ion channel at the membrane (Makara et al. 2014).

The many protein-protein interactions involved in electrical coupling are overall regulated by the post-translational modifications discussed below.

Regulation of electrical coupling by post-translational modifications Among the most prominent forms of PTMs, phosphorylation, methylation, acetylation, and ubiquitination play a role in regulating the electrical coupling of cardiomyocytes. One of the best-studied PTMs is phosphorylation of both connexin-43 and $Na_v1.5$. Specifically, β-adrenergic receptor stimulation, which activates cAMP-dependent PKA, results in connexin-43 and $Na_v1.5$ phosphorylation. PKA-dependent connexin-43 phosphorylation leads to its increased localization at the ID. $Na_v1.5$ phosphorylation via PKA also promotes $Na_v1.5$ channel trafficking to the cell membrane and results in a shift in the voltage dependence of inactivation towards negative potentials (Matsuda et al. 1992; Schreibmayer et al. 1994; Schubert et al. 1989). In addition to PKA, PKC also phosphorylates and regulates the activities of both connexin-43 and $Na_v1.5$. PKC phosphorylation of connexin-43 results in the protein's internalization and a decrease in gap junction intercellular communication (Lampe et al. 2000; Nimlamool et al. 2015; Solan and Lampe 2018). PKC phosphorylation of $Na_v1.5$ causes a reduction in the peak sodium current and shifts steady-state current inactivation in the hyperpolarized direction, leading to a decreased probability of channel opening. In addition, $Na_v1.5$ phosphorylation via PKC induces slowed channel inactivation and increased late sodium current, which is associated with increased arrhythmias (Hallaq et al. 2012; Ma et al. 2012; Qu et al. 1994). Finally, phosphorylation of $Na_v1.5$ via CaMKII affects channel inactivation by shifting the voltage dependence of inactivation towards negative potentials, while enhancing intermediate inactivation (Ma et al. 2012; Wagner et al. 2006). This phosphorylation also induces slower recovery following channel inactivation and increased sodium late current, which results in a prolonged action potential and slower cardiac conduction. Other modifiers of connexin-43 and $Na_v1.5$ phosphorylation levels include casein kinase 1, MAPKs, Src kinases, and Akt (for a thorough review of PTM via kinases, please see these most recent reviews (Delmar and Liang 2012; Hood et al. 2017; Leithe et al. 2018; Marionneau and Abriel 2015; Palatinus et al. 2012; Rook et al. 2012; Solan and Lampe 2009, 2018)).

In addition to phosphorylation, methylation, acetylation, and ubiquitination are known to modulate connexin-43 and $Na_v1.5$ (Leithe et al. 2018; Marionneau and Abriel 2015; Rook et al. 2012). Specifically, methylation of $Na_v1.5$ increases its expression on the surface of the myocyte and therefore results in increased sodium current density (Xu et al. 2013). Methylation may also regulate select phosphorylation events at key serine residues of $Na_v1.5$, resulting in altered phosphorylation (Beltran-Alvarez et al. 2011, 2014, 2015; Detta et al. 2015). Modulation of connexin-43's acetylation state by histone acetylases and deacetylases contributes to its proper localization at the ID. Specifically, acetylation of connexin-43 triggered by electrical activation mediates its internalization and increased degradation from the ID during normal physiology (Meraviglia et al. 2015). Finally, ubiquitination by the E3 ubiquitin ligase Nedd4 targets both connexin-43 and $Na_v1.5$ for degradation (Girao et al. 2009; Leykauf et al. 2006; Rougier et al. 2005; van Bemmelen et al. 2004).

Perturbation of any of the above-described regulatory mechanisms can have profound consequences for electrical coupling of cardiomyocytes and can mediate disease onset and progression.

Electrical coupling in pathophysiology

Aberrant cardiac conduction, which can trigger fatal arrhythmias, is a key component of most cardiomyopathies. In fact, one of the hallmarks of arrhythmogenic cardiomyopathy is reduced conduction velocity through the myocardium. In addition, the progression of dilated (Ehler et al. 2001; Perriard et al. 2003; Seidman and Seidman 2001) as well as hypertrophic (Ferreira-Cornwell et al. 2002; Seidman and Seidman 2001) cardiomyopathy leads to extreme remodeling and abnormal ID structure (please see below). ID remodeling in these cardiomyopathies represents a high-risk factor for sudden cardiac death (Oxford et al. 2007; Seidman and Seidman 2001; Vermij et al. 2017). Alterations in cardiac conduction can result from structural remodeling and/or modified function of the electrical components of the ID.

Pathophysiology of connexin-43 In select types of cardiomyopathy, connexin-43 is reduced or lost at the ID membrane and relocated to lateral membranes. This is likely due to alterations in binding partners and/or modifications in connexin-43's phosphorylation state (Fontes et al. 2012). Notably, reduced levels of connexin-43 phosphorylation have been observed in arrhythmogenic cardiomyopathy and can occur in the absence of gap junction mis-localization, likely suggestive of an early disease phenotype (Gehmlich et al. 2011). In addition, models of dilated and ischemic cardiomyopathy as well as failing human heart tissues show reduced phosphorylation of connexin-43, which results in a decrease in functional gap junctions and ultimately leads to electrical uncoupling (Michela et al. 2015). Indeed, increased phosphatase activity is associated with cardiovascular disease and correlates with atrial and ventricular arrhythmias.

Pathophysiology of $Na_v1.5$ Sodium channel function is greatly influenced by phosphorylation. In disease states, both hyper- and hypo-phosphorylation have been linked with long QT and

Brugada syndromes, respectively (Abriel 2010; Detta et al. 2015; Mohler et al. 2004). Specifically, hyperphosphorylation by CaMKII and PKA at select residues leads to action potential prolongation due to increased late current, which promotes early and delayed after-depolarizations and can lead to ventricular arrhythmias (Hoch et al. 1999; Koval et al. 2012). On the contrary, increased PKC phosphorylation results in decreased sodium current density, also increasing the propensity to develop ventricular tachycardia (Makita et al. 2002; Wang et al. 1995). Consistent with this, PKC protein is increased at the intercalated disc in mouse models of dilated cardiomyopathy (DCM) and end-stage heart failure patients (Lange et al. 2016). In addition, hypo-phosphorylation at select sites reduces the surface expression of $Na_v1.5$ and consequently decreases the sodium current density (Hoch et al. 1999; Koval et al. 2012). More recently, a phenomenon of drug-induced long QT syndrome has emerged. In patients and animal models, inhibition of PI3 kinase via chemotherapeutics results in increased late sodium current, prolongation of the action potential, and drug-induced arrhythmias (Qiu et al. 2016; Song et al. 2012).

Based on the abundance of literature supporting aberrant electrical coupling at the ID resulting in fatal arrhythmias, it is essential to develop more targeted therapeutic approaches through the identification of clear molecular mechanisms.

Mechanical coupling and cardiomyocyte growth

In addition to electrically connecting individual cardiomyocytes, the ID contains specific domains, such as desmosomes and adherens junctions. Desmosomes are specialized to link transverse membranes with intermediate filaments, which spread throughout the myocyte forming a network around the myofilaments, and adherens junctions allow attachment of transverse membranes to the actomyosin filament bundles within the sarcomere (Sessions and Engler 2016). With this in mind, it is clear that alteration in ID architecture, composition, and function can dramatically modify the contractile properties of cardiomyocytes as well as influence their hypertrophic growth and remodeling.

In recent years, evidence for the critical role of the ID in regulation of cardiomyocyte hypertrophy has emerged, and it has become apparent that components of the ID are not only functioning as structural support for cell-cell junctions but also have important regulatory roles permitting cardiomyocytes to sense and respond to stress. For example, upon stress, β-catenin, which links the cytoplasmic tail of N-cadherin to actin, translocates into the nucleus to activate transcriptional changes that can drive cardiomyocyte remodeling (Baurand et al. 2007).

Specific roles of the ID in physiologic and pathologic cardiomyocyte growth are described in detail below.

Normal development and physiological hypertrophic growth Embryonic cardiomyocytes are relatively spheroid in shape, surrounded by adherens junctions, with a great deal of their cell area taken up by the nucleus; this leaves little cytoplasmic room for myofilament organization. As mammalian cardiomyocytes develop through the embryonic and into the neonatal periods, they exhibit progressive myofibrillar organization, with adherens junctions becoming more and more localized to the longitudinal poles of the cell (Hirschy et al. 2006). By 1-week post-birth, there is a dramatic switch in cardiomyocyte development where hyperplastic growth (i.e., cell growth via division) is replaced with hypertrophic growth (i.e., cell growth in size). As the developing cardiomyocytes make this switch, they begin to lengthen dramatically via activation of MEK5/Erk5 signaling pathways (Hirschy et al. 2006) with a concurrent increase in their width, which is tightly controlled by MEK1/ERK1/2 signaling (Kehat et al. 2011). Cardiomyocytes then develop highly organized myofibrils with sarcomeres being added in series and in parallel, and components of the ID orienting at the poles of the myocyte (Hirschy et al. 2006). The short axis of the cell, containing the naïve intercalated discs, begins to form and maintain cell-cell contacts via inclusion of adherens junctions and desmosomes (Ehler 2016). By 2 weeks post-birth, cardiomyocytes have the shape and ID structure characteristic of adult cardiomyocytes. At this time and as cardiomyocytes mature further, they maintain their stepped ID connections with neighboring cells, with whom they often laterally overlap (Perriard et al. 2003; Wilson et al. 2014). Around 2 or 3 months of age, mature cardiomyocyte width stabilizes and longitudinal growth slows to a point of only about one sarcomere added in series, per week of life (Wilson et al. 2014). In this normal developmental process, cardiomyocytes grow due to the addition of myofibrillar sarcomeres in series, the terminal sarcomeres of which organize with the highly structured ID to allow for myocyte lengthening.

Pathological cardiac dilation The ID, as an important structure both in cardiac development and cardiomyocyte hypertrophy (described above), is also implicated in cardiomyopathy—hereditary hypertrophic and dilated cardiomyopathies are often due to mutations in proteins that make up the myofibrils or IDs (Ehler 2016). Generally, hypertrophic cardiomyopathies are due to mutations in proteins that make up the myofibers, whereas DCM is a genetically heterogeneous disease and involves genes encoding ID components, among many others. DCM genes encode proteins of diverse cellular functions, including those involved in the cytoskeleton, sarcomere, mitochondria, nuclear membrane, RNA binding, and cell-cell adhesion. Specifically, cellular adhesion proteins that are associated with DCM include desmin, desmocollin, desmoplakin, plakoglobin, and vinculin (Kimura 2016; Maeda et al. 1997; McNally et al. 2013). In addition, DCM is often associated

with subtle structural changes in cardiomyocytes that affect the ID (McNally and Mestroni 2017). On a cellular level, DCM cardiomyocytes have a highly irregular structure, with an increased number of cell-cell contacts and increased branching. The structural changes in DCM cardiomyocytes are associated with alterations of the ID's molecular makeup, specifically upregulation of proteins comprising the adherens junctions, which are the site of myofibril attachment (Perriard et al. 2003). Mutations in proteins are associated with cytoskeletal stabilization and force translation proteins that lead to the DCM phenotype and require cardiomyocytes to reinforce their myofibrillar attachments, therefore altering the ID. In addition, MEK5 activation is associated with a specific lengthening of cardiomyocytes, which leads to DCM in mouse models. Targeted deletion of MEK5 leads to embryonic death at E10.5 due to impaired cardiac development, the timing of which in a normal heart corresponds to myofibril elongation (Hirschy et al. 2006).

The structure of the ID, which is normally characterized by small-amplitude (generally, 0.2–1 μm) plicate regions in the membranes of neighboring cardiomyocytes, becomes disrupted in DCM. ID folds become large and tortuous, often allowing space for additional sarcomeres to be added in series, thus lengthening the cell (Wilson et al. 2014; Yoshida et al. 2010). Using high-resolution transmission electron microscopy, A.J. Wilson et al. examined the ID fold amplitude between control and DCM mouse and human heart tissues to elucidate how these plicate regions are regulated in cardiomyocytes (2014). Although there is natural variation in the amplitude of the ID plicate regions, with aging and DCM, the amplitude of these plicate regions can increase to as much as 2 μm, roughly ten times their physiological size. This has also been observed in a volume-overloaded rabbit heart model (Wilson et al. 2014; Yoshida et al. 2010). Whereas, thin actin filaments are the primary structure in small-amplitude ID folds, in large-amplitude folds found in DCM cardiomyocytes, thick filaments begin to appear, corresponding to a fully formed sarcomere within the fold (Wilson et al. 2014; Yoshida et al. 2010). However, the sarcomere addition that occurs within large-amplitude plicate IDs in DCM cardiomyocytes does not happen to every cardiomyocyte—this phenomenon instead tends to occur in alternating cells and rarely, if at all, in neighboring cells. This has been shown previously by Wilson et al., who notes that in DCM hearts, the ID fold amplitude variation between two cells is significantly larger than that in controls, as new sarcomeres are added within the ID of one cell only (Wilson et al. 2014). To complicate cell physiology further, the added sarcomeres frequently demonstrate a highly disordered structure, in stark contrast to the meticulously organized non-terminal sarcomeres of the same cell. In this way, pathologic remodeling of cardiomyocytes in DCM, characterized by widening of ID plicate regions and subsequent insertion of additional, disorganized sarcomeres at the ends of the cells, contributes to a vicious cycle of cardiomyocyte damage, lengthening, and impaired force generation.

In addition to direct mechanical regulation of cardiomyocyte remodeling by ID structures, components of the ID are also implicated in intracellular signaling events that further affect cardiomyocyte growth and function by modulating gene expression. These pathways are described in the next section.

Intracellular signaling mediated through ID components

It has long been accepted that the ID and its components participate in intercellular signaling through electrical and mechanical coupling. But recent findings also show the involvement of ID components in modulating intracellular signaling pathways that mediate cell growth and differentiation, as well as the regulation of fibrotic lesions in the heart (Chen et al. 2014; Li et al. 2011; Lombardi et al. 2009; Zhou et al. 2015). These pathways, which often occur through the relocation of ID components to facilitate transcriptional regulation, are essential for normal physiology but can be detrimental during pathological states.

Normal transcriptional regulation originating from the ID

A key signaling pathway that links ID to gene expression regulation in the heart is the Wnt/β-catenin signaling pathway. Wnt/β-catenin signaling is mediated through β-catenin-dependent transcription and plays a key role in embryonic development of the heart and in cardiac progenitor cell differentiation, but also has specific functions in terminally differentiated cardiomyocytes (Gessert and Kuhl 2010). Wnt/β-catenin signaling activity is regulated by the stability, localization, and phosphorylation state of β-catenin. Two pools of β-catenin exist in the cell, membrane-bound and cytoplasmic. At the ID, membrane-bound β-catenin associates with the cytoplasmic portion of cadherins in the adherens junction complex, described above. Cytoplasmic β-catenin translocates into the nucleus and activates transcription of genes necessary for growth and/or differentiation. There are also two populations of cytoplasmic β-catenin, free and phosphorylated β-catenin. Phosphorylated β-catenin is targeted for degradation. In the cytoplasm, β-catenin complexes with a multi-molecular destruction complex and is phosphorylated by casein kinase 1 (CK1) and glycogen synthase kinase 3β (GSK3β). Phosphorylation of β-catenin at select residues in its NH_2-terminal region results in recognition of β-catenin protein by the E3 ubiquitin ligase β-Trcp and subsequent ubiquitination and degradation by the proteasome (as reviewed in (Clevers 2006; MacDonald et al. 2009)). Wnt signaling is activated in two ways: (1) binding of Wnt ligands to specific membrane-bound receptors and (2) inactivation of proteins of the destruction complex, with both resulting in reduced phosphorylation

and increased free β-catenin. β-catenin protein accumulates in the cytoplasm and translocates to the nucleus, where it complexes with TCF-4/LEF transcription factors to activate Wnt target gene expression (MacDonald et al. 2009). Some target genes of this pathway include members of the destruction complex for feedback inhibition of the Wnt/β-catenin pathway signaling (Clevers 2006; MacDonald et al. 2009).

β-catenin target genes have been heavily studied in terms of their roles in embryonic development and differentiation of cardiac progenitor cells, but much less is known regarding β-catenin mediated transcription in adult cardiomyocytes (Clevers 2006; Cohen et al. 2008). In normal cardiomyocytes, a low level of Wnt/β-catenin signaling is maintained by tight regulation of free β-catenin protein by the destruction complex. However, Wnt/β-catenin signaling modulation is necessary for physiologic hypertrophy during the addition of myofibrillar sarcomeres for cell lengthening over time (Chen et al. 2006). The role for β-catenin in physiologic hypertrophy was first identified in a mouse model expressing a dominant negative form of the LEF transcription factor. In this murine model, β-catenin is unable to bind and activate transcription through LEF, which results in a dramatic reduction in cardiomyocyte hypertrophic growth (Chen et al. 2006). In addition, stabilization of cytoplasmic β-catenin results in increased heart weight and cardiomyocyte size (Lengauer et al. 1998). Collectively, this suggests that β-catenin is a regulator of hypertrophic growth in adult cardiomyocytes through TCF-4/LEF transcription factors.

Alteration of ID signaling in pathology

Due to its important role in both cellular adhesion and transcriptional regulation, β-catenin expression and activation is tightly regulated. In fact, its expression has been shown to be upregulated in DCM in humans (Perriard et al. 2003). Consistent with this, stabilization of β-catenin or decreased β-catenin turnover also leads to a DCM phenotype with early fatalities in mice (Hirschy et al. 2010). In addition, improper activation of β-catenin-mediated transcription is linked to cardiomyopathies including pathologic hypertrophy. This occurs through both Wnt-dependent and Wnt-independent mechanisms via inhibition of GSK3β. GSK3β is inactivated following Wnt stimulation and also post-hypertrophic stimuli (pressure overload in vivo or α-adrenergic or endothelin-1 stimulation in vitro) (Haq et al. 2003; ter Horst et al. 2012). Both mechanisms result in decreased phosphorylation of β-catenin and increased translocation to the nucleus and subsequent activation of transcription through TCF-4/LEF (Haq et al. 2000; Haq et al. 2003). Additionally, acute human infarction and rat hypertension models show elevated levels of β-catenin in the myocardium, resulting in increased transcription and hypertrophic growth (Lee et al. 2017). Similarly, Yu et al. found the anti-aging compound klotho attenuated angiotensin-II-stimulated activation of Wnt/β-catenin signaling and subsequent cardiac hypertrophy (Yu et al. 2016).

Several studies have identified contradictory roles for Wnt/β-catenin signaling in cardiac hypertrophy, suggesting it is necessary for adaptive cardiac remodeling but may be detrimental to pathological hypertrophy (Baurand et al. 2007). In two studies, conditional deletion of β-catenin did not impair hypertrophy in response to angiotensin-II infusion as would be expected (Baurand et al. 2007; Zelarayan et al. 2008). Similarly, constitutively active β-catenin transgenic murine models show a blunted hypertrophic response to angiotensin-II and no altered hypertrophy after infarct (Zelarayan et al. 2008). Additionally, β-catenin protein accumulates at the ID of hamster and human cardiomyopathic hearts, resulting in a deprivation of β-catenin available for activation of transcription in the nucleus. Masuelli et al. attributes the reorganization of cellular adhesion in cardiomyopathic hearts to the interaction of cadherins/catenins and that this increased adhesion could result the observed myocardial wall stiffness in these hearts (Masuelli et al. 2003). These contradictory roles for β-catenin-mediated transcription activity in cardiomyocyte hypertrophy likely stem from the differences associated with each model.

Alteration of the Wnt/β-catenin signaling pathway is also implicated in the pathogenesis of arrhythmogenic cardiomyopathy (ACM). ACM is characterized by the classical pathogenic hallmarks of increased fibro-adipogenesis, loss of conduction velocity, and increased ventricular arrhythmias (Chen et al. 2014; Lombardi et al. 2011) and is considered a disease of the ID associated with clinical variants in genes encoding desmosomal components (Calore et al. 2015). Specifically, of the 12 genes that are associated with ACM, half of them can be mapped to genes encoding desmosomal proteins, and desmosomal gene mutations account for more than 50% of patients with reported ACM (Marcus et al. 2013; van der Zwaag et al. 2009). Desmosomal gene mutations can lead to impairment of intercellular electrical activity and gap junction function, which are vulnerable to mechanical stress and can also contribute to the molecular mechanisms inducing fibro-adipogenesis through the inactivation of Wnt/β-catenin signaling (Xu et al. 2017). β-catenin and plakoglobin (also known as γ-catenin), both key members of the ID proteome, are important mediators in the activation and suppression of Wnt/β-catenin signaling. Notably, plakoglobin and β-catenin are ~ 85% similar in their primary structure but play opposing roles in the regulation of Wnt/β-catenin signaling (Lombardi et al. 2011). Interactions between plakoglobin and β-catenin with TCF-4/LEF transcription factors differentially regulate transcription of Wnt/β-catenin target genes. Translocation of plakoglobin to the nucleus, commonly seen in ACM, suppresses β-catenin-mediated transcription (Lombardi et al. 2009, 2011).

Recently, transforming growth factor beta 1 (TGFβ1) has also been implicated in controlling intracellular signaling

through the ID by altering expression of neural adhesion molecule 1 (NCAM1) in cardiomyocytes in a p38-dependent pathway (Ackermann et al. 2017b; Lal et al. 2015). In addition to the established role for TGFβ1 in regulating myocardial fibrosis and extracellular matrix remodeling, these findings suggest a role for TGFβ1 in cell-cell adhesion in ventricular myocytes and highlight the increasingly recognized role for the ID as an integrator of multiple signaling pathways.

Overall, the integration of TGFβ, GSK3β, and Wnt/β-catenin and its antagonist plakoglobin in the signaling network has emerged as a significant regulator of myocardial function and the interactions between these signaling pathways highlight the complex response to defective ID structure within the heart.

Concluding remarks

The intercalated disc has emerged as a complex structure that functions in both inter- and intracellular communication between and within cardiomyocytes in the heart. It is also evident that the intercalated disc is dynamically regulated to allow adaptation to stress and perturbation of its regulation has detrimental consequences that can lead to arrhythmogenic, hypertrophic, or dilated cardiomyopathy depending on the specific signaling pathways that are defective. These considerations emphasize the central importance of the intercalated disc for the understanding of heart disease and the development of new therapeutics.

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Compliance with ethical standards

Conflict of interest Heather R. Manring declares that she has no conflicts of interest. Lisa E. Dorn declares that she has no conflicts of interest. Aidan Ex-Willey declares that he has no conflicts of interest. Federica Accornero declares that she has no conflicts of interest. Maegen A. Ackermann declares that she has no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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