Xin Scaffolding Proteins and Arrhythmias

Qinchuan Wang and Jim Jung-Ching Lin*

Department of Biology, University of Iowa, USA

Intercalated disc (ICD), a unique specialized structure in cardiac muscle, transmits mechanical force and electrical impulses among cardiomyocytes. Recent studies also suggest that ICD, via scaffolding/anchoring proteins, can spatially organize and maintain key ion channel assemblies required for controlling the cardiac action potential. Defects in these processes can lead to arrhythmias and cardiac sudden death. For example, human Nav1.5 E1053K missense mutation disrupts its binding to ankyrin G, a scaffolding protein required for targeting Nav1.5 to ICD and transverse (T) tubule/lateral membranes of cardiomyocytes. As a consequence, this mutation causes Brugada syndrome [1]. Conversely, ankyrin G-deficient cardiomyocytes show reduced Nav1.5 surface expression and localization as well as reduced I\textsubscript{k,slow} current density [2]. These findings clearly demonstrate a link between ankyrin G (a scaffolding protein) dysfunction and human arrhythmias. Another scaffolding protein, synapse-associated protein97 (SAP97), a member of membrane-associated guanylate kinase (MAGUK) family, is preferentially localized to the ICDs and responsible for anchoring the pool of Nav1.5 to the ICDs through its PDZ domain interacting with the 3 last residues (Ser-Ile-Val) of Nav1.5 [3]. Thus, the question remaining to be addressed is whether the roles of these scaffolding proteins in targeting and maintaining Nav1.5 to the ICD membrane are complementary, cooperative, competitive or redundant.

In addition to Nav1.5, Kv4.2/Kv4.3 (α-subunit of transient outward K\textsuperscript{+} channel, I\textsubscript{to,f}) and Kv1.5 and Kcne2 (α-subunit and transmembrane ancillary-subsutitut, respectively, of delayed K\textsuperscript{+} rectifier, I\textsubscript{k,slow1} in mouse) are reported to be associated with ICD and T-tubule/lateral membranes [4-6]. Interestingly, SAP97 also interacts with the 3 last residues of Kv4.2/4.3 (Ser-Ala-Leu) and Kv1.5 (Thr-Asp-Val) to potentially target and/or anchor ion channels to cell surface [6-8]. However, the molecular mechanisms underlying the targeting and maintaining of these channel assemblies to ICD membrane remain unclear. In cardiac diseases, I\textsubscript{to,f} and I\textsubscript{k,slow1} are often altered, thus contributing to the risk of arrhythmias and cardiac sudden death. Three recent publications together have addressed that a novel scaffolding protein family, Xin, may play important roles in targeting and/or maintaining I\textsubscript{to,f} and I\textsubscript{k,slow1} channels to the ICDs [5,9,10]. The Xin family of proteins was originally identified to contain 15~28 repeats of the 16-amino acid residues (termed the Xin repeat-containing protein) and that further identified KChIP2, filamin and p120-catenin as mXinα-interacting partners [9,11]. KChIP2 is a cytoplasmic ancillary subunit of I\textsubscript{to,f} channel assembly and can quantitatively regulate channel activity. The KChIP2-null mice completely lose I\textsubscript{to,f} and are highly susceptible to the induction of cardiac arrhythmias [17]. The facts that mXinα directly interacts with KChIP2 and filamin and that mXinα-null cardiomyocytes have a reduced Ito,f current density suggest a novel role for mXin in I\textsubscript{to,f} channel surface expression. Consistent with this role, Chan et al (2011) have found a significant reduction of both KChIP2 and filamin but not Kv4.2/4.3 in the membrane fraction of the mXinα-null hearts [9]. Recent studies also implicate that mXinα participates in the surface expression of additional ion channels; both mXinα and Kv1.5, which regulates I\textsubscript{k,slow1}, have been recently shown to associate with cortactin [5,10]. Cortactin is one of the key molecules involved in regulating cortical actin dynamics [18], whose activity may be critical for I\textsubscript{k,slow1} channel surface expression and localization. In mXinα-null cardiomyocytes, the ICD-localized...
population of cortactin is drastically reduced, whereas the other population of cortactin underneath the lateral membrane remains unaltered [10]. These findings suggest that mXinβ may recruit or stabilize cortactin together with Kv1.5 to the ICDs. Consistent with this role, electrophysiological studies indicate that total Iκ (including both Iκ1,slow1 and Iκ1,slow2) current density is depressed in mXin−null cardiomyocytes [9]. In addition to showing the association of Kv1.5 with cortactin, Radice group used cardiac-specific N-cadherin conditional knockout mice to provide strong evidence for essential roles of N-cadherin in ICD integrity, cardiac conduction & rhythms, and Iκ1,slow, surface expression [5,19-21]. Cardiac-specific loss of N-cadherin in mice leads to complete dissolution of the ICD structure, gap junction remodeling and slow conduction of ventricles. The mutant mice are more susceptible to arrhythmias and cardiac sudden death. Similar to mXin−null cardiomyocytes, N-cadherin conditional knockout cells also display prolonged action potential duration at 75% and 90% repolarization, higher incidence of EAD, and attenuated Iκ1,slow[5]. Unlike that in mXin−null cardiomyocytes, the loss of N-cadherin in the heart results in a global reduction of cortactin at both ICD and lateral membranes [5], even though N-cadherin is known to be exclusively localized to the ICD. This global reduction of cortactin may be secondary to a cell shape change in N-cadherin conditional knockout cardiomyocytes due to the complete dissolution of the ICD structure. Co-immunoprecipitation with anti-cortactin or anti-N-cadherin did not reveal a direct association between cortactin and N-cadherin [5]. It is reasonable to hypothesize that Xin repeat-containing proteins may be required for this association. It is known that mXinα interacts not only with cortactin but also with p120-catenin [10] and β-catenin [11]. Both of catenins are important determinants for N-cadherin stability and function.

Recently, mXinβ has been shown to be essential for the postnatal maturation of ICDs and for the localization of mXinα and N-cadherin to the ICDs [22,23]. Based on these converging lines of evidence, a compelling hypothesis is that mXinβ also plays a role in cardiac electrophysiology. Studies are currently underway in our laboratory to explore the roles of mXinβ in surface expression of ion channels and the intricate regulation of cardiomyocyte excitability.

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REFERENCES


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