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Molecular Basis of Functional Myocardial Potassium Channel Diversity

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INTRODUCTION

The normal mechanical functioning of the mammalian heart depends on proper electrical function, evident in the sequential generation of action potentials in cells in the “pacemaker” regions and the propagation of activity through the ventricles.^{1–3} The waveforms of action potentials in individual cardiac cells (Fig. 1) reflect the coordinated activation and inactivation of inward (Na⁺ and Ca²⁺) and outward (K⁺) current-carrying ion channels.¹ The propagation of electrical activity and the coordinated electromechanical functioning of the heart also depend on electrical coupling between cells, mediated by gap junctions.⁴ The rapid upstroke of action potentials in atrial and ventricular myocytes, attributed to inward currents through voltage-gated Na⁺ (Nav) channels, is followed by slower repolarization and plateau phases (see Fig. 1), reflecting increased outward currents through multiple types of K⁺ channels and inward currents through voltage-gated Ca²⁺ (Cav) channels. Cell-type-specific and regional differences in the waveforms of action potentials, which impact the normal spread of excitation in the myocardium and the dispersion of repolarization in the ventricles, reflect differences in the expression and/or the properties of inward Nav and Cav, as well as several outward K⁺ channels.^{1–3}

In contrast to the Nav and Cav channels, there are multiple types of cardiac K⁺ channels, both voltage-gated K⁺ (Kv) and non-voltage-gated, inwardly rectifying, K⁺ (Kir) channels (Table 1)^{5–7} encoded by Kv and Kir subunits (Fig. 2). As in other tissues and cell types, there are additional (non-voltage-gated) “leak” K⁺ channels thought to be encoded by a novel class of K⁺ channel (K2P) subunits with 2 pore domains (see Fig. 2), several of which are also expressed in the heart.¹ It is well-documented that changes in the densities, distributions, and properties of Kv and Kir channels are evident in a variety of myocardial

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diseases, and these changes alter repolarization, influence propagation, and decrease rhythmicity, effects that can produce substrates for the generation of life-threatening arrhythmias.¹ Although less well studied, changes in K2P channel expression and/or function in inherited/acquired cardiac disease would also be expected to impact myocardial excitability and arrhythmia susceptibility.¹

Considerable progress has been made in defining the biophysical properties, the functional roles, and the cell-type-specific differences in expression of the various myocardial K⁺ currents (see **Table 1**). In addition, a large number of Kv, Kir, and K2P channel pore-forming (α) subunits⁸ that encode the underlying K⁺ current-carrying ion channels have been identified (see Fig. 2), and many of these are expressed in the heart.¹ Considerable progress also has been made in defining the relationships between expressed Kv and Kir α subunits and functional myocardial Kv and Kir channels, and studies completed to date have revealed that the various types of Kv and Kir channels distinguished electrophysiologically (see **Table 1**) are encoded by different α subunits.¹ To date, there have been many fewer studies focused on defining the functional correlates of expressed K2P subunits. A rather large number of K⁺ channel, particularly Kv channel, accessory subunits also have been identified, and accumulating evidence suggests that myocardial K⁺ channels,^{9–12} like other types of ion channels,^{13–16} likely function in macromolecular protein complexes comprising the pore-forming α subunits and one or more different types of (cytosolic or transmembrane) auxiliary proteins. Identification of the molecular components and the stoichiometric native myocardial Kv, Kir, and K2P channels is necessary for future studies focused on defining the mechanisms controlling regional differences in the expression of these channels in the normal myocardium, as well as the derangements in the expression/functioning of these channels associated with myocardial disease.

MYOCARDIAL Kv CHANNELS: TRANSIENT OUTWARD AND DELAYED RECTIFIER Kv CHANNELS

Voltage-gated K⁺ (Kv) currents, activated on membrane depolarization, influence the amplitudes and durations of myocardial action potentials and, in most cardiac cell types, 2 broad classes of Kv currents have been distinguished: transient outward K⁺ currents, I_{to}; and delayed, outwardly rectifying K⁺ currents, I_K (see **Table 1**). The transient currents (I_{to}) activate rapidly and underlie early (*phase 1*) repolarization, whereas the delayed rectifiers (I_K) determine the latter phase (*phase 3*) of membrane repolarization (see Fig. 1) back to the resting membrane potential.

These are broad classifications, however, and there are multiple functionally (and molecularly) distinct types of transient (I_{to}) and delayed rectifier (I_K) Kv currents (see **Table 1**) expressed in cardiac cells. Electrophysiologic and pharmacologic studies in mouse myocytes, for example, have revealed the presence of 2 types of rapidly activating and inactivating, “transient” outward K⁺ currents, referred to as I_{to}, fast (I_{to,f}) and I_{to}, slow (I_{to,s}).¹⁷ The rapidly activating and inactivating transient outward K⁺ current, I_{to,f}, is also characterized by rapid recovery from inactivation, whereas I_{to,s} recovers slowly.^{17,18} In

addition, $I_{to,f}$ is readily distinguished from other Kv currents, including $I_{to,s}$,^{17,18} using the Heteropoda toxin-2 or toxin-3.¹⁹

Although originally identified in Purkinje fibers, $I_{to,f}$ is a prominent repolarizing Kv current in atrial and ventricular myocytes, as well as in nodal cells, in most species.^{20–22} There are, however, marked regional differences in $I_{to,f}$ densities, with the highest densities typically in atrial myocytes.²¹ In addition, $I_{to,f}$ and $I_{to,s}$ are differentially expressed in ventricular myocytes. In adult mouse ventricles, for example, $I_{to,f}$ density is higher in ventricular myocytes isolated from the right, compared with the left, ventricle and, within the left ventricle, $I_{to,f}$ densities are significantly higher in the apex than in the base.^{17,18} In addition, all interventricular septum cells express $I_{to,s}$, and most ($\approx 80\%$) also express $I_{to,f}$.¹⁷ When present, however, $I_{to,f}$ density is significantly ($P < .001$) lower in septum than in right or left ventricular cells.^{17,18} Also, $I_{to,s}$ is not detected in mouse heart cells other than septum cells.^{17,18} $I_{to,f}$ and $I_{to,s}$ are also differentially expressed in ferret left ventricles, and $I_{to,s}$ is detected only in endocardial left ventricular cells.²³ In spite of heterogeneities in functional expression, the time-dependent and voltage-dependent properties of $I_{to,f}$ and $I_{to,s}$ in different cardiac cell types and species are remarkably similar, suggesting that the molecular determinants of the underlying ($I_{to,f}$ and $I_{to,s}$) channels are also similar.

Electrophysiologic and pharmacologic studies have also distinguished multiple types of cardiac delayed rectifier K^+ currents, I_K (see **Table 1**). In atrial myocytes, for example, the dominant repolarizing K^+ current is a very rapidly activating (ultrarapid), noninactivating K^+ current, I_{Kur} (IK, ultrarapid), which is not detected in ventricular or nodal cells.^{1,5–7} In ventricular myocytes, in contrast, there are 2 prominent components of delayed rectification, I_{Kr} (IK, rapid) and I_{Ks} (IK, slow), that are distinct from I_{Kur} in terms of time-dependent and voltage-dependent properties: I_{Kr} activates and inactivates rapidly, and displays marked inward rectification, whereas I_{Ks} activates slowly and is outwardly rectifying.²⁴ Similar to the transient outward K^+ currents, I_{Ks} and I_{Kr} are differentially expressed in the ventricular cells.^{1,5} The density of I_{Ks} in guinea pig left ventricular free wall is significantly higher in subepicardial than in subendocardial or midmyocardial cells.²⁵ At the base of the left ventricle, in contrast, I_{Kr} and I_{Ks} densities are lower in myocytes in the endocardium, compared with either midmyocardium or the epicardium.²⁵ Heterogeneities in I_{Kr} and I_{Ks} densities also contribute to the stereotypical differences in action potential waveforms recorded in different regions (eg, in atria and ventricles, right and left ventricles, apex and base of the ventricles) and through the thickness of the left and right ventricular free walls.^{1,2}

In mouse ventricles, additional novel components of I_K , with properties distinct from I_{Ks} and I_{Kr} , have also been identified (see **Table 1**) and referred to as IK, slow1, IK, slow2, and I_{ss} .^{17,18,26,27} IK, slow1 is blocked by μM concentrations of 4-aminopyridine and appears to be indistinguishable from human atrial I_{Kur} , whereas IK, slow2 is blocked selectively by tetraethylammonium (see **Table 1**). In addition to being functionally distinct, IK, slow1 and IK, slow2 also reflect the expression of unique molecular entities.^{28–31} An additional component of the total depolarization-activated outward K^+ current in mouse ventricular myocytes is noninactivating and has been referred to as Isteady-state or I_{ss} .^{17,18} Similar currents are evident in voltage-clamp recordings from ventricular myocytes isolated from a

number of other species, although, to date, these currents have not been extensively studied. In contrast to the differential distribution of $I_{to,f}$ and $I_{to,s}$, the densities of I_K , I_{K1} , I_{K2} , and I_{Ks} are similar in mouse atrial and ventricular myocytes.^{17,18,27-32}

In addition to the K_v channels, it has recently been demonstrated that apamin-sensitive, small-conductance Ca^{2+} -dependent K^+ (I_{SK}) channels are also expressed in mammalian atrial myocytes.^{33,34} Importantly, these channels have been shown to contribute to action potential repolarization in mouse atrial myocytes,³⁵ and dysregulation of I_{SK} has been linked to atrial arrhythmias.^{35,36} In addition, it has been reported that I_{SK} is upregulated in ventricular myocytes in the failing heart, and it was suggested that this upregulation increases the susceptibility to ventricular arrhythmias.^{37,38} A recent study has also suggested a role for large-conductance K^+ (BK) channels in mouse sino-atrial nodal cells,³⁹ although it is unclear whether there are BK channels in nodal cells in other species. In addition, Na^+ -dependent K^+ channels have been described in (guinea pig) ventricular myocytes,³⁹ a channel that may be activated under conditions of elevated intracellular Na^+ and play a protective role.

INWARDLY RECTIFYING (Kir) MYOCARDIAL K^+ CHANNELS

In addition to the K_v currents, inwardly rectifying K^+ (Kir) currents, including I_{K1} and the ATP-dependent K^+ current, I_{KATP} (see **Table 1**), are expressed in the mammalian myocardium.³³⁻³⁵ Similar to the K_v currents, the densities of the Kir currents vary in different regions; that is, in atria, ventricles, and conducting tissue. In contrast to the K_v currents, however, myocardial Kir current densities are similar in myocytes in different regions of the ventricles.¹ In mammalian atrial and ventricular myocytes, I_{K1} is thought to play a role in establishing resting membrane potentials and plateau potentials, and to contribute to phase 3 repolarization (see **Fig. 1**). The fact that I_{K1} conductance is high at negative membrane potentials has been suggested to be important in the establishment of the relatively hyperpolarized resting membrane potentials of ventricular and atrial myocytes.⁴⁰ Although the properties of I_{K1} channels are such that conductance is low at potentials positive to -40 mV, these channels do contribute outward K^+ currents during the action plateau potential, as well as during phase 3 repolarization,⁴⁰ potentials at which the driving force on K^+ is high.

In contrast with I_{K1} channels, myocardial ATP-dependent K^+ channels are weakly inwardly rectifying, and these channels are inhibited by intracellular ATP and activated by nucleotide di-phosphates, suggesting a link between I_{KATP} channels and cell metabolism.⁴¹ In ventricular myocytes, activation of I_{KATP} channels during periods of hypoxia/ischemia results in action potential shortening,⁴¹⁻⁴³ and the opening of I_{KATP} channels is thought to contribute to cardioprotection in ischemic preconditioning.⁴²⁻⁴⁵ Interestingly, and in contrast with I_{K1} (and K_v) channels, however, I_{KATP} channels have high single channel conductance, such that activation of only a few I_{KATP} channels is expected to result in marked action potential shortening.⁴¹ I_{KATP} channels appear to be distributed uniformly and at high density^{41,43} in the right and left ventricles and through the thicknesses of the right and left ventricular walls.

Acetylcholine, which is released on stimulation of the vagus, has negative chronotropic and inotropic effects on the heart, mediated by activation of acetylcholine (ACh)-regulated K^+ channels, I_{KACh} .⁴⁶ In atrial myocytes, application of ACh reveals large conductance inwardly rectifying K^+ channels, a process that requires GTP⁴⁷ and is mediated by the $\beta\delta$ subunits of heterotrimeric GTP-binding proteins.⁴⁸ Interestingly, although the expression of I_{KACh} in atrial and nodal cells has long been appreciated, it is also clear that I_{KACh} channels are expressed in ventricular myocytes.⁴⁹ In addition, although somewhat less sensitive to ACh than atrial or nodal I_{KACh} channels, the properties of single ventricular I_{KACh} channels are similar to atrial/nodal I_{KACh} ,⁴⁹ suggesting that the molecular determinants of I_{KACh} channels in different cardiac cell types and in different species are the same. It is also of interest to note that accumulating evidence indicates that I_{KACh} channels can be open (ie, constitutively active) in the absence of ACh,⁵⁰ suggesting a role for these channels under baseline conditions.

PORE-FORMING (α) AND ACCESSORY/AUXILIARY SUBUNITS OF MYOCARDIAL K^+ CHANNELS

Multiple K^+ channel pore-forming (α) subunits have been identified in the genome, and these have been organized into subfamilies based on sequence and structural similarities (see Fig. 2). Kv channel α subunits are 6 transmembrane spanning domain proteins (see Fig. 2) with a region between the fifth and sixth transmembrane domains that contributes to the K^+ -selective pore.⁸ The positively charged fourth transmembrane domain in the Kv α subunits (see Fig. 2) is homologous to the corresponding regions in Nav and Cav channel α subunits, placing them in the “S4” superfamily of voltage-gated channels.⁸ In contrast to Nav and Cav channels, in which only a single α subunit is required to form a channel, however, functional Kv channels comprise 4 α subunits. Similar to the diversity of functional myocardial Kv channels (see Table 1), multiple Kv α subunits in several distinct Kv α subunit subfamilies, including Kv1.x, Kv2.x, Kv3.x, Kv4.x (see Fig. 2), have been identified. In addition, many of the individual Kv α subunits in several different subfamilies have been shown to be expressed in the mammalian heart.¹ Further functional Kv channel diversity could arise through alternative splicing of transcripts, as well as through the formation of heteromultimeric channels between 2 or more Kv α subunit proteins in the same Kv α subunit subfamily,^{1,8} although the physiologic roles of alternative splicing and heteromeric assembly of Kv α subunits in the generation of native cardiac Kv channels remain to be determined.

Additional subfamilies of Kv α subunits were revealed with the cloning of the human eag-related (HERG) gene, *KCNH2*, which encodes the Kv11.1 α subunit and has been identified as the locus of mutations underlying familial long-QT syndrome type 2 (LQT2) and *KCNQ1*, which encodes Kv7.1, the locus of mutations in another inherited long-QT syndrome, LQT1.⁵¹ Expression of Kv11.1 in heterologous cells reveals inwardly rectifying Kv currents⁵¹ with properties similar to cardiac I_{Kr} (see Table 1). Although expression of *KCNQ1* (Kv7.1) in heterologous cells reveals rapidly activating, noninactivating Kv currents, the addition of the Kv channel accessory subunit, minK, results in the production of slowly activating Kv currents⁴³ that resemble the slow component of cardiac delayed

rectification, I_{Ks} . Additional Kv α subunit gene sub-families that underlie the generation of Ca^{2+} and Na^{+} regulated K^{+} channels also have been identified (see **Fig. 2**). Structurally much simpler than the Kv α subunits, the inwardly rectifying K^{+} (Kir) α subunits have only 2 transmembrane domains flanking the pore region (see **Fig. 2**). Similar to the Kv family, however, there are multiple subfamilies of Kir α subunits. The Kir2.x subfamily members underlie I_{K1} , whereas the Kir6 and Kir3 subfamilies generate I_{KATP} and I_{KACh} channels, respectively. Another novel type of K^{+} channel α subunit (K2P) with 4 transmembrane-spanning regions and 2 pore domains (see **Fig. 2**) was identified with the cloning of TWIK-1.⁵² Both pore domains contribute to the formation of the K^{+} selective pore, and TWIK-1 subunits assemble as dimers,⁵² rather than as tetramers, like the Kir and Kv channels. Like the Kir and Kv subunits, however, a large number of 2 pore domain K^{+} (K2P) channel α subunit genes also have been identified (see **Fig. 2**), and several of these are expressed in the mammalian myocardium.⁵³ Heterologous expression of K2P subunits reveals currents with distinct biophysical properties and sensitivities to several potential intracellular and extracellular modulators, including anesthetics, pH, and fatty acids.⁵³

In addition to the Kv α subunits, a number of Kv channel accessory (Kv β) subunits also have been identified. The first of these was *KCNE1*, which encodes a small (130 amino acid) protein (minK) with a single transmembrane spanning domain.⁵⁴ It appears that minK coassembles with Kv7.1 (KvLQT1) to form functional cardiac I_{Ks} channels.⁵¹ Additional minK homologues, MiRP1 (*KCNE2*), MiRP2 (*KCNE3*), and MiRP3 (*KCNE4*) also have been identified, and it has been suggested that MiRP1 (*KCNE2*) functions as an accessory subunit coassembling with Kv11.1 to generate cardiac I_{Kr} .⁵⁵ It also has been reported that the MiRP subunits interact with multiple Kv α subunit subfamilies and modify channel properties.⁵⁴ MiRP2, for example, coassembles with Kv3.4 in mammalian skeletal muscle⁵⁶ and MiRP1 coassembles with Kv4.x α subunits when coexpressed in heterologous cells.⁵⁷ These observations suggest that the MiRP (*KCNE*) accessory subunits can assemble with a variety of Kv α subunits and contribute to the formation of multiple types of myocardial Kv channels. Direct experimental support for this hypothesis, however, has not been provided to date, and the roles of the various *KCNE* subunits in the generation of functional cardiac Kv (or other) channels remain to be identified.

Several cytosolic accessory Kv β subunits, Kv β 1, Kv β 2, and Kv β 3, first identified in brain⁵⁸ as well as alternatively spliced transcripts, are expressed in heart,¹ and biochemical studies suggest that Kv β subunits interact with the intracellular domains of Kv1 α subunits and alter the time-dependent and voltage-dependent properties and the cell surface expression of Kv1 α subunit-encoded Kv currents.⁵⁸ Although Kv β 1 and Kv β 2 reportedly associate with Kv4 α subunits in the mouse myocardium and the targeted deletion of Kv β 1 results in the attenuation of Kv4-encoded $I_{to,f}$ in mouse ventricular myocytes,⁵⁹ the role(s) of Kv β subunits in the generation of myocardial Kv channels in other species has not been explored.

There are 4 Kv Channel Interacting Proteins, KChIP1-4 in brain,⁶⁰ although only KChIP2 is expressed in heart.^{60,61} KChIP2, like the other KChIPs, belongs to the recoverin family of neuronal Ca^{2+} -sensing (NCS) proteins,⁶² containing 4 EF-hand domains.⁶⁰ There are multiple splice variants of KChIP2 in heart,⁶³⁻⁶⁵ although the relative abundances of these variants, particularly in the human heart, and the functional significance of splicing are not

known. When coexpressed with Kv4 α subunits, the KChIPs increase K⁺ current densities, slow inactivation, speed recovery from inactivation, and shift the voltage-dependence of current activation.⁶⁰ Although KCHIP2 does not appear to affect non-Kv4-encoded K⁺ channels, it has been reported that loss of KCHIP2 affects myocardial Cav channels.^{27,66} In addition, although KCHIP binding to Kv4 α subunits does not appear to be Ca²⁺-dependent, mutations in EF-hand domains 2, 3, and 4 eliminate the modulatory effects of KCHIP1 on Kv4-encoded Kv currents,⁶⁰ suggesting a role for voltage-dependent Ca²⁺ entry and intracellular Ca²⁺ levels in the regulation of functional cardiac (Kv4-encoded) I_{to,f} channels, as has been demonstrated for neuronal Kv4-encoded channels.⁶⁷

The transmembrane diaminopeptidyl transferase-like proteins (DPP6 and DPP10) have also been suggested to be an accessory subunit of cardiac⁶⁸ and neuronal⁶⁹ Kv4-encoded channels. Coexpression with DPP6 increases the cell surface expression of Kv4 α subunits, shifts the voltage dependences of Kv4-encoded current activation and inactivation, and accelerates the rates of current activation, inactivation, and recovery.^{68,69} Interestingly, heterologous coexpression of DPP6 with Kv4.3 and KCHIP2, produces Kv currents that closely resemble native cardiac I_{to,f}.⁶⁸ DPP10, which has been demonstrated to associate with Kv4.2 and KCHIP3 in brain and to have regulatory effects similar to DPP6 on heterologously expressed Kv4,^{70,71} is expressed in human ventricles.⁷² The expression levels of both DPP6 and DPP10, however, are quite low in the heart, raising some concern about the likely physiologic relevance of DPP6- (or DPP10-) mediated regulation of cardiac I_{to,f} channels. Interestingly, however, it was recently suggested that the molecular compositions of I_{to,f} channels in ventricular and Purkinje cells are distinct, and that DPP6 plays a unique role in the generation of Purkinje cell (but not ventricular) I_{to,f} channels.⁷³ A selective role for Neuronal Calcium Sensor-1 (NCS-1), previously shown to associate with Kv4 α subunits in mouse ventricles,⁷⁴ was also suggested to play a role (with DPP6) in the generation of I_{to,f} in canine (and human) Purkinje cells.⁷³

MOLECULAR DETERMINANTS OF NATIVE MYOCARDIAL Kv CHANNELS

Critical insights into the roles of individual Kv α subunits or subunit subfamilies in the generation of native cardiac Kv channels were provided in studies of I_{to,f} channels in rat and mouse ventricular myocytes. Using antisense oligodeoxynucleotides (AsODNs) targeted against Kv4.2 or Kv4.3, for example, it was shown that I_{to,f} density is selectively reduced by approximately 50%.^{75,76} Rat ventricular I_{to,f} density was also reduced in cells exposed to an adenoviral construct encoding a truncated Kv4.2 subunit (Kv4.2ST) that functions as a dominant negative.⁷⁷ In addition, I_{to,f} was eliminated in ventricular and atrial myocytes isolated from transgenic mice expressing a dominant negative Kv4.2 pore mutant, Kv4.2W362 F (Kv4.2DN).^{78,79} Although biochemical and electro-physiologic studies suggested that Kv4.2 and Kv4.3 are associated in mouse ventricles and that functional mouse ventricular I_{to,f} channels are heteromeric,⁷⁶ targeted deletion of Kv4.2 eliminates mouse ventricular I_{to,f},⁸⁰ whereas elimination of Kv4.3 has no measureable effects.⁸¹ In mouse ventricles, therefore, Kv4.2 is the critical α subunit required for the generation of functional I_{to,f} channels.^{80,81} Given the similarities in the time-dependent and voltage-dependent properties of the fast transient currents in other species, it seems reasonable to suggest that Kv 4 α subunits also underlie I_{to,f} in other species. In canine and in human

myocardium, however, the candidate subunit is Kv4.3, rather than Kv4.2.⁸² Although 2 splice variants of Kv4.3 have been identified,⁸³ the expression levels of the 2 predicted Kv4.3 proteins and the functional roles of these variants in the generation of functional cardiac $I_{to,f}$ channels have not been determined.

The Kv channel accessory subunit KChIP2 coimmunoprecipitates with Kv4 α subunits from adult mouse ventricles, consistent with a role in the generation of Kv4-encoded mouse ventricular $I_{to,f}$ channels.⁷⁶ In ferret heart, a gradient in KChIP2 message expression is observed through the thickness of the ventricular wall,⁶⁴ leading to suggestions that the differential expression of KChIP2 underlies the epicardial-endocardial differences in $I_{to,f}$ densities. The patterns of expression of the KChIP2 message, the KChIP2 protein and $I_{to,f}$ densities are similar in canine ventricles,⁸⁴ consistent with an important role for KChIP2 in determining functional canine, as well as human, ventricular $I_{to,f}$ densities. In contrast, in rat and mouse ventricles, there is little or no gradient in KChIP2^{80,85} expression, and it appears that regional differences in Kv4.2 expression underlie the heterogeneities in $I_{to,f}$ densities in rodent ventricles.^{85,86} Molecular insights into the regulation of regional variations in Kv4.2 (transcript) expression were provided with the demonstrations that expression of the transcription factors, Irx5 and NFAT, are positively and negatively (respectively) correlated with the differences in Kv4.2 expression and $I_{to,f}$ densities.^{87,88} Interestingly, approximately 25 transcription factors have been shown to be differentially expressed in the ventricles.⁸⁹

Functional analysis of the role of KChIP2 in the generation of $I_{to,f}$ revealed that the targeted deletion of KChIP2 results in the elimination of $I_{to,f}$ ^{27,90} and, interestingly, the complete loss of the Kv4.2 protein.²⁷ Additional putative channel regulatory proteins, including the voltage-gated Nav channel accessory subunit 1, Nav β 1,⁹¹ and semaphorin 3A,⁹² have been shown to associate with Kv4 α subunits and suggested to function in the generation of native Kv4-encoded channels. The functional roles of these and other putative Kv4 channel accessory subunits, including the *KCNE* and *DPPX* subunits, in the generation of native myocardial $I_{to,f}$ channels and/or in determining regional differences in myocardial $I_{to,f}$ densities remain to be defined. Although accumulating evidence suggests that cardiac $I_{to,f}$ channels function in macromolecular complexes, comprising Kv4 α subunits and multiple cytosolic and transmembrane accessory subunits (**Fig. 3**), the molecular composition(s) of native myocardial $I_{to,f}$ channels have not been determined directly.

The kinetic and pharmacologic properties of the slow transient outward K^+ currents, $I_{to,s}$, in ventricular myocytes are quite different from $I_{to,f}$ (see **Table 1**), observations interpreted as suggesting that the molecular correlates of ventricular $I_{to,s}$ and $I_{to,f}$ channels are also distinct. Direct experimental support for this hypothesis was provided in electrophysiologic experiments on myocytes isolated from mice with a targeted deletion of the Kv1.4 gene, Kv1.4^{-/-},⁹³ demonstrating that $I_{to,s}$ is undetectable in septum cells.⁹⁴ The properties and the densities of $I_{to,f}$, I_K , slow1, I_K , slow2, and I_{ss} in Kv1.4^{-/-} left and right ventricular (and in atrial) myocytes, however, are indistinguishable from those in wild-type cells.⁹⁴ Interestingly, upregulation of $I_{to,s}$ is evident in the ventricles of Kv4.2DN-expressing mice in which $I_{to,f}$ is eliminated,⁷⁸ and this upregulation (of $I_{to,s}$) is eliminated on crossing Kv4.2DN with Kv1.4^{-/-} mice.⁹⁵ Given the similarities in the time-dependent and voltage-dependent properties of the slow transient outward K^+ currents in other species with mouse $I_{to,s}$,¹ it

seems reasonable to suggest that Kv1.4 likely also encodes $I_{to,s}$ in ferret, rabbit, and perhaps human, ventricular myocytes.

Heterologous expression of ERG1 reveals voltage-gated, inwardly rectifying K^+ -selective channels that are similar to cardiac I_{Kr} .⁵¹ Alternatively processed forms of ERG1, with unique N-termini and C-termini, also have been identified in mouse and human heart and suggested to play roles in the generation of native cardiac I_{Kr} channels.^{96–98} It also has been suggested that functional cardiac I_{Kr} channels are multi-meric, comprising ERG1 and minK, and biochemical studies have demonstrated coimmunoprecipitation of ERG1 and minK from equine ventricles.⁹⁹ It is presently not clear, however, if ERG1 and minK or other members of the KCNE family are also found in association in other species.

Although heterologous expression of *KCNQ1*, the locus of mutations in LQT1, reveals rapidly activating, noninactivating Kv currents, coexpression with minK produces slowly activating Kv currents similar to cardiac I_{Ks} .⁵¹ These observations, together with biochemical data demonstrating that heterologously expressed KvLQT1 and minK associate, were interpreted as suggesting that minK coassembles with KvLQT1 to form functional cardiac I_{Ks} channels.⁵¹ Biochemical evidence for the in situ coassembly of KvLQT1 and minK in equine ventricles has been reported,⁹⁹ although similar data for human ventricular I_{Ks} has yet to be provided. Unexpectedly, however, it has been reported that KvLQT1 modulates the distribution and properties of ERG1-encoded channels, an observation interpreted as suggesting that cardiac I_{Ks} and I_{Kr} channels are regulated through direct Kv α subunit–Kv α subunit interactions.¹⁰⁰ The mechanisms controlling the cell surface expression of functional I_{Ks} channels, the regional differences in I_{Ks} densities, and the interaction(s) between I_{Ks} and I_{Kr} remain to be determined.

Similar to the transient outward Kv currents, molecular methods, in combination with biochemistry and electrophysiology, have provided insights into the molecular basis of functional delayed rectifier Kv channel diversity in the mouse myocardium. A role for Kv1 α subunits in the generation of mouse ventricular IK, slow1, for example, was suggested by the observation that IK, slow is selectively attenuated in ventricular myocytes isolated from transgenic mice expressing a truncated, dominant negative Kv1 α subunit, Kv1.1DN.¹⁰¹ It was subsequently shown, however, that IK, slow is also reduced in ventricular myocytes expressing a dominant negative Kv 2.1 mutant, Kv2.1DN,²⁸ revealing that there are 2, molecularly distinct components of mouse ventricular IK, slow: IK, slow1, which is sensitive to μ M concentrations of 4-aminopyridine and encoded by Kv1 α subunits and IK, slow2, which is sensitive to TEA and encoded by Kv2 α subunits.²⁸ Subsequent studies revealed that IK, slow1 is eliminated in ventricular myocytes isolated from mice harboring the targeted disruption of the *KCNA5* (Kv1.5) locus, revealing that Kv1.5 encodes IK, slow1.²⁹ These findings, together with the previous studies completed on cells from Kv1.4^{-/-} animals,⁹³ in which $I_{to,s}$ is eliminated,⁹⁴ reveal that, in contrast to the Kv 4 α subunits, Kv4.2 and Kv4.3,⁷⁶ the Kv 1 α subunits, Kv1.4 and Kv1.5, do not associate in adult mouse ventricles in situ. Rather, functional Kv1 α subunit-encoded Kv channels in mouse ventricular myocytes are homomeric, composed of Kv1.4 α subunits ($I_{to,s}$)⁹³ or Kv1.5 α subunits (IK,slow1).²⁹ The role(s) of Kv accessory subunits in the generation of

native $I_{to,s}$, I_K , slow1, and I_K , slow2 channels and the mechanisms controlling the expression of these channels remain to be determined.

MOLECULAR DETERMINANTS OF NATIVE MYOCARDIAL Kir AND K2P CHANNELS

Inwardly rectifying K^+ channels in cardiac and other cells are encoded by a large and diverse subfamily of inward rectifier K^+ (Kir) channel pore-forming α subunit genes,⁸ each of which encodes a protein with 2 transmembrane domains (see **Fig. 2**) that assemble as tetramers to form K^+ selective pores. Based on the properties of the currents produced in heterologous expression systems, Kir2 α subunits were long thought to encode the strongly inwardly rectifying cardiac I_{K1} channels,¹⁰² and several members of the Kir 2 subfamily are expressed in the myocardium.¹ Direct insights into the role(s) of Kir 2 α subunits in the generation of cardiac I_{K1} channels was provided in studies completed on myocytes isolated from mice lacking *KCNJ2* (Kir2.1^{-/-}) or *KCNJ12* (Kir2.2^{-/-}).¹⁰³ Although Kir2.1^{-/-} mice have cleft palate and die shortly after birth, precluding electrophysiologic studies on adult myocytes, voltage-clamp recordings from newborn Kir2.1^{-/-} ventricular myocytes revealed that I_{K1} is absent, whereas I_{K1} was reduced (but not eliminated) in adult Kir2.2^{-/-} ventricular myocytes,¹⁰³ suggesting that both Kir2.1 and Kir2.2 contribute to (mouse) ventricular I_{K1} and that functional cardiac I_{K1} channels are heteromeric. The quantitative differences between the effects of the deletion of *KCNJ2* and *KCNJ12* further suggest that Kv2.1 (*KCNJ2*) is the critical subunit underlying native (mouse) I_{K1} channels.¹⁰³

Mutations in *KCNJ2* have been linked to congenital long QT (Andersen-Tawil syndrome or LQT7), as well as short QT, syndromes,^{104,105} and increasing expression of Kir2.1 in the mouse heart, which results in the upregulation of I_{K1} , is proarrhythmic.^{106,107} Previous studies have identified regional differences in myocardial I_{K1} expression and properties in adult mouse heart^{108,109} and it has been suggested that these differences reflect the variable subunit composition(s) of the channels, as well as differences in polyamine concentrations.¹¹⁰ Studies focused on testing these hypotheses directly and on defining the mechanisms controlling regional differences in the expression and functioning of native I_{K1} channels in species other than mice are also clearly warranted.

In the heart, I_{KATP} channels appear not to contribute to action potential repolarization, but rather are thought to be important in myocardial ischemia and preconditioning.^{41,42} In heterologous cells, I_{KATP} channels can be reconstituted by coexpression of Kir6.x subunits with the accessory ATP-binding cassette sulfonylurea receptors, SURx, proteins.¹¹¹ Cardiac sarcolemmal I_{KATP} channels are encoded by Kir6.2 and SUR2A, and the essential role of Kir6.2 was demonstrated directly in experiments on ventricular myocytes from Kir6.2^{-/-} animals.¹¹²

In addition, cardiac I_{KATP} channel activity is reduced in SUR2^{-/-} myocytes¹¹³ and unaffected in SUR1^{-/-} myocytes,¹¹⁴ suggesting an important role for SUR2. Interestingly, the properties of the residual I_{KATP} channels in SUR2^{-/-} myocytes are similar to those produced in heterologous cells on coexpression of Kir6.2 and SUR1,¹¹³ suggesting that

SUR1 may also contribute to the generation of cardiac I_{KATP} channels by coassembling with Kir6.2 α subunits alone or in combination with SUR2A.

Although action potential waveforms in Kir6.2^{-/-} and wild-type ventricular myocytes are indistinguishable, the action potential shortening observed in wild-type cells during ischemia is not observed in Kir6.2^{-/-} myocytes.¹¹² Action potential durations are also largely unaffected in transgenic animals expressing mutant I_{KATP} channels with markedly (40-fold) reduced ATP sensitivity, suggesting that there are also additional inhibitory mechanisms that regulate cardiac I_{KATP} channel activity in vivo.¹¹⁵ Similar to myocardial I_{K1} channels, further studies focused on defining the mechanisms controlling the regional differences in the expression and properties of myocardial I_{KATP} channels will be of interest.

The multiplicity of K2P α subunits, the widespread distribution of expressed subunits, and the finding(s) that the properties of the channels encoded by K2P subunits are regulated by a variety of physiologically (and pathophysiologically) relevant stimuli^{52,53} suggest that K2P channels likely subserve a variety of important functions. As in other cell types, the physiologic roles of these subunits/channels in the myocardium are just beginning to be explored. The transcripts encoding TREK-1 and TASK-1 are detected in heart, and heterologous expression of either of these subunits gives rise to instantaneous, noninactivating K^+ currents that display little or no voltage dependence.^{116,117} These properties suggest that K2P subunits likely contribute to “background” or “leak” K^+ channels; that is, channels with properties similar to the “steady-state” noninactivating K^+ current (I_{ss}) characterized in adult mouse and rat ventricular myocytes.^{17,18,116-119} Clearly, experiments focused on testing these hypotheses directly are needed to provide clear insights into the molecular basis of I_{ss} and to allow further studies focused on defining the mechanisms controlling the physiologic and the pathophysiologic regulation of these (I_{ss}) channels.

MECHANISMS CONTRIBUTING TO THE MOLECULAR REGULATION OF MYOCARDIAL K^+ CHANNELS

Considerable evidence suggests that multiple mechanisms contribute to the regulation of myocardial K^+ channel expression and functioning.¹²⁰ These include transcriptional mechanisms to control the temporal and spatial expression of K^+ channel pore-forming and accessory subunits and regulatory proteins during normal development and in response to myocardial damage or disease. Interestingly, signaling pathways, such as signaling mediated by phosphoinositide 3-kinase, also have been linked to transcriptional regulation of multiple cardiac K^+ channels.¹²¹ Similarly, posttranscriptional/translational mechanisms, including pre-mRNA processing, RNA editing, microRNAs, and, perhaps other noncoding RNAs, also have been linked to the regulation of functional myocardial K^+ channel expression.¹²⁰ The various K^+ channel subunit proteins also are potential targets for posttranslational modifications, such as phosphorylation, sumoylation, glycosylation, and palmitoylation, and/or associations with membrane lipids, each of which has been implicated in the regulation of myocardial K^+ channel stability, trafficking, and functioning.¹²⁰ In addition, considerable evidence suggests that K^+ channel subunit

expression levels are regulated epigenetically; that is, by modifications, such as methylation, through mechanisms that involve changes in DNA structure (and resulting transcription), but not changes in DNA sequences.¹²⁰ Future studies focused on defining the roles of each of these mechanisms in the generation and regulation of myocardial K^+ (and other) channels will be of considerable interest and import.

SUMMARY, OPEN QUESTIONS, AND FUTURE CHALLENGES

Cellular electrophysiologic studies have distinguished multiple types of voltage-gated inward and outward currents that contribute to action potential repolarization in mammalian cardiac cells (see **Table 1**). The outward (K^+) currents are more numerous and more diverse than the inward (Na^+ , Ca^{2+}) currents, and most cardiac cells express a repertoire of voltage-gated and non-voltage-gated K^+ channels (see **Table 1**). In addition, some of these K^+ channels are expressed differentially in the heart, contributing to regional and cell-type-specific differences in action potential waveforms. Multiple voltage-gated (K_v), non-voltage-gated, inwardly rectifying (K_{ir}) and weakly rectifying, noninactivating (K_{2P}) K^+ channel pore-forming α subunits and a number of channel accessory (β) subunits have been identified and suggested to play roles in the generation of the native K^+ channels (see **Table 1**). Indeed, considerable progress has been made in identifying the pore-forming K_v and K_{ir} α subunits (see **Fig. 2**) contributing to the formation of most of the K^+ channels expressed in mammalian cardiac myocytes. In addition, biochemical studies have provided some insights into the molecular mechanisms underlying the observed heterogeneities in the expression of myocardial K_v and K_{ir} currents. For cardiac $I_{to,f}$, for example, regional differences in current densities are correlated with differences in $K_v4.2$ protein expression in rodents,⁸⁶ whereas variable expression of the $I_{to,f}$ channel accessory protein, $KChIP2$, has been suggested to underlie the transmural gradient in $I_{to,f}$ densities in canine and human ventricles.^{61, 84} For cardiac I_{K1} channels, in contrast, recent studies suggest that differences in K_{ir} channel α subunit composition and/or differences in the concentrations of intracellular polyamines play roles in regulating the functional diversity of these channels.⁴⁰

Considerable evidence suggests that native myocardial K^+ channels, like other ion channels,¹³⁻¹⁶ likely function in macromolecular protein complexes (see **Fig. 3**), comprising pore-forming α subunits and multiple cytosolic and transmembrane accessory/regulatory subunits, although the molecular composition(s) of native myocardial K^+ channels have not been determined directly to date. In addition, and in contrast to the progress made in defining the α subunits encoding native myocardial K^+ channels/currents, very little is known about the functional roles of most of the K^+ channel auxiliary subunits that have been identified. An important focus of future work will likely be on defining the physiologic roles of the many K^+ channel accessory subunits in the generation of native myocardial K^+ channels and on defining the molecular mechanisms controlling the properties and the cell surface expression of native cardiac K^+ channels. In addition, as numerous studies have documented changes in functional K^+ channel expression in a variety of myocardial disease states, changes that could reflect modifications in channel properties, as well as alterations in the molecular compositions of the channels and/or in the (posttranslational) processing of the underlying channel subunits, it seems clear that a major focus of future research will be on defining these mechanisms in detail. As discussed previously, there are a number of

possible mechanisms, including transcriptional, posttranscriptional, translational, posttranslational, and epigenetic, that may play roles in regulating the functional expression and the biophysical properties of myocardial K^+ channels in the normal, as well as in the damaged or diseased, myocardium. Efforts to explore these mechanisms in depth will likely be enhanced by the increased availability and application of induced pluripotent stem cell-derived cardiac myocytes.^{122,123} In addition to providing new insights into the molecular determinants of native cardiac K^+ channel functioning, studies focused on defining these mechanisms will facilitate efforts to develop novel therapeutic strategies to prevent or reverse K^+ channel remodeling associated with systemic or myocardial disease.

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KEY POINTS

- Cellular electrophysiological studies have distinguished multiple types of voltage-gated inward and outward currents that contribute to action potential repolarization in mammalian cardiac cells.
  - Considerable progress has been made in identifying the pore-forming Kv and Kir α subunits contributing to the formation of most of the K^+ channels expressed in mammalian cardiac myocytes.
  - Biochemical studies have provided some insights into the molecular mechanisms underlying the observed heterogeneities in the expression of myocardial Kv and Kir currents.
- Considerable evidence suggests that native myocardial K^+ channels, like other ion channels, likely function in macromolecular protein complexes, comprising pore-forming α subunits and multiple cytosolic and transmembrane accessory/regulatory subunits.
- An important focus of future work will likely be on defining the physiologic roles of the many K^+ channel accessory subunits in the generation of native myocardial K^+ channels and on defining the molecular mechanisms controlling the properties and the cell surface expression of native cardiac K^+ channels.

Fig. 1.

Action potentials and underlying ionic currents in adult human ventricular and atrial myocytes. The major ionic currents shaping action potential waveforms in human atrial and ventricular myocytes are schematized. The names of the individual ionic currents are indicated to the left of the records, and the main pore-forming (α) subunits encoding the K^+ channel underlying these currents are indicated to the right of the records. There are differences in the relative expression levels of several of the repolarizing K^+ currents and/or in the relative contributions the various K^+ currents make to shaping action potential waveforms and controlling repolarization in ventricular and atrial myocytes.

Fig. 2.

Pore-forming (α) subunits of cardiac Kir, K2P, and Kv channels. (A) Schematics illustrating the transmembrane topologies of the α subunits encoding inwardly rectifying (Kir), 2-pore domain (K2P), and voltage-gated (Kv) K⁺ channels. (B) Phylogenetic dendrograms of K⁺ channel α subunits of the Kir, K2P, and Kv (including KCa and KNa) α subunit subfamilies.

Fig. 3.

Native Kv4.3-encoded, myocardial $I_{to,f}$ channels function in macromolecular protein complexes. (A) Cross section of a schematicized cardiac $I_{to,f}$ channel complex in a membrane showing 2 Kv4.3 α subunits (blue), generated based on the structure of Kv1.2,¹²⁴ each interacting with a cytosolic KChIP2 (red) and a cytosolic Kv β (green) accessory subunit (in a 1:1:1 stoichiometry) through distinct, nonoverlapping N-terminal domains. The transmembrane accessory subunits, DPP6/10¹²⁵ (brown), MinK/MiRPs (yellow), and Nav β 1/Nav β 2 (red), which also have been proposed to interact with Kv4.3 α subunits (each illustrated in a 2:1 stoichiometry) and to contribute to the formation of native Kv4-encoded channels, are also shown. (B) Structural analyses of Kv4.3N-KChIP1 complexes¹²⁶ revealed a 1:1 stoichiometry with each KChIP (red) bridging 2 adjacent Kv4.3 N termini (blue) and anchoring each hydrophobic Kv4.3 N terminus in a hydrophobic KChIP1 binding pocket. Protein structures illustrated were generated based on published structural data using PyMOL.

Table 1

Functional and molecular diversity of cardiac potassium currents

Channel Type	Current Name	Activation	Gating	Function	Pharmacology	Human α Subunit Gene	Chromosomal Location	α Subunit Protein	Auxiliary Subunits
Kv	$I_{to,f}$	Fast	Voltage	Plateau potential, repolarization	mM 4-AP HaTX HpTX Ba^{2+}	<i>KCND3</i>	1p13.3	Kv4.3 or Kv4.2	KChIP2, DPP6/10, NCS-1 (minK, MIRP2/3 ?)
	$I_{to,s}$	Fast	Voltage	Plateau potential, repolarization	μ M 4-AP	<i>KCNA4</i>	11p14	Kv1.4	??
	I_{Kr}	Fast	Voltage	Plateau potential, repolarization	E-4031 Dofetilide	<i>KCNH2</i>	7q36.1	Kv12.1 (hERG)	minK, MiRP1/2??
	I_{Ks}	Slow	Voltage	Repolarization	NE-10064 NE-10133	<i>KCNQ1</i>	11p15.5	Kv7.1 (KvLQT1)	minK (MiRPs?)
	I_{Kur}	Fast	Voltage	Repolarization	μ M 4-AP	<i>KCNA5</i>	12p13	Kv1.5	SAP97
	$[I_{K,slow2}]^a$	Slow	Voltage	Repolarization	mM TEA	$[Kcnb1]^b$	2H3	Kv2.1	Amigo?
	K2P	$[I_{ss}]^a$	—	H ⁺ , fatty acids, anesthetics	Resting potential, repolarization, diastolic potential	mM TEA A1899	$[Kcnk2/3]^b$	1q41, 2p23	K2p2 (TREK1)/k2p3 (TASK1)
	$[I_{Kr}]^c$	—	??	Resting potential, repolarization	Ba^{2+}	??	??	??	??
KCa	I_{SK}	Slow	Ca^{2+} - Calmodulin	Repolarization	Apamin	<i>KCNN1/2/3</i>	19p13.1, 5q22.2, 1q21.3	KCa2.1, KCa2.2, KCa2.3	??
KNa	I_{NaK}	Fast	Na	$??^b$	Quinidine Clofilium	<i>KCNT1/2</i>	9q34.3, 1q31.3	KNa1.1 (Slick), KNa1.2 (Slack)	??
Kir	I_{K1}	—	Spermines Mg^{2+}	Resting potential, diastolic potential	Ba^{2+}	<i>KCNJ2/4/12</i>	17q24.1, 17p11.2, 22q13.1	Kir2.1, Kir2.2, Kir2.3	??
	$I_{K(Ach)}$	—	Ach	Resting potential, diastolic potential	Tertiapin-Q	<i>KCNJ3/5</i>	2q24.1, 11q24	Kir3.1, Kir3.4	??
	$I_{K(ATP)}$	—	ATP ADP	$??^d$	SURs	<i>KCNJ8/11</i>	12p11.23, 11p15.1	Kir6.1, Kir6.2	SUR1/2

Abbreviations: 4-AP, 4-aminopyridine; HaTX, hanatoxin; HpTX, heteropodatoxin; SURs, sulfonylureas; TEA, tetraethylammonium.

^aCurrent found in rodents, but has not, to date, been reported in human cardiac cells.

^bPore-forming subunit encoding K^+ current in mouse heart.

^cCurrent reported in guinea pig ventricular myocytes.

Current has been suggested to function to hyperpolarize membrane potential under conditions of ischemia/metabolic stress.
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