Intercalated discs are located at the bipolar ends of cardiac myocytes and contain specialized junctions that mechanically and electrically couple cardiac myocytes. These junctions are responsible for maintaining intercellular adhesion while allowing contractile force to be transmitted between adjacent myocytes and ensuring that the heart contracts with a normal rhythm. Approximately 200 known proteins are associated with intercalated discs, and ≥40% of these have been reported to cause cardiac dysfunction and/or arrhythmias.1 Within intercalated discs there are 3 major types of junctional complexes: adherens junctions (AJs), desmosomes, and gap junctions (Figure). AJs consist of proteins, including nectins, cadherins, and catenins, that provide intercellular contact and mechanical stability by providing anchorage to the actin cytoskeleton. Proteins within desmosomes, including desmoglein, desmplakin, plakoglobin, and catenin, provide mechanical stability by anchoring the intermediate filament system. Gap junctions consist of connexins, which are protein channels that enable electric coupling of adjacent cardiac myocytes by allowing ions and small molecules to move freely across the gap.

Using genetically modified mouse models, the roles of a number of AJ proteins, including α-E-catenin,2 mxin,3 N-cadherin,4 and vinculin,5 have been examined in the heart. Loss of each of these proteins was associated with disruption of the intercalated disc and cardiac dysfunction. In this issue of Hypertension, Satomi-Kobayashi et al6 examine the role of nectin-2 in the heart. Before this report, the role of nectins in the heart had not specifically been addressed. Nectins are transmembrane proteins that are primarily involved in calcium-independent cell adhesion and are composed of a family consisting of 4 members (nectin-1 through -4).7 The cytoplasmic region of nectin is associated with the actin cytoskeleton through afadin (Figure). Satomi-Kobayashi et al6 examined the role of nectin-2 in the heart using global knockout (KO) mice under basal/physiological conditions and under a setting of cardiac stress (pressure overload). The authors firstly demonstrate, by immunoblotting and immunofluorescence confocal microscopy, that nectin-2 and -4 are selectively localized to the intercalated discs of cardiac myocytes in wild-type (WT) mice, whereas nectin-1 and -3 were not detected. It was further illustrated that nectin-2 and N-cadherin colocalize in hearts of WT mice.

Importance of Nectin-2 for the Maintenance of Cardiac Function

Under physiological conditions, cardiac function of nectin-2 KO mice was indistinguishable from that of WT mice. Loss of nectin-2 did not appear to alter the expression or distribution of other AJ proteins (N-cadherin, α-catenin, β-catenin, and afadin), the distribution of connexin43 (gap junction protein) was normal, and the structure of the intercalated disc appeared normal. These findings are in contrast to previous studies that examined the deletion of other AJ proteins (α-E-catenin,2 mxin,3 N-cadherin,4 and vinculin5) in which disruption of the intercalated disc and cardiac pathology were observed under basal conditions. The only notable difference between hearts of nectin-2 KO and WT mice was reduced phosphorylation of Akt, suggesting a link between nectin-2 and Akt signal transduction.

In response to pressure overload for 4 weeks (ascending aortic-constriction/banding), nectin-2 KO mice and WT mice developed a similar degree of cardiac hypertrophy; however, nectin-2 KO mice displayed more cardiac dysfunction as assessed by echocardiography (systolic function ≈25% lower), and this was associated with more fibrosis (≈4.5-fold higher) and apoptosis (≈3-fold higher) than in WT mice. Despite the greater cardiac dysfunction in nectin-2 KO mice in response to aortic banding, AJ proteins (N-cadherin, afadin, β1-integrin, and α-catenin) remained to be expressed and distributed normally and did not differ in comparison with WT mice subjected to pressure overload. The authors subsequently concluded that nectin-2 protects the heart in response to a cardiac insult independent of other AJ proteins. The only observed difference between WT and nectin-2 KO hearts was connexin43 expression after aortic banding. Expression of connexin43 in the heart was reduced in both WT and nectin-2 KO mice in response to pressure overload, but the reduction was greater in nectin-2 KO mice (≈56%) than in WT mice (≈34%). Of note, loss of another AJ protein, N-cadherin, also led to a decrease in connexin43 levels.4 In
the study by Satomi-Kobayashi et al, the fall in connexin43 expression was not sufficient to induce arrhythmia under basal conditions.

Satomi-Kobayashi et al also examined signal transduction in hearts from nectin-2 KO mice subjected to pressure overload. Pressure overload is known to activate G protein–coupled receptors and downstream signaling proteins, including mitogen-activated protein kinases (extracellular signal–regulated kinase 1/2, p38, c-Jun N-terminal kinase) and calcineurin (Figure), and nectins have been shown to regulate intracellular signal transduction. Phosphorylation of Akt, a protein downstream of phosphoinositide 3-kinase known to mediate cell survival, was depressed in nectin-2 KO hearts compared with WT hearts under basal conditions and remained lower 2 weeks after pressure overload. This was associated with a significant increase in the phosphorylation of p38 mitogen-activated protein kinase in nectin-2 KO hearts compared with WT hearts under physiological conditions and remained lower 2 weeks after pressure overload. This was associated with a significant increase in the phosphorylation of p38 mitogen-activated protein kinase in nectin-2 KO hearts 2 weeks after pressure overload and a trend for an increase in phosphorylated c-Jun N-terminal kinase. The reduced activation of Akt, together with the increased activation of p38 and c-Jun N-terminal kinase, may contribute to the increased levels of apoptosis and fibrosis in banded nectin-2 KO hearts. We and others have demonstrated previously that phosphoinositide 3-kinase (p110α) and Akt1 protect the heart against cardiac dysfunction and fibrosis possibly via inhibition of signaling proteins downstream of G protein–coupled receptors, for example, mitogen-activated protein kinases.

Four weeks after aortic banding, phosphorylated Akt, phosphorylated c-Jun N-terminal kinase, and p38 were all greater in nectin-2 KO hearts compared with WT hearts. The authors suggest that the increase in Akt activation may reflect a compensatory mechanism that has been reported previously in the failing heart.

In summary, the data presented by Satomi-Kobayashi et al demonstrate that nectin-2 plays a critical role in protecting the heart against cardiac dysfunction in response to pressure overload but is not necessary under physiological conditions. Somewhat surprisingly, nectin-2 appears to act largely independently of other AJ proteins. However, differential activation of signaling proteins in nectin-2 KO mice under physiological and pathological conditions highlights the links between mechanical coupling of myocytes and signal transduction. A greater understanding of the extensive interactions and diverse functions of proteins associated with the intercalated disc will allow for the continual unraveling of the mechanisms that cause cardiomyopathy and heart failure.

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**Disclosures**

None.

**References**


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