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Mechanisms Contributing to Myocardial Potassium Channel Diversity, Regulation and Remodeling

Kai-Chien Yang[1,2] and **Jeanne M. Nerbonne**[3,*]

[1]Department of Pharmacology, National Taiwan University, Taipei, Taiwan

[2]Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

[3]Departments of Developmental Biology and Internal Medicine, Cardiovascular Division, Washington University School of Medicine, St Louis, Missouri, USA

Abstract

In the mammalian heart, multiple types of K^+ channels contribute to the control of cardiac electrical and mechanical functioning through the regulation of resting membrane potentials, action potential waveforms and refractoriness. There are similarly vast arrays of K^+ channel pore-forming and accessory subunits that contribute to the generation of functional myocardial K^+ channel diversity. Maladaptive remodeling of K^+ channels associated with cardiac and systemic diseases results in impaired repolarization and increased propensity for arrhythmias. Here, we review the diverse transcriptional, post-transcriptional, post-translational and epigenetic mechanisms contributing to regulating the expression, distribution and remodeling of cardiac K^+ channels under physiological and pathological conditions.

Keywords

myocardial excitability; arrhythmias; microRNAs; transcription factors; long non-coding RNAs; cardiac hypertrophy; heart failure; diabetes

Introduction

Cardiac action potentials are generated by the coordinated activation and inactivation of ion channels conducting depolarizing, inward (Na^+ and Ca^{2+}) and repolarizing, outward (K^+) currents (Figure 1) [1]. While only a few Na^+ and Ca^{2+} channels account for cardiomyocyte depolarization, multiple types of voltage-gated (Kv) and non-voltage-gated inwardly rectifying (Kir) K^+ channels contribute to repolarization, determining action potential

*Address correspondence to: Jeanne M. Nerbonne, PhD, Alumni Endowed Professor of Molecular Biology and Pharmacology, Departments of Developmental Biology and Internal Medicine, Director, Center for Cardiovascular Research, Washington University School of Medicine, Box 8086, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO 63110, Tel: (314) 362-2564, jnerbonne@wustl.edu.

amplitudes, durations and waveforms (Figure 1; Table 1) [1]. Myocardial Kv and Kir channels are differentially expressed, resulting in regional- and cell type-specific differences in excitability and action potential waveforms (Figure 1). The expression, distribution, and functioning of Kv and Kir channels are altered in a variety of cardiac and systemic diseases, leading to abnormal myocardial repolarization and increased propensity for life-threatening arrhythmias. A large number of Kv and Kir channel pore-forming (α) and accessory (β) subunits have been identified and the roles of many of these subunits in the generation of native myocardial Kv and Kir channels (Table 1) have been defined [1]. In addition, two pore domain (K2P) K^+ channels [2] and small conductance (SK) [3] Ca^{2+}-activated K^+ channels have been shown to be expressed and demonstrated to play roles in cardiac electrophysiological functioning. Here, the factors contributing to the diverse properties and functional roles of myocardial K^+ channels are reviewed, and the molecular mechanisms contributing to the physiological regulation and pathological remodeling of myocardial K^+ channels are discussed.

Molecular Determinants of Myocardial K^+ Channel Diversity

Although the hyperconserved (GYGD) sequence that underlies K^+ selectivity is a common feature of all K^+ channels, the activation, inactivation, and regulatory mechanisms vary markedly among different types of K^+ channels. The common ancestor of prokaryotic and eukaryotic K^+ channels formed a primitive channel structure with two transmembrane domains (TM) [4], which has evolved into over 100 different K^+ channel pore-forming (α) subunit genes (Figure 2) through extensive gene duplication and divergence; more than 40 K^+ channel α subunit genes are expressed in the heart [1]. There are three types of K^+ channel α subunits: (1) the six transmembrane-domain (6-TM) family, which includes Kv and SK channels; (2) the two-transmembrane-domain (2-TM) Kir channels; and, (3) the four-transmembrane-domain (4-TM) K2P channels (Figure 2). Some K^+ channel α subunit genes undergo alternative splicing [5] and different K^+ channel α subunits in the same subfamily can, in principle, heteromultimerize, thereby increasing the potential for functional K^+ channel diversity.

In addition to the pore-forming α subunits, multiple types of cytosolic and transmembrane K^+ channel accessory subunits, including Kvβ subunits, minK and minK-related proteins (MiRPs), K^+ channel interacting proteins (KChIPs), K^+ channel associated protein (KChAP) and the membrane-associated guanylate kinase homologs (MAGUK proteins), have been identified [1]. The various K^+ channel accessory subunits contribute to regulating trafficking, membrane anchoring, organization and biophysical properties of assembled, functional K^+ channel complexes.

Myocardial K^+ Channel Regulation

Multiple mechanisms contribute to the regulation of K^+ channel expression and functioning in cardiomyocytes (Figure 3).

Transcriptional Regulation of Myocardial K^+ Channels

Transcriptional mechanisms control the temporal and spatial expression of cardiac K^+ channels during development and in response to cardiac damage or disease. The fast component of the Kv4-encoded transient outward current, $I_{to,f}$, for example, is expressed at higher densities in epicardial than in endocardial myocytes, resulting in the transmural repolarization gradient that is critical for normal cardiac electrical and contractile and function [6]. The transmural $I_{to,f}$ gradient has also been suggested to underlie the ST-segment elevation of the Brugada type ECG pattern [7]. In the mouse, the homeodomain transcription factor Irx5, which is expressed in a gradient opposite that of Kv4.2, represses Kv4.2 mRNA expression by recruiting the cardiac transcriptional repressor mBop [8]. Deletion of Irx5 results in the selective increase in Kv4.2 (and $I_{to,f}$) in endocardial myocytes, flattening the transmural repolarization gradient [8].

The densities of the transient outward current, $I_{to,f}$, and of the delayed rectifier currents, I_{Ks} and I_{Kr}, are higher in right (RV), compared with left (LV), ventricles, contributing to differences in action potential durations in RV (shorter) and LV (longer) myocytes [9]. The expression levels of the transcripts encoding the I_{Ks} and I_{Kr} channel α subunit proteins, KvLQT1 and HERG1, respectively, are also higher in RV than in LV [10]. It has been reported that the transcription factor Sp1 modulates the activities of the *KCNQ1* (which encodes KvLQT1) and *KCNH2* (which encodes HERG1) promoters, suggesting that the differential expression of Sp1 (RV>LV) may account for the interventricular gradients of KvLQT1 and HERG1 protein expression [10, 11].

The expression of $I_{K,ATP}$ also exhibits atrioventricular and interventricular gradients: the Kir 6.1 and SUR1A mRNAs are 4- to 12-fold higher in the atria than in ventricle, and SUR2B mRNA is 6-fold higher in RV than in LV [12]. The forkhead transcription factors FoxO1, FOXO3 and FOXF2 modulate the expression levels of $I_{K,ATP}$ channel subunits, contributing to the observed regional differences. These transcription factors also coordinate the expression of genes encoding $I_{K,ATP}$ channel subunits and genes involved in glycolysis and β-oxidation [12]. The transcriptional activity of *Kcnj2*, which encodes inwardly rectifying I_{K1} channel subunit Kir2.1, is regulated transcription factors Sp1, Sp3 and NF-Y [13]. Importantly, several transcriptional regulators, including T-box-containing transcriptional repressors (Tbx3, Tbx5 and Tbx18) and Notch, play critical roles in programming specific cardiac cell types. For example, Tbx18 guides the formation of sinus node head from mesenchymal precursors, followed by Tbx3-mediated pacemaker gene programming [14]. In addition, Tbx5 cooperates with Nkx2.5 to modulate the expression of Id2, a transcription factor that promotes ventricular conduction system differentiation [15]. Myocardial Notch signaling, on the other hand, promotes the differentiation of chamber cardiac progenitors into specialized conduction system-like cells [16].

In addition to transcription factors, multiple signaling pathways have been implicated in the transcriptional control of K^+ channel expression. Phosphoinositide 3-kinase alpha (PI3Kα) signaling activation, for instance, has been shown to upregulate multiple cardiac K^+ channel transcriptionally through an Akt-independent mechanism [17]. The calcium-activated phosphatase, calcineurin, increases the transcriptional activity of *Kcnd2* (Kv4.2) and $I_{to,f}$

density in neonatal rat ventricular myocytes by activating nuclear factors of activated T-cells (NFATs) [18]. *In vivo* overexpression of calcineurin in the mouse heart, however, downregulates $I_{to,f}$ and $I_{K,slow}$, which can be reversed by the treatment of the calcineurin inhibitor, cyclosporin A [19].

Post-Transcriptional Regulation of Myocardial K^+ Channels

Following synthesis by RNA polymerase II, the primary transcripts (pre-mRNAs) of most eukaryotic genes are extensively processed through 5′ capping, 3′ polyadenylation, RNA editing and splicing [20]. These pre-mRNA processing steps are coupled spatially and temporally and determine the fate of the transcript, affecting the nuclear export, translation, localization and stability of the mature mRNAs and resulting in the rapid and efficient fine tuning of gene expression levels [20]. Although there are few reports demonstrating a functional role for RNA editing of myocardial K^+ channel subunit transcripts, the expression levels of K^+ channel subunit transcripts and the properties of the resulting proteins have been shown to be regulated by RNA editing. The inactivation properties of the channels formed by human Kv1.1, for example, are controlled by adenosine-to-inosine RNA editing mediated by human adenosine deaminase acting on RNA-2 [21].

In contrast, abnormal K^+ channel subunit gene splicing has been implicated in human cardiac arrhythmias. Mutation-mediated splicing errors in *KCNQ1*, for example, lead to reduced I_{Ks} and type 1 Long QT syndrome (LQT1) [22, 23]. Similarly, abnormal splicing of *KCNH2*, resulting from intronic branch point [24] or 5′ splice site [25] mutations, impairs the functioning of the resulting HERG-encoded I_{Kr} channels, causing type 2 Long QT syndrome (LQT2).

MicroRNAs (miRs) (Figure 3) are small non-coding RNAs that regulate gene expression by targeting 3′ untranslated regions (3′ UTRs) to impede target protein translation or enhance target mRNA degradation [26]. Several miRs have been shown to contribute to post-transcriptional regulation of cardiac K^+ channels. One of the muscle-specific miRs, miR-1, for instance, has been shown to regulate $I_{to,f}$ by targeting the *Kcnd2*-repressing transcription factor Irx5 [27]. Targeted deletion of miR-1 in mouse heart leads to increased Irx5 expression, resulting in reduced *Kcnd2* expression and impaired repolarization [27]. In addition, miR-1 is known to target *Kcnj2* (Kir2.1) and the dysregulation of miR-1 has been shown to contribute to post-myocardial infarction (MI) arrhythmias (miR-1 up, Kir2.1 down) [28] and atrial fibrillation (miR-1 down, Kir2.1 up) [29]. Increased expression of another muscle-specific miR, miR-133a, has been demonstrated to prolong QT intervals by reducing KChIP2 levels and attenuating $I_{to,f}$ [30]. Increased miR-212 expression is often observed with heart failure, and the upregulation of miR-212 has been reported to reduce Kir2.1 and I_{K1} density [31].

Post-Translational Regulation of Myocardial K^+ Channels

K^+ channel subunit proteins are subjected to post-translational modifications such as phosphorylation, sumoylation, palmitoylation and glycosylation, all of which have been implicated in the dynamic regulation of K^+ channel trafficking, stability or function [32–34]. Of these, phosphorylation (Figure 3) is the most studied, and effects on K^+ channel gating

and trafficking have been described [32]. Both Kv4.2 and Kv4.3, the pore-forming α subunits underlying $I_{to,f}$, for example, are phosphorylated by calmodulin-dependent protein kinase II (CaMKII) in cardiomyocytes [35, 36], and the inhibition of CaMKII accelerates inactivation of human atrial $I_{to,f}$ [37]. Kv4.2- and Kv4.3-encoded currents expressed in *Xenopus* oocytes and native $I_{to,f}$ in adult rat epicardial myocytes are suppressed by PKC activation [38]. The activity of Kir6.2-encoded K^+ channels is increased by PKC-dependent phosphorylation, through stabilization of the open state, in the presence and in the absence of the auxiliary subunit SUR2A [39]. Tyrosine kinase c-Src-mediated phosphorylation has also been shown to suppress Kv1.5-encoded currents [40], presumably by destabilizing channel complexes in the plasma membrane [41] and enhancing channel endocytosis [42].

Post-translational modification of Kv1.5 by small ubiquitin-like modifier (SUMO) proteins also modulates the properties of Kv1.5-encoded K^+ channels; loss of Kv1.5 sumoylation, for example, results in a hyperpolarizing shift in the voltage-dependence of steady-state inactivation of Kv1.5-encoded currents [43]. SUMO modification has also been shown to shift the voltage-dependence of activation of currents encoded by other Kv α subunits, including Kv2.1 [33]. Palmitoylation also regulates Kv1.5 channel trafficking; S-palmitoylation occurs early during Kv1.5 biosynthesis and the inhibition of palmitoylation leads to accumulation of Kv1.5 in intracellular compartments, increased degradation, and diminished cell surface Kv1.5 protein expression [44]. Palmitoylation of KChIP2 appears to also be essential for its membrane localization and for augmentation of Kv4.2- and Kv4.3-encoded currents [34]. Glycosylation has also been shown to modulate the stability of K^+ channel subunit proteins, including HERG [45] and Kv1.x [46].

Effects of Lipid Environment on Myocardial K^+ Channels

In addition to the regulatory mechanisms affecting the expression levels and intrinsic properties of K^+ channels, various extrinsic factors, such as membrane lipids and redox environment, also contribute to the modulation of functional K^+ channels. Membrane stiffness, for example, which is determined by membrane lipid composition, has been shown to affect the open probabilities of Kv and Kir channels [47, 48]. Arachidonic acid, which is abundant in plasma membrane lipids, speeds inactivation of otherwise non-inactivating delayed rectifier Kv channels [49]. Cholesterol, on the other hand, directly inhibits Kir2.1 channels by stabilizing closed states [50]. In addition, depletion of membrane cholesterol increases the recruitment of Kv1.5 channels to the plasma membrane through Rab11-mediated channel recycling [51]. Lipid rafts and caveolae, two specialized membrane lipid structures, function as platforms for clustering of K^+ channels and signaling molecules in macromolecular complexes, thereby modulating K channel properties [52, 53].

Epigenetic Regulation of Myocardial K^+ Channels

Epigenetic mechanisms (Figure 3) modulate physiological trait variations without changes in DNA sequence and result from changes in DNA methylation, chromatin remodeling or histone modification [54]. Importantly, these changes can be heritable or acquired [54], and reflect interactions between the environment and gene expression. Considerable evidence suggests that epigenetic mechanisms are involved in the regulation of the expression of cardiac K^+ channel subunit genes. Inducible cardiac ablation of PAX-interacting protein 1

(PTIP), a key component of the histone H3 lysine 4 (H3K4me) complex, for example, has been demonstrated to increase the transcript expression levels of the genes, *Kcnip2*, *Kcnd2* and *Kcnd3*, encoding $I_{to,f}$ channel subunits [55]. The protein expression levels of KChIP2 (*Kcnip2*), but not Kv4.2 (*Kcnd2*) or Kv4.3 (*Kcnd3*), were reported to be reduced significantly in PTIP$^{-/-}$ mouse hearts, leading to decreased $I_{to,f}$ densities and action potential prolongation, as well as impaired calcium handling and contractility [55]. Promoter DNA methylation modulates the expression of the I_{KATP} channel subunits, SUR1 and SUR2, in mouse cardiomyocytes [56]. The extent of promoter CpG methylation inversely correlates with the expression of SUR1 and SUR2, and treatment with the DNA methylation inhibitor 5′-Aza-2′ deoxycytidine significantly reduced both methylation at the SUR2 CpG island and SUR2A mRNA expression [56]. In addition, *KCNQ1* is located in an imprinted gene cluster, where a paternally expressed anti-sense transcript, *KCNQ1ot1*, transcribed from a promoter located in intron 10 of the *KCNQ1* gene, represses the expression of the *KCNQ1* imprinted gene cluster [57]. The promoter region of *KCNQ1ot1* contains a CpG island and is methylated on the maternal chromosome, thereby preventing *KCNQ1ot1* expression and allowing the *KCNQ1* gene cluster to be transcribed from the maternal allele [57]. These data suggest that variable *KCNQ1* imprinting or mutations affecting the CpG island in the *KCNQ1ot1* promoter could potentially contribute to LQT1 in the absence of mutations in the coding region of KCNQ1.

Myocardial K^+ Channel Remodeling in Acquired Cardiac Disease

Marked changes in the densities and/or properties of myocardial K^+ currents, typically referred to as K^+ channel remodeling, are observed in association with both cardiac and systemic diseases, including cardiac hypertrophy, heart failure, atrial fibrillation, diabetes and in the ischemic myocardium (Table 2).

K^+ Channel Remodeling in Cardiac Hypertrophy

Cardiac hypertrophy, defined as ventricular wall thickening and enlargement of the heart, is associated with increased cardiomyocyte size secondary to pathological stresses (valvular heart disease, hypertension, myocardial infarction etc.), physiological loading (exercise training or pregnancy), and sarcomeric protein mutations [58]. Cardiac hypertrophy induced by pathological stresses (pathological hypertrophy) is associated with increased risk of ventricular arrhythmias and sudden death. In contrast, exercise training-induced physiological hypertrophy is not associated with electrical abnormalities or increased arrhythmia risk [59].

Pathological hypertrophy results in prolonged ventricular action potential durations and increased dispersion of repolarization, changes that are evident (prolonged QT internal and increased QT dispersion) in surface ECG recordings [60] and that reflect, at least in part, reduced repolarizing K^+ current densities [61]. Impaired repolarization and increased dispersion are arrhythmogenic [61, 62]. Recent studies in a mouse model of pressure overload-induced left ventricular hypertrophy (LVH), produced by transverse aortic constriction, revealed that the repolarizing K^+ current densities are reduced because K^+ channel subunit expression levels are not increased in proportion with cellular hypertrophy, i.e., the increase in myocyte size [62]. We have recently demonstrated that, in marked

contrast with pathological hypertrophy, physiological cardiac hypertrophy, induced by chronic exercise (swim) training or cardiac specific transgenic expression of constitutive active PI3Kα, is associated with increases in myocardial repolarizing K^+, as well as depolarizing Na^+ and Ca^{2+}, currents, reflecting upregulation of the transcripts encoding the underlying channel subunits [63]. The transcriptional upregulation of ion channel subunits with physiological hypertrophy is in proportion to increased myocyte size and the global increases in RNA and protein expression, resulting in the normalization of current densities, action potential waveforms and myocardial functioning [63]. Interestingly, further experiments revealed that exercise training and enhanced PI3Kα signaling-mediated transcriptional upregulation of myocardial ion channel subunits is independent of cellular hypertrophy and Akt signaling [17].

K^+ Channel Remodeling in Heart Failure

Heart failure, irrespective of the underlying etiology, is associated with increased risk of life-threatening arrhythmias and the incidence of sudden cardiac death in individuals with heart failure is estimated at a staggering 50% [64]. The increased incidence of lethal ventricular arrhythmias in heart failure is a consequence of complex pathological remodeling of cardiac structural [65], neurohumoral [66] and electrophysiological properties [67]. Electrical remodeling in the failing heart [67] reflects, at least in part, reductions in the densities of repolarizing K^+ currents, including $I_{to,f}$ [67, 68], I_{Ks}, I_{Kr} [69] and I_{K1} [67, 70], resulting in action potential prolongation, early afterdepolarizations and increased dispersion, all of which are arrhythmogenic. Activation of pathological signaling cascades in the failing heart results in decreased repolarizing K^+ current amplitudes/densities, attributed to transcriptional and post-transcriptional downregulation of channel subunit expression [71]. Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), for example, is chronically activated in heart failure; increased CaMKII activity has been shown to reduce functional $I_{to,f}$ density through multiple mechanisms, including transcriptional downregulation of *KCND*3 (Kv4.3) [72] and changes in the kinetics of $I_{to,f}$ inactivation [36]. Interestingly, the small conductance Ca^{2+}-activated K^+ current (I_{SK}), which is not normally expressed in ventricular myocytes, has been shown to be unpregulated in the ventricles of failing hearts [73] and following myocardial infarction [74]. In addition, pharmacological blockade of I_{SK} has been shown to suppress ventricular arrhythmias associated with both heart failure [73] and acute myocardial infarction [74].

K^+ Channel Remodeling in Atrial Fibrillation

Atrial fibrillation (AF) is one of the most common arrhythmias seen in clinical practice, and the prevalence of AF increases with age, rising from the <1% in individuals < 60 years to ~20% among those 85 years or older [75]. AF dramatically impacts morbidity and mortality, and yet current therapeutic options are very limited. The rapid atrial rate during AF induces electrical remodeling that further potentiates the generation and maintenance of AF, a fact that led to the concept that “AF begets AF” [76]. Altered expression and functioning of multiple K^+ channels are observed with AF-induced electrical remodeling. The transcript and protein expression levels of Kir2.1, for example, are increased in AF [77], accompanied by increased I_{K1} densities and hyperpolarized membrane potentials [78]. Another inwardly rectifying K^+ current, I_{KACh} (produced by Kir3.1 and Kir3.4), which is activated by

muscarinic receptors in response to increased vagal input, is also enhanced in AF. The increase in I_{KACh} in AF, however, is attributed to changes in channel open probability, not to alterations in channel subunit expression levels [79]. Increased I_{KACh} contributes to action potential shortening and to reentrant rotor stabilization during AF [80]. The density of $I_{to,f}$ and the expression of *KCND3*/Kv4.3 mRNA/protein are reduced with AF [78, 81]. There are also reports of remodeling of delayed rectifier K^+ currents, such as I_{Kur}, I_{Kr} and I_{Ks}, although the effects described are variable and somewhat controversial.

K^+ Channel Remodeling in Diabetes

Abnormal cardiac repolarization, QT-interval prolongation and T wave abnormalities are observed in some patients with diabetes [82]. Studies focused on defining the cellular and molecular mechanisms of diabetes-induced repolarization abnormalities have consistently shown downregulation of repolarizing Kv currents [83, 84]. Post-translational effects on Kv channels by increased levels of free fatty acid metabolites, such as palmitoylcarnitine and palmitoyl-CoA, has been described [85]. Acute treatment with insulin has been shown to reverse diabetes-induced Kv current remodeling, suggesting a critical role for insulin-dependent regulation of cardiac Kv channel functioning [83]. In addition, the peroxisome proliferator-activated receptor α (PPARα), a critical regulator of glucose/fatty acid metabolism, has been shown to be upregulated in the heart in diabetes and to result in the transcriptional downregulation of cardiac Kv channel subunit expression [86]. Consistent with this model, cardiac-specific over-expression of PPARα downregulates the transcript/protein expression levels of the $I_{to,f}$ channel subunits *Kcnd*2/Kv4.2 and *Kcnip*2/KChIP2 [86], whereas targeted deletion of PPARα upregulates $I_{to,f}$ [86].

K^+ Channel Remodeling in Myocardial Ischemia and Infarction

Myocardial ischemia leads to ATP depletion and acidosis [87], and the activation of sarcolemmal I_{KATP} channels. The opening of I_{KATP} channels shortens action potential durations and decreases inward Ca^{2+} currents, thereby reducing Ca^{2+}-mediated energy consumption and preventing Ca^{2+} overload-induced cell death. Increased I_{KATP} channel opening, however, also results in cardiomyocyte hyperpolarization and renders cells inexcitable [88], creating a current sink that slows or blocks propagation and predisposes the heart to the development of ventricular arrhythmias [89, 90]. Pharmacological inhibition of I_{KATP} channels in the ischemic heart reduces the incidence of ventricular arrhythmias in animal models and in humans [91, 92].

Myocardial infarction (MI) is associated with marked changes in K^+ channel expression and functioning, and is also associated with increased arrhythmia risk. In a canine model of myocardial infarction, multiple K^+ currents, $I_{to,f}$ [93], I_{Kr}, I_{Ks} [94] and I_{K1} [95] are downregulated in cells in the infarct border zone. The downregulation of $I_{to,f}$ is most noticeable during the acute phase (within days) following the infarct and appears to resolve over the course of 2 months [93]. The expression levels of the transcripts encoding I_{Kr} (HERG) and I_{Ks} (KvLQT1 and minK) channels are also decreased in day 2 post-infarct border-zone myocytes; the expression levels of HERG and KvLQT1, but not minK, recover by day 5 [94, 96]. The finding that KvLQT1, but not minK, expression has recovered may contribute to the observed rapid kinetics of activation of I_{Ks} that is observed in post-infarct

border-zone myocytes [96]. In the myocardium distant to the infarct area (remote-zone), multiple K^+ currents are also altered, likely reflecting the effects of myocyte hypertrophy or failure following the infarct. The densities of the currents, as well as the expression levels of subunits underlying $I_{to,f}$, I_{K1} and I_K, for example, are consistently downregulated in remote-zone myocytes, leading to prolonged APD [97].

Perspective: Long non-coding RNAs as Potential Myocardial K^+ Channel Regulators

It has become increasingly clear that the transcription of the eukaryotic genome is far more pervasive and complex than previously appreciated [100]. While the expression of mRNAs and miRNAs account for only ~1% of all transcribed species, up to 90% of the mammalian genome is transcribed as long non-coding RNAs (lncRNAs), a heterogeneous group of non-coding transcripts longer than 200 nucleotides [100]. LncRNAs have been shown to be functional and involved in specific physiological and pathological processes through epigenetic, transcriptional and posttranscriptional mechanisms. Although the roles of lncRNAs in various biological processes are beginning to emerge, our understanding of the functioning of lncRNAs in the cardiovascular system remains in its infancy.

Several antisense lncRNAs have been implicated in regulating genes that are critical for cardiac function, including cardiac troponin I [101] and myosin heavy/light chains [102]. A cardiac-specific lncRNA, *Braveheart*, for example, has been demonstrated to be essential for the epigenetic regulation of cardiac lineage commitment in mouse embryonic stem cells [103]. Recently, a cardiac-specific lncRNA *Myheart* (*Mhrt*), originating from MYH7 loci, was shown to be protective against stress-induced (pathological) cardiac hypertrophy in adult mouse heart by a mechanism involving ATP-dependent chromatin remodeling [104]. Aside from the anti-sense transcript of *KCNQ1*, *KCNQ1ot1*, which, as discussed above, represses the expression of the *KCNQ1* imprinted gene cluster [57], there is little information available on lncRNA-mediated regulation of cardiac K^+ channel expression or function. Indeed, there have been few, if any, studies focused on examining the role(s) of lncRNAs in the regulation of myocardial K^+ (or other) channels. With more cardiac lncRNA expression profiling data becoming available and the advances in technologies to facilitate studies of lncRNA structure and functioning, it seems reasonable to expect that insights into lncRNA-mediated regulation of myocardial K^+ channels will be forthcoming in the near future.

Conclusion

Electrophysiological and molecular studies have demonstrated that the K^+ channels that underlie action potential repolarization in the mammalian heart are far more numerous and diverse than depolarizing Na^+ or Ca^{2+} channels (Figure 1; Table 1). Accumulating evidence indicates that the expression and the functioning of myocardial K^+ channels are regulated by transcriptional, post-transcriptional, post-translational, and epigenetic mechanisms (Figure 3). In addition to controlling repolarization, the molecular and functional diversity of myocardial K^+ channels underlie regional differences in excitability, action potential propagation and the maintenance of normal cardiac rhythms. Maladaptive K^+ channel

remodeling and impaired channel function, associated with inherited and acquired cardiac and systemic diseases, can impair repolarization and increase the risk of potentially life-threatening arrhythmias. Advancing our understanding of the mechanisms involved in K^+ channel regulation and modulation in cardiac physiology and pathology is the key to developing new therapeutic strategies to treat or prevent lethal arrhythmias associated with cardiac/systemic disease.

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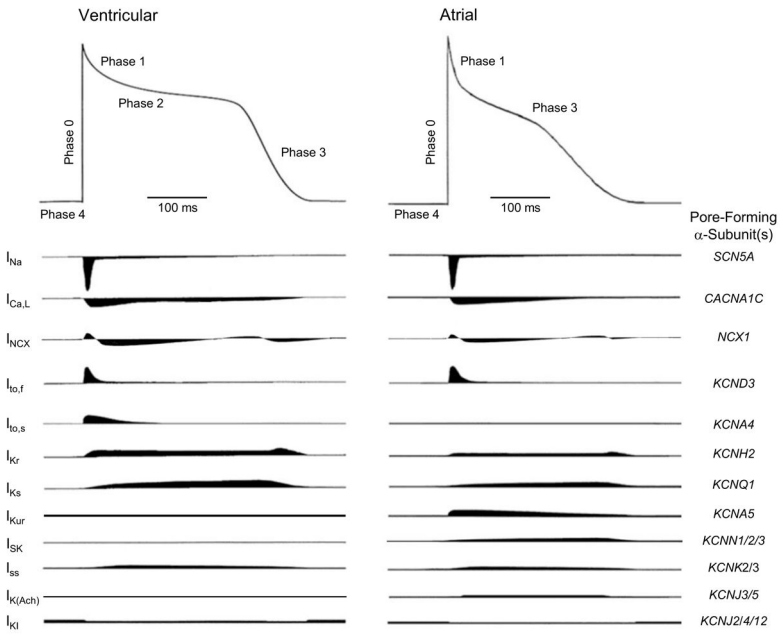

Figure 1. Schematics of action potential waveforms and underlying ionic currents in human ventricular (left) and atrial (right) myocytes

Note that relative inward (downward) and outward (upward) current densities and waveforms, estimated from voltage-clamp data and modeling studies, in non-diseased ventricular and atrial are shown. The voltage-gated inward Na^+ (Nav) and Ca^{2+} (Cav) currents in human atrial and ventricular myocytes are similar. In contrast, there are multiple types of outward K^+ currents, particularly Kv currents, contributing to atrial and ventricular action potential repolarization. In addition, the time- and voltage-dependent properties of the various Kv currents are distinct. Differences in the densities and in the detailed time- and voltage-dependent of the repolarizing Kv and Kir channels contribute to differences in the waveforms of atrial and ventricular action potentials. The genes encoding the pore-forming (α) subunits underlying the various cardiac ion channels are also indicated (on the right).

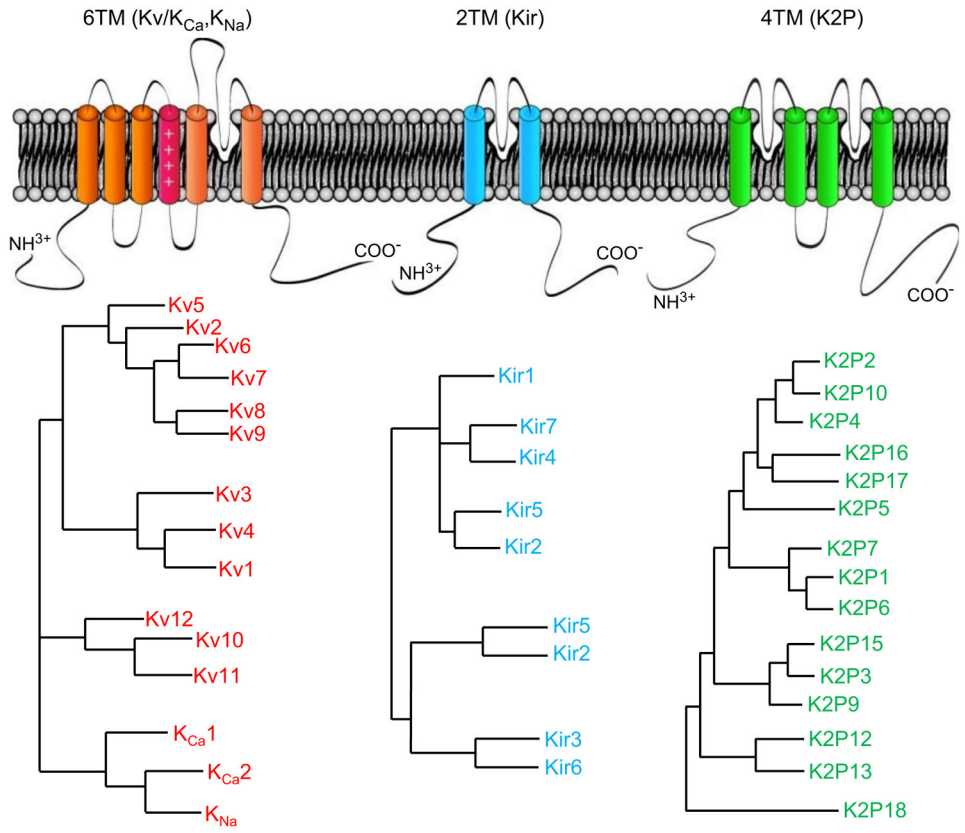

Figure 2. Pore-forming subunits of cardiac Kv, Kir and K2P channels

(A) Schematics illustrate the membrane topologies of Kv, Kir and K2P pore-forming (α) subunits. (B) Phylogentic dendrograms of K^+ channel α subunits of the Kv (KCA), Kir and K2P subfamilies.

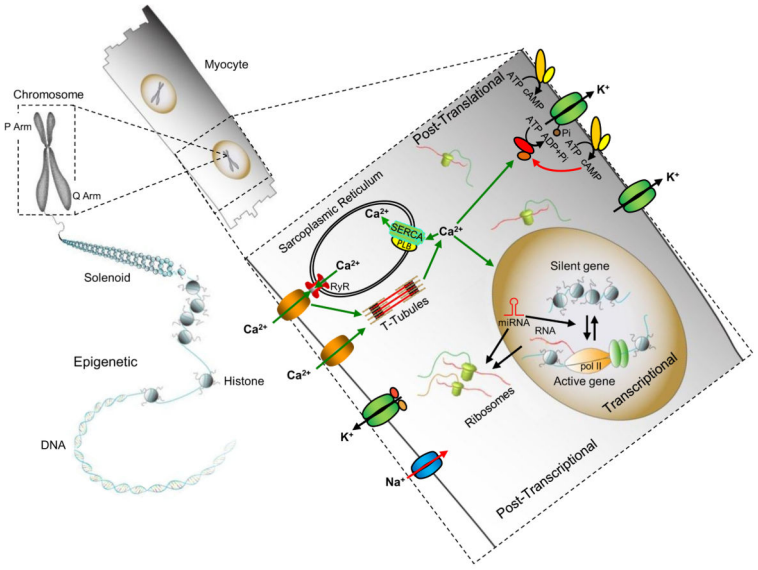

Figure 3. Multiple mechanisms contribute to the regulation of myocardial K^+ channel expression, localization and properties

Myocardial K^+ channel expression and function are regulated by transcriptional, post-transcriptional, post-translational and epigenetic mechanisms. Various transcription factors and signaling pathways are involved in regulating the temporal and spatial expression of K^+ channels during cardiac development and in response to cardiac injury or illness. Alternative splicing, RNA editing and K^+ channel-targeting miRNAs contribute to the post-transcriptional regulation of K^+ channels. Post-translational modifications, including phosphorylation, sumoylation, palmitoylation and glycosylation also contribute to the dynamic regulation of K^+ channel trafficking and functioning. Myocardial Ca^{2+} homeostasis also impacts K^+ channel expression and properties by modulating Ca^{2+}-sensitive transcriptional programs and $Ca2^+$-dependent enzymes, including protein kinases and phosphatases. The membrane lipid environment also modulates myocardial K^+ channel functions. Although less well studied, it is increasingly clear that epigenetic mechanisms also contribute to the regulation of cardiac K^+ channel gene expression.

Table 1

Potassium Conductances in the Mammalian Myocardium

Channel Type	Current Name	Activation	Gating	Function	Pharmacology[1]	α Subunit Gene	Chromosomal Location	Auxiliary Subunits
Kv	$I_{to,f}$	fast	Voltage	Plateau Potential, Repolarization	mM 4-AP HaTX HpTX Ba^{2+}	*KCND3*	1p13.3	KChIP2, DPP6/10 (minK, MiRP2/3)
	$I_{to,s}$	fast	Voltage	Plateau Potential, Repolarization	μ4-AP	*KCNA4*	11p14	??
	I_{Kr}	fast	Voltage	Plateau Potential, Repolarization	E-4031 Dofetilide	*KCNH2*	7q36.1	minK, MiRP1/2
	I_{Ks}	slow	Voltage	Repolarization	NE-10064 NE-10133	*KCNQ1*	11p15.5	minK
	I_{Kur}	fast	Voltage	Repolarization	μM 4-AP	*KCNA5*	12p13	SAP97
	$I_{K,slow2}$[2]	slow	Voltage	Repolarization	mM TEA	*Kcnb1*	2H3	Amigo?
K2P	I_{ss}[2]	–	H^+, Fatty Acids, Anesthetics	Resting potential, Repolarization, Diastolic Potential	mM TEA A1899	*Kcnk2/3*	1q41, 2p23	??
	I_{Kp}	–	??	Resting Potential, Repolarization	Ba^{2+}	??	??	??
KCa	I_{SK}	slow	Ca^{2+}-Calmodulin	Repolarization	Apamin	*KCNN1/2/3*	19p13.1, 5q22.2,1q21.3	??
KNa	I_{NaK}	fast	Na^+	??[3]	Quinidine Clofilium	*KCNT1/2*	9q34.3, 1q31.3	??
Kir	I_{KI}	–	Spermines Mg^{2+}	Resting Potential, Diastolic Potential	Ba^{2+}	*KCNJ2/4/12*	17q24.1, 17p11.2 22q13.1	??
	$I_{K(Ach)}$	–	Ach	Resting Potential, Diastolic Potential	Tertiapin-Q	*KCNJ3/5*	2q24.1, 11q24	??
	$I_{K(ATP)}$	–	ATP ADP	??[3]	SURs	*KCNJ8/11*	12p11.23, 11p15.1	SUR1/2

[1] 4-AP=4-aminopyridine; HaTX=hanatoxin; HpTX=heteropodatoxin; TEA=tetraethylammonium; SURs=sulfonylureas;

[2] Current found in rodent, not clear if also present in other species, including human.

[3] Suggested to function to hyperpolarize membrane potential with ischemia or metabolic stress.

Table 2

Remodeling of Myocardial K^+ Currents in the Diseased Heart

Ionic Current	Disease	Change	Observed Cardiac Effect(s)	Molecular Mechanism(s)
$I_{to,f}$	HF, MI, LVH	↓	APD prolongation; EADs	Transcriptional & post-transcriptional
	AF	↓	APD shortening	Transcriptional & post-transcriptional
I_K	HF, MI, LVH	↓	APD prolongation; EADs; DADs	Transcriptional & post-transcriptional
	AF	Variable	APD shortening	Transcriptional & post-transcriptional
I_{K1}	HF, MI, LVH	↓	APD prolongation; EADs	Transcriptional & post-transcriptional
	AF	↑	APD shortening; V_m ↓	Transcriptional
I_{KATP}	MI	↑	APD shortening; Conduction slowing	ATP depletion and acidosis ↑ P_0
I_{SK}	HF, MI	↑	APD shortening	Channel sensitivity to Ca^{2+} ↑
I_{KACh}	AF	↑	APD shortening	↑ P_0

$I_{to,f}$: fast transient outward K^+ current; I_K: delayed rectifier K^+ currents; I_{K1}: inwardly rectifying K^+ current; I_{KATP}: ATP-sensitive K^+ current; I_{SK}: small conductance Ca^{2+}-activated K^+ currents; I_{KACh}: acetylcholine activated K^+ current; HF: heart failure; MI: myocardial infarction; LVH: pathological left ventricular hypertrophy; AF: atrial fibrillation; APD: action potential duration; V_m: membrane potential; EAD: early after-depolarization; DAD: delayed after-depolarization; P_0: channel open probability.