Disrupted Intercalated Discs
Is Kindlin-2 Required?

Cathy J. Hatcher, Craig T. Basson

Intermediate filaments are cytoskeletal structures that maintain the structural and mechanical integrity of cells, tissues, and organs. These filaments are associated with the nuclear surface but extend out into the cytoplasm and interact with other cytoskeletal elements and cytoplasmic organelles. Eventually, their impingement on the plasma membrane in certain tissues allows them to be tethered by specialized membrane structures, such as hemidesmosomes in epithelial cells, costameres in striated muscle, and intercalated discs in cardiac muscle. At an intercalated disc, the cell membranes of 2 adjacent cardiomyocytes are extensively intertwined and bound together by gap junctions and desmosomes. These connections help stabilize the positions of the cells relative to each other and also help maintain the 3D structural integrity of the tissue. Thus, the intercalated discs ensure proper function of the heart with efficient ejection of blood with each contraction.

Kindlin-2, a member of the kindlin family of focal adhesion proteins, is expressed in cardiac muscle and is enriched at intercalated discs and costameres. Kindlin-1 and kindlin-2 have been shown to play an essential role in integrin-mediated adhesion and spreading. Kindlin-2 can interact with integrin-linked kinase (ILK) and is also able to bind migfilin, a LIM domain–containing protein capable of binding Filamin. In this issue of Circulation Research, Dowling et al demonstrate a novel role for kindlin-2 in embryonic development as well as cardiac development and function. Complete loss of murine kindlin-2 produces embryonic lethality by embryonic day 7.5. These findings demonstrate the essential role of kindlin-2 in early embryogenesis, but given the early lethality of the mice, the contribution of kindlin-2 to murine cardiac morphogenesis remains unknown. Antisense knockdown of kindlin-2 expression in the zebrafish sheds further light on the role of kindlin-2 in cardiac development. Dowling et al were able to show that knockdown of z-kindlin-2 induces abnormalities in zebrafish cardiac structure and function. Kindlin-2–deficient zebrafish display ventricular hypoplasia, abnormalities in ventricular contractility, and abnormal cardiac morphology. At the microscopic level, these mutant hearts also display disrupted intercalated discs and disorganized skeletal myofibrils with apparent vacuoles. Thus, these studies support the requirement of kindlin-2 in the establishment of the intercalated disc and the attachment of myofibrils to membrane junctions in both cardiac and skeletal muscles and imply an important role for kindlin-2 in maintenance of normal cardiac function, myofibrillar organization, and cytoskeletal structure. Given the role of kindlin-2 in organization of intercalated discs and the association of intercalated discs with cardiac disease, it is intriguing to speculate that naturally occurring mutations in KIND2 may produce human cardiomyopathies.

Junctional complexes must be properly organized in the intercalated disc to mediate normal electromechanical coupling between cardiomyocytes. The expression and distribution of junctional components are often perturbed in cardiovascular disease. Among these components, gap junctions, some of which localize to intercalated discs, play a key role in electrically coupling the myocardium. Tissue-specific mutations in GJA5, the gene encoding the connexin 40 gap junction, cause altered electric coupling and lead to arrhythmogenesis. Because ions, small molecules, and even small peptides are capable of traversing these junctions, disorganization of the intercalated discs may make gap junctions more susceptible to improper impulse propagation, as well as intercellular transfer of molecules. Another junctional component, the adherens junctions, mediates strong homophilic cell–cell adhesion via linkage to the actin cytoskeleton. Of these adherens junctions, the cadherin family of proteins is an integral component. These calcium-dependent proteins maintain electromechanical coupling between cells. Cardiac-specific loss of murine N-cadherin leads to a modest dilated cardiomyopathy with impaired cardiac function before sudden cardiac death. In these animals, myofibril organization is relatively normal with the exception of compression of the sarcomeres. Mice haploinsufficient for N-cadherin have an increased susceptibility to induced arrhythmias and display a reduction in Cx43-containing gap junctions. These observations suggest that disturbances in one intercalated disc protein can affect the expression or distribution of surrounding disc proteins and compound the deleterious effects. The existence of mutations in genes encoding intercalated disc proteins adds to the speculation that mutations in KIND2 may contribute to human cardiac disease.

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Aberrations in kindlin-2 activity may potentially contribute to the pathogenesis of cardiomyopathy via kindlin-2 interaction with integrin signaling. In both Caenorhabditis elegans and the mouse, kindlin-2 interacts with ILK. ILK binds to the cytoplasmic tail of β integrins, thus linking cell–extracellular matrix interactions to signals regulating cytoskeletal remodeling and cellular processes including growth, proliferation, survival, and differentiation. ILK is quite abundant in the heart and is believed to transduce β1 integrin–dependent biomechanical stresses in contractile cells. Cardiomyocyte-targeted ablation of ILK in the murine heart causes early onset of dilated cardiomyopathy, as well as spontaneous heart failure. Cardiomyocyte-specific ablation of β1 integrin also causes dilated cardiomyopathy but only in response to an applied cardiac stress such as pressure overload, suggesting that ILK is an effecter of other critical signaling pathways. In some cases, ILK mutations have been identified in human patients with dilated cardiomyopathy, and it is conceivable that these mutations may be modified by kindlin-2 activity. Moreover, future strategies for manipulation of kindlin-2 activity may be useful in promoting cardiac remodeling and repair.

In earlier studies, investigators have shown that kindlin-2, also known as mig-2, mediates interactions with a number of genes that are expressed in the heart. Kindlin-2 is capable of binding to the C-terminal LIM region of the mouse homolog of migfilin, Cal, which is a widely expressed component of actin–cytoskeleton–membrane junctions. Migfilin/Cal in turn associates with Nkx2.5, a transcription factor crucial for normal heart development, and promotes cardiomyocyte differentiation. Thus, this molecular cascade provides an alternative pathway for kindlin-2 to participate in cardiogenesis. It is noted that mutations in NKKX2.5 are responsible for several forms of human congenital heart disease. These include simple congenital structural defects such as atrial septal defects, complex congenital conotruncal malformations such as tetralogy of Fallot, and progressive atrioventricular conduction disease. Human mutations in other transcription factors such as TBX5 and GATA4 that interact with NKX2.5 have overlapping phenotypes. To date, human mutations in KIND2 and migfilin have not been identified in congenital heart disease patients, and it will be intriguing to see whether future research does so. However, it may also be useful to consider the kindlin-2/migfilin interaction as one that may modify the effects of NKKX2.5 mutations and thereby contribute to the highly variable expressivity of these genotypes in human patients.

Although the findings of Dowling et al are exciting and open new doors to consider regulatory mechanisms in cardiac structure and function, it is important to recognize that the precise mechanisms by which kindlin-2 deficiency produces such devastating effects on the heart remain unclear. Dowling et al speculate that lethality may be attributable to defects in epiblast polarity and epiblast adhesion, given the known association among β1 integrin, ILK, and kindlin-2, and such mechanisms have been implicated in lethality of β1 integrin– and ILK-knockout mice. However, such pathogenic processes remain to be demonstrated in the early lethality of kindlin-2–deficient mice. Moreover, although the presumption that impaired cardiac contractility in kindlin-2 morphant zebrafish is related to abnormal intercalated disc mechanics is reasonable, it is also plausible that other mechanisms may be at play. It is currently difficult to tease out what effects impaired cardiomyocyte differentiation and ventricular organization may have on the impact of altered myofibrillar integrity.

In summary, the findings of Dowling et al provide novel linkage among cardiomyocyte structure, heart development, and cardiac physiology. Future studies will likely shed light on the details of a variety of kindlin-2–dependent events in the heart. The identification of a pleiotropic role of kindlin-2 in cardiac structure and function promotes novel hypotheses about the pathogenesis of cardiovascular disease and fostering new treatment strategies to promote cardiac repair.

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**References**


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