Novel Mechanism of Transient Outward Potassium Channel Current Regulation in the Heart
Implications for Cardiac Electrophysiology in Health and Disease

Michael S. Bohnen, Vivek Iyer, Kevin J. Sampson, Robert S. Kass

The cardiac action potential (AP) results from the summation of ion channel activity that depolarizes and then repolarizes the plasma membrane, allowing for contraction and relaxation of the atrial and ventricular chambers. After the initial depolarization, a brief repolarization event occurs in human hearts that sets the critically important plateau phase of the AP during which calcium enters the cytosol, leading to contraction; alteration of the plateau predisposes to arrhythmia. The brief repolarization before the plateau phase results from rapid activation of voltage-gated potassium channels known collectively as transient-outward potassium channels. The K+ efflux through these channels causes a transient outward current known as $I_{to}$.1

$I_{to}$ may be further subdivided into a fast component $I_{to,f}$ and a slow component $I_{to,s}$.2 Both $I_{to}$ subtypes activate rapidly at membrane voltages positive to −30 mV; the primary difference between them is the time to inactivation because $I_{to,f}$ inactivates over tens of milliseconds, whereas $I_{to,s}$ inactivates over hundreds of milliseconds.3 $I_{to,f}$ is comprised of pore forming alpha subunits Kv4.2 and Kv4.3, encoded by the KCND2 and KCND3 genes, respectively. The alpha subunit coassembles with accessory subunits KChIP2 and DPP6 to form the functional channel.4

$I_{to,f}$ is abundantly expressed throughout the human heart, with a greater $I_{to,f}$ current density present in the atria and Purkinje fibers than in the ventricular myocardium.5 The regional differential expression of $I_{to,f}$ within the human heart contributes to the observed differences in the morphology of AP waveforms throughout different cells in the heart. For example, atrial myocytes, where $I_{to,f}$ is large, have a more triangular AP shape and repolarize faster than ventricular myocytes. The differences in AP morphology and duration serve physiological roles (eg, the longer plateau phase duration in the ventricles allows for a more prolonged and greater force of contraction), and alterations to them can lead to a wide variety of cardiac disease phenotypes. For $I_{to}$ alone, studies demonstrate a correlation between increased $I_{to}$ and early-onset lone atrial fibrillation, Brugada syndrome, and idiopathic ventricular fibrillation, whereas decreases in $I_{to}$ have been demonstrated in heart failure.2,6 The clinical phenotypes can be tied to the regulation of ion channel subunit expression. Gain-of-function mutations in KCND3 give rise to early-onset lone atrial fibrillation, whereas there is a relatively consistent decrease in $I_{to}$ because of reduction in Kv4.3 expression in the setting of heart failure and concomitant ventricular remodeling.7 Implicit in this discussion is the understanding that regulation of $I_{to}$ subunit expression has functional consequences on the AP waveforms of different regions of the heart.

The continued improvements in our understanding of the molecular components of cardiac ion channels and post-transcriptional regulation of these components deepen our understanding of the pathophysiology of cardiac arrhythmia. Although specific mutations in the pore forming subunits of $I_{to}$ have been studied in patients with cardiac disease, a growing interest in the role of post-transcriptional and post-translational modifications of ion channels has evolved. Recent $I_{to}$ studies have explored the impact of microRNAs on protein expression and channel phosphorylation on $I_{to}$ current density, which together highlight the importance of regulation of the $I_{to}$ channel in cardiac myocytes.2 In the study by Li et al8 in this issue of Circulation Research, the authors illustrate, for the first time, regulation of $I_{to}$ by a cold-inducible RNA-binding protein (CIRP).9

RNA-binding proteins act as important regulators of gene expression.10 CIRP, which was first identified in murine germ cells exposed to low temperatures, is constitutively expressed in many bodily tissues, including the brain, testis, lung, and heart.11 CIRP acts as an RNA chaperone and regulatory molecule, controlling cellular processes, such as RNA splicing, initiation of translation, and aiding the assembly, disassembly, and transport of proteins.12 In the setting of cell stressors, such as cold and hypoxia, CIRP expression is upregulated.13 In the setting of hemorrhagic shock and sepsis, overactivity of CIRP causes overproduction of inflammatory cytokines, furthering hemodynamic instability. Before the work by Li et al, the role of CIRP in the heart was unclear.

Using CIRP-knockout rats, Li et al8 reveal that the absence of CIRP results in a shortened rate-corrected QT (QTc) interval on ECG and decreased AP duration, tightly linked to an increase in $I_{to}$ (Figure A). Moreover, the CIRP-knockout rats did not have altered transcription of KCND2 or KCND3, but rather had increased expression of Kv4.2 and Kv4.3 subunits, resulting in
an approximate doubling of \( I_{\text{to}} \) density in ventricular myocytes. KChIP2 expression was unaffected, and expression of other key ion channels was not altered in the CIRP-knockout rats. These data suggest that CIRP selectively regulates \( \text{Kv4.2} \) and \( \text{Kv4.3} \) gene expression in rat heart by preventing excessive protein expression of the corresponding Kv4.2 and Kv4.3 subunits.

This new finding adds to our understanding of the regulation of cardiac ion channels and AP characteristics. Extrapolating the result from the rat model to larger mammals will prove interesting as alterations in \( I_{\text{to}} \) produce differing effects on APs depending on the morphology of the AP. Computational modeling, for example, predicts that in human ventricle, small decreases in \( I_{\text{to}} \) increase AP duration slightly, whereas large increases can shunt the AP and cause rapid repolarization (Figure B). Modeling also predicts that this effect is altered in the atria and conducting system where a less pronounced spike-and-dome AP is the baseline. This diversity of effects of altering \( I_{\text{to}} \) in different regions of the heart likely explains the variety of cardiac disease phenotypes attributable to alterations in \( I_{\text{to}} \).

Because \( I_{\text{to}} \) plays a significant role in generating the normal cardiac AP, pharmacological modulations, in addition to naturally occurring modulation, are active topics of research. One example, the experimental drug NS5806, increases peak \( I_{\text{to}} \) currents and slows channel inactivation in canine ventricular myocytes and can recapitulate the Brugada Syndrome phenotype. Furthermore, in failing hearts in which a decrease in \( I_{\text{to}} \) expression has been shown to occur and to contribute to failure-induced AP prolongation, NS5806 has been shown to rescue, at least in part, \( I_{\text{to}} \) expression, suggesting that activation of \( I_{\text{to}} \) may serve in the treatment of heart failure. This proof-of-concept that \( I_{\text{to}} \) may be pharmacologically manipulated for therapeutic benefit potentially extends to other cardiac disease conditions wherein \( I_{\text{to}} \) imbalance occurs.

The discovery that CIRP regulates \( I_{\text{to}} \) expression brings CIRP to the forefront of gene regulation and pharmacology in \( I_{\text{to}} \)-dependent cardiovascular disease. CIRP may be actively released from cells and a prior study developed neutralizing antisera containing IgG directed against CIRP, which successfully blocked CIRP and improved survival outcomes of hemorrhagic and septic animals. This study suggests that CIRP represents a potential novel therapeutic target and opens the door for important questions to address: how does CIRP regulation impact the human heart? Does CIRP activity change in specific pathophysiologic settings, such as ischemic heart disease or heart failure? As for the interaction of CIRP with \( I_{\text{to}} \) channel components, does CIRP normally interfere with translation initiation of the alpha subunits Kv4.2 and Kv4.3 or another post-transcriptional process? Does CIRP affect normal folding of Kv4.2/Kv4.3 or does CIRP increase disassembly rates of Kv4.2/Kv4.3? These important questions, brought to the forefront by the article by Li et al., remain unanswered, with the field open to uncovering how exactly CIRP regulates \( I_{\text{to}} \) in health and in disease, and the therapeutic potential for CIRP regulation in the human heart.

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## References


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