A glimpse at cardiac ion channel macromolecular complexes

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This editorial refers to ‘Re-trafficking of hERG reverses long QT syndrome 2 phenotype in human iPS-derived cardiomyocytes’ by A. Mehta et al., pp. 497–506, this issue.

This editorial refers to ‘βIV-Spectrin regulates TREK-1 membrane targeting in the heart’ by T.J. Hund et al., 2014;102: 166–175.

Normal cardiac electrical activity depends on the proper membrane expression of a number of ion channels in specialized domains of the sarcolemma of cardiac myocytes. A myriad of protein partners, not yet fully identified, are involved in the trafficking of channel subunits from the endoplasmic reticulum (ER) and Golgi export to the cell surface and in their anchoring into macromolecular complexes.1 Nowadays, a very challenging task is to understand how these partners work together to fine tune the functional expression of ion channels and control cardiac excitability. Two recent articles in Cardiovascular Research bring new building blocks to the emerging scheme of molecular cardiac electrophysiology.2,3

The article of Hund et al.7 reports a new role of the actin-associated protein, βIV-spectrin. In cardiac myocytes, this protein regulates the targeting of ion channels into the intercalated disc by binding to the adapter protein ankyrin-G. The authors found that the expression of a mutant βIV-spectrin allele with a premature stop codon prior to the ankyrin-binding site is associated with the prolongation of cardiac repolarization and the lengthening of the action potential (AP) in mice that also show sinus node pauses. The effect of the mutated βIV-spectrin (qv IV) on cardiac repolarization does not involve classical voltage-gated potassium channels, but the two-pore K+ channels TREK-1 that activate in response to mechanical stress or arachidonic acid accumulation. In addition to the identification of an unexpected role for TREK-1 in shaping the AP, this study emphasizes the striking complexity of the molecular organization of ion channels in cardiac myocytes. Indeed, this article follows a previous one from the same laboratory, reporting that the deletion of the CaMKII-binding site of βIV-spectrin causes an opposite effect on cardiac repolarization than the one reported in the present article, i.e. a marked shortening of the AP that cannot adapt anymore to heart rate.4 This effect was attributed to the disruption of the macromolecular complex formed by βIV-spectrin, CaMKII, and the cardiac sodium channel Nav1.5. Therefore, the same anchoring protein, βIV-spectrin, restricted to a specific microdomain can have opposite effects on the cardiac repolarization depending on its interaction with distinct ion channels. There are other examples of scaffolding or anchoring proteins interacting with various ion channels in cardiac myocyte. For instance, the MAGUK (‘membrane-associated guanylate kinase’) protein SAP97 (‘synapse-associated protein 97’) regulates the formation of a macromolecular complex formed by Nav1.5 and Kir2.1 potassium channels.5 This molecular organization could have important implications in the activation of the rising phase of the AP. By clamping the resting membrane potential close to the K+ equilibrium potential, Kir channels could function to maintain surrounding Nav1.5 channels in the closed state. Another example is the interaction between connexin-Cx43 and Nav1.5 mediated by plakoglobin (PKG) at the desmosome that could be crucial for normal AP propagation.6,7 Finally, different populations of the cardiac Nav1.5 channels have been identified based on their localization in the cardiac myocyte and their interaction with either SAP97 or the dystrophin/glycoprotein complex8 that could play role in the anisotropic propagation of the AP.

Therefore, a global scheme appears to emerge from these observations which is that the spatial organization of ion channels and adaptor proteins in myocytes could confer specific roles to these macromolecular complexes in the generation and/or the propagation of the AP. Besides the architectural organization of ion channels and partners, the dynamics of these interactions should also be explored as anchoring is just one step in the trafficking process. Indeed, the stability of these interactions should also settle the fate of ion channels such as degradation or recycling.

We are just beginning to appreciate the extraordinary complexity of the spatio-temporal regulation of the surface expression of ion channels in cardiac myocyte. A major task now will be to integrate these processes into a comprehensive model of cardiac electrophysiology and pathogenesis of arrhythmias. These considerations point to the crucial importance to develop experimental approaches which, on the one hand, allow easy manipulation of the various partners involved in ion channel expression and, on the other hand, reproduce the native environment and electrical

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phenotype of cardiac myocytes. In this line, the use of inducible pluripotent stem cells (hiPSCs) has been a major breakthrough. These cells can differentiate into cardiomyocyte and recapitulate the electrical phenotypes of the donor. In their study, Mehta et al. generated hiPSCs cells from dermal fibroblast obtained in a 13-year-old man suffering from LQTS2 syndrome due to a missense mutation in KCNH2 gene encoding human ether-a-go-go related gene (hERG) channels. The generation of LQTS2-specific cardiomyocytes allows the authors to identify the precise mechanisms underlying the defective hERG trafficking. They found that the miss-processed mutated hERG results in an up-regulation of the proteasome pathway, the inhibition of which using the calpain inhibitor ALLN rescues the channel expression and normalizes the electrical phenotype. The availability of ion channels at the plasma membrane appears more and more as a major determinant of cardiac electrical activity. Anterograde and retrograde pathways continuously regulate the density of functional ion channels in response to various stimuli contributing likely to the adaptation and the plasticity of the cardiac electrical phenotype. The availability of ion channels at the plasma membrane appears more and more as a major determinant of cardiac electrical activity. Anterograde and retrograde pathways continuously regulate the density of functional ion channels in response to various stimuli contributing likely to the adaptation and the plasticity of the cardiac electrical activity. An example is the regulation of hERG expression by external potassium concentration. In atrial myocytes, the surface expression of the main repolarizing channel, Kv1.5, is also labile, depending on the working conditions of the atria. For instance, shear stress stimulates the delivery of Kv1.5 channels from the recycling endosome through an integrin/FAK-triggered exocytosis process. During atrial haemodynamic overload and dilation, this process is up-regulated and more Kv1.5 channels are inserted in the plasma membrane contributing to the shortening of the AP. The study by Mehta et al. shows that the re-trafficking of hERG can normalize the activity of mutated channels (otherwise functional) and the electrical cardiac phenotype indicates that targeting ion channels trafficking could be an alternative strategy to classical antiarrhythmic agents. Therefore, there is a great interest to dissect the machinery regulating ion channel availability and to understand the physiological regulation of this process. This effort of research should lead to the identification of new therapeutic targets for the treatment of cardiac arrhythmias.

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