Molecular Crosstalk Between Mechanical and Electrical Junctions at the Intercalated Disc

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Since the first electron-microscopic description of the intercalated disc over half a century ago, it has become increasingly clear that this apparently simple boundary between individual cardiomyocytes exhibits a highly complex structural and molecular makeup which conveys a number of different key functions. Adherens junctions and desmosomes (“adhesion junctions”) within the intercalated disc are tied up by linker proteins to cytoskeletal proteins of neighboring cardiomyocytes, thus resulting in a network of proteins which is strong enough to absorb mechanical forces exerted during contraction. Secondly, gap junctions consisting of tightly packed connexins permit intercellular exchange of small molecules and excitatory current flow between neighboring cells, the latter being a prerequisite for the safe and rapid propagation of electrical activation along the network of cardiomyocytes. Thirdly, there exists evidence that a number of structural and molecular makeup which conveys a number of different key functions. Adherens junctions and desmosomes (“adhesion junctions”) within the intercalated disc are tied up by linker proteins to cytoskeletal proteins of neighboring cardiomyocytes, thus resulting in a network of proteins which is strong enough to absorb mechanical forces exerted during contraction. Secondly, gap junctions consisting of tightly packed connexins permit intercellular exchange of small molecules and excitatory current flow between neighboring cells, the latter being a prerequisite for the safe and rapid propagation of electrical activation along the network of cardiomyocytes. Thirdly, there exists evidence that a number of ion channels like sodium channels and potassium channels are targeted to the intercalated disc with as yet not fully defined functional consequences for the excitation process of cardiac tissue. Whereas all of these components of the intercalated disc are topologically segregated and serve distinct functions, recent studies of gene mutations which afflict structural proteins of the intercalated disc suggest that there exists extensive crosstalk between both mechanical and electrical junctions at the molecular level which ultimately can predispose the heart to arrhythmias.

The Importance of Adhesion Junctions for Gap Junction Formation and Maintenance

Whereas the topological segregation of adhesion junctions and gap junctions might be interpreted as a sign of structural independence between these 2 major components of the intercalated disc, a number of observations in fact suggest that the presence of stable mechanical contacts based on adhesion junctions is of paramount importance for both the formation and stabilization of functional gap junctional plaques. Evidence in support of this hypothesis stems, eg, from the in vitro observation that the establishment of adhesion junctions consisting of N-cadherin, desmoplakin, α-catenin, and plakoglobin precedes the formation of gap junctional plaques between cultured adult rat ventricular cardiomyocytes. Once mature gap junctional plaques are formed, it can be intuitively appreciated that they must be further mechanically stabilized because the membrane regions containing gap junctions are relatively rigid and are constantly exposed to shear stress during contractions which might cause disruption of the complexes. The importance of such continued mechanical stabilization is illustrated by the finding that dominant negative suppression of N-cadherin in cultured adult rat cardiomyocytes causes destabilization of adhesion junctions and results in disruption of cell–cell contacts and the disassembly of gap junctions. Similarly, induced deletion of the N-cadherin gene in adult mice was shown to lead to a disassembly of the intercalated disc structure with a prominent decrease in levels of connexin43. Thus, presently available evidence is in favor of the view that both the formation and maintenance of gap junction plaques is critically dependent on the presence of sufficient mechanical stabilization of the intercalated disc by adhesion junctions. This interdependence between mechanical and electrical junctions seems to be unilateral in the sense that, as shown in an animal model with cardiac specific conditional knockout of connexin43, the absence of connexin43 does not seem to change the structure of the intercalated disc in respect to the spatial organization of adherens junctions and desmosomes.

Gene Mutations, Defects in Intercalated Disc Proteins, and Arrhythmias

Apart from basic science considerations, the concept that mechanical stabilization of intercalated discs by protein components of adhesion junctions is a prerequisite for gap junction plaque formation and preservation is gaining increasing support from the analysis of gene mutations involved in a number of hereditary cardiac diseases like dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy (ARVC). In a significant number of these cardiac diseases, mutations affect structural proteins of the intercalated disc which are present both in adherens junctions (plakoglobin and vinculin/metavinculin) and desmosomes (plakoglobin, desmoplakin, desmoglein and plakophilin-2). For the case of defects in desmoplakin (Carvajal syndrome) and plakoglobin (Naxos disease), investigations of the ultrastructure of cardiac tissue have revealed substantial abnormalities in intercalated discs and a reduction in the size and abundance of gap junctional plaques. Ultrastructural abnormalities of the intercalated disc have recently also been described for ARVC related mutations in the desmoglein-2 gene which causes defects in the desmosomal protein desmoglein. In all of these cases, precipitation of arrhythmias might be facilitated by the reduction in intercellular gap

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Defects in Plakophilin-2 Affect Gap Junctional Communication

Among the plakophilins 1 to 3, only plakophilin-2 (PKP2) is present in desmosomes of the intercalated disc. PKP2 belongs to the armadillo family of proteins. It can bind to a large number of desmosomal proteins, including desmoplakin, plakoglobin, the desmogleins, and the desmocollins. Moreover, PKP2 was shown to also interact with α-catenin suggesting that it might be part of adherens junctions as well. PKP2 gene ablation in mice results in lethal alterations in heart morphogenesis characterized by defects in intercellular adhesion and wall ruptures in mid-gestation. Mutations in the PKP2 gene are relatively common in ARVC with incidence rates varying among different studies. In their in vitro study, Oxford et al now describe structural and functional implications of a reduction of PKP2 on connexin43 expression and gap junction formation in cultured cardiomyocytes and epicardium-derived cells. They show convincingly, using small interference RNA techniques, that inhibition of PKP2 expression in primary cultures of neonatal rat ventricular cardiomyocytes leads to a reduction of connexin43 content, a redistribution of connexin43 from the intercalated disc to intracellular pools, and a remodeling of desmin and desmoplakin. Functionally, gap junctional remodeling after suppression of PKP2 expression is accompanied by a significant reduction of intercellular dye transfer which indicates compromised intercellular communication. Thus, at least in vitro, these results represent a further piece of evidence in favor of the concept that the integrity of adhesion junctions at the intercalated disc is a prerequisite for the normal targeting and function of connexin43.

Interestingly, Oxford and colleagues observe gap junctional remodeling also in the case of PKP2 suppression in epicardium-derived epithelial cells which, in vitro, are not exposed to the mechanical stress of phasic contractions. Intuitively, stabilization of cell–cell contacts in this “static” cells seems less important than for contracting cardiomyocytes. Nevertheless, epicardium-derived cells undergo remodeling of gap junctions after PKP2 suppression which is highly similar to that observed in cardiomyocytes. This suggests that either (1) static tensions exerted by the cytoskeletons of neighboring epicardium-derived cells is still sufficient as to cause reorganization of the cell–cell contacts in the absence of PKP2, or that (2) PKP2 is directly involved in the stabilization of connexins within the gap junctional plaque.

The latter possibility is supported by pulldown experiments showing that PKP2 associates with connexin43. In this respect, PKP2 represents of further member of the list of binding partners of connexin43 (zonula occludens-1, v-Src, c-Src, α-catenin, β-catenin, caveolin-1, tubulin) which are thought to be involved in connexin43 trafficking, stabilization, and shaping of the junctional plaque.

Given that PKP2 is both a component of the desmosomes and seems to be capable of direct molecular interaction with connexin43, it will be of future interest to sort out the differential involvement of this protein in connexin43 trafficking, in the direct stabilization of gap junctional plaques, and in the mechanical stabilization of the intercalated disc by adhesion junctions. This knowledge will help to advance our understanding of the complex influence that molecular constituents of mechanical junctions exert on the formation and preservation of gap junctional plaques.

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References


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