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Advances in Cardiac ATP-Sensitive K+ Channelopathies From Molecules to Populations

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ATP-sensitive K^+ (K_{ATP}) channels are nucleotide-gated bioenergy sensors that enable high-fidelity feedback communication between cellular energy dynamics and membrane electrical activity.[1-4] Particularly dense in cardiac sarcolemma where they are composed through heteromultimeric assembly of inwardly rectifying K^+ channel pores, typically *KCNJ11*-encoded Kir6.2 proteins, and regulatory ATP-binding cassette proteins, namely *ABCC9*-encoded SUR2A subunits, K_{ATP} channels are increasingly recognized as integral to tissue energy conservation and optimization of energy use.[5] Integrated with intracellular energy pathways, sarcolemmal K_{ATP} channels are established cardioprotectors implicated in the sustenance of wellness.[6-8]

Knockout of the Kir6.2 K_{ATP} channel pore induces inefficient cardiac energetics associated with altered metabolic fuel selection and remodeling of the myocardial proteome, highlighting a distinct role of the channel in heart energy homeostasis.[9,10] K_{ATP} channel ablation alters the expression of one tenth of largely metabolism-related protein species, exposing within the K_{ATP} channel-deficient ventricle markers of cardiovascular disease susceptibility.[9,11] Indeed, disruption of the Kir6.2 K_{ATP} channel compromises cardiac protection afforded by ischemic preconditioning, impairs myocardial tolerance to sympathetic surge, and aggravates the impact of endurance challenge or hemodynamic overload precipitating heart failure under stress.[12] Conversely, overexpression of channel subunits generates a protective phenotype at cellular and organ levels.[13,14]

High-throughput molecular technologies applied to phenotypically characterized patient and population cohorts have contributed to the deciphering of human K_{ATP} channelopathies, disease entities caused by genetic disruption of ion channel function.[15-19] In cardiovascular

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medicine, mutations in the regulatory SUR2A subunit have been linked to K_{ATP} channelopathy-associated electrical and cardiomyopathic disorders, namely the syndromes of adrenergic atrial fibrillation and dilated cardiomyopathy with tachycardia.[19-21] Moreover, in clinical heart failure, a common polymorphism in the Kir6.2 K_{ATP} channel pore subunit has been identified as a robust biomarker for impaired performance in stress-test.[22] Furthermore, the Kir6.2 K23 allele, present in over half the population, has been pinpointed as an independent risk factor for susceptibility to maladaptive cardiac remodeling in hypertension.[23] Cardiovascular disorders associated with genetic variation in K_{ATP} channel genes also include myocardial infarction and ventricular fibrillation. Collectively, advances in molecular medicine have enabled a growing understanding of genetically-determined channel (mal)function, underscoring the broadening awareness of the impact of the K_{ATP} channel complex on individual and public cardiovascular health.

K_{ATP} channel complexes: Nucleotide-gated heteromultimers

K_{ATP} channels were originally identified in the plasma membrane of cardiomyocytes,[24] and shortly thereafter in other metabolically active tissues, such as pancreatic β-cells, as well as in subcellular compartments, including mitochondria.[2,4,25,26] Plasmalemmal K_{ATP} channels, the focus of this overview, are defined as compulsory heteromultimers formed by octameric assembly of inward-rectifier K^+ channels (Kir6.1/Kir6.2) with ATP-binding-cassette (ABC) proteins (SUR1/SUR2A/SUR2B).[27-32] Human Kir6.1 and Kir6.2 genes – *KCNJ8* and *KCNJ11* – map to chromosome 12p11.23 and 11p15.1, and comprise two and one coding exons respectively. SUR genes, *SUR1* (or *ABCC8*) at locus 11p15.1 and *SUR2* (or *ABBC9*) at locus 12p12.1 comprise 39 and 38 exons respectively (Fig. 1). Alternative splicing gives rise to SUR2 protein variants, SUR2A and SUR2B. Tissue diversity, cellular distribution, and regulatory specificity are ensured by the assortment of subunit and isoform combinations. Biophysical properties are largely shared among plasmalemmal K_{ATP} channels, and include potassium selectivity and inward rectification imparted by the Kir protein, whereas responsiveness to cellular energetic signals is conferred by nucleotide interaction with both Kir and SUR channel subunits.[33]

Kir6.2 is integral in the make-up of myocellular K_{ATP} channels, and targeted disruption of *KCNJ11* generates a Kir6.2-deficient state characterized by lack of functional K_{ATP} channels in ventricular myocytes.[34] Sarcolemmal K_{ATP} channels in the ventricle are composed primarily through co-assembly of Kir6.2 and SUR2A subunits (Fig. 1). Indeed, recombinant Kir6.2/SUR2A channels match features of native ventricular myocyte K_{ATP} channels.[35] The molecular channel architecture may however exhibit plasticity, in particular in response to metabolic challenge. Kir6.1 mRNA expression, for example, is significantly elevated following ischemia or hypoxia, raising the possibility that Kir6.1 may be upregulated in myocytes in response to stress.[36] Moreover, a disparate structure of atrial compared to ventricular K_{ATP} channels has been proposed, implicating SUR1-based channels in atrial specific functions, such as coupling atrial stretch with secretion of the atrial natriuretic peptide.[37,38]

Crosstalk of cardiac K_{ATP} channel proteins with myocellular energetics is facilitated by privileged associations of channel subunits with phosphotransfer and glycolytic enzymes.[39] Metabolism-related proteins with established links to the cardiac K_{ATP} channel include creatine kinase, adenylate kinase, glyceraldehyde-3-phosphate dehydrogenase, lactate dehydrogenase, long chain acyl-CoA dehydrogenase, pyruvate kinase, and triosephosphate isomerase.[40-45] More broadly, over 100 K_{ATP} channel-dependent proteins have been identified through deconvolution of the K_{ATP} channel knockout heart proteome.[8-10] Categorization of proteomic changes in the K_{ATP} channel-deficient myocardium have demonstrated a highly represented metabolic theme that includes members of the

tricarboxylic acid cycle, fatty acid β-oxidation, glycolysis, as well as amino acid and nucleic acid metabolism.[8-10]

ATP/ADP modulation of channel function is a defining property of K_{ATP} channels as metabolic sensors (Fig. 1).[5,8,33,46] The interface between Kir6.2 subunits is critical for ATP-mediated pore inhibition.[47] Nucleotide binding domains (NBD1 and NBD2) of SUR2A harbor intrinsic ATPase activity, endowing this regulatory K_{ATP} channel subunit with the ability to modulate ATP-induced Kir6.2 pore inhibition and thereby K^+ efflux to reduce myocyte excitability.[48-52] It is thought, that by relying on the intactness of cooperative NBD1/2 interaction, a stabilized ADP-bound post-hydrolytic conformation at NBD2 of SUR in the presence of Mg^{2+}, promotes K_{ATP} channel opening.[1,53-55] Furthermore, the nucleotide-bound conformations of SUR mediate the regulation of K_{ATP} channel activity by pharmacological agents, such as sulfonylurea inhibitors and potassium channel openers (KC0).[33,55]

K_{ATP} channels: Stress without distress

Vital in the adaptive response to metabolic stress, cardioprotective K_{ATP} channels are a recognized energy-sparing system that limits muscle energy expenses during the propagation of action potentials.[7,8,33,56] Defined as the most densely expressed K^+ channels in the myocardium, K_{ATP} channels are critical endogenous elements for cardiac energy homeostasis and electrical stability across a spectrum of stress conditions, including acute ischemia, the “fight-or-flight” response, chronic exertion, and heart failure.[12,19,57]

Ischemic stress

In ischemia, K_{ATP} channel opening shortens the duration of cardiac action potential (Fig. 1) and controls Ca^{2+} influx.[58,59] Sarcolemmal K_{ATP} channel activation is apparently responsible for the electrical current that underlies ST-segment elevation of transmural ischemic injury, and has been implicated in protection afforded by ischemic preconditioning.[12] Ablation of K_{ATP} channels disrupts the homeostatic mechanism integral to energetic myocardial stability under ischemic stress. Specifically, in the Kir6.2-knockout mouse following transmural anterior myocardial infarction, absence of significant and sustained ST-segment change has been documented and contrasts the wild-type counterpart that demonstrates prompt and pronounced ST-segment elevation following ischemic injury.[60] K_{ATP} channel activity in ischemia appears to have a diagnostic implication of clinical significance. In particular, patients with diabetes mellitus presenting with acute myocardial infarction demonstrate attenuated ST-segment elevation when taking sulfonylureas, inhibitors of K_{ATP} channel activity, resulting in a failure to meet criteria for emergent revascularization therapy and, as a consequence, inappropriate withholding of proven beneficial therapy.[12] Moreover, K_{ATP} channels have been implicated in the ischemic preconditioning mechanism by which exposure to brief ischemia preceding a sustained ischemic insult reduces subsequent infarct size.[61] Analogous to ischemic preconditioning, pharmacologic activation of the channel by K_{ATP} channel openers has also protective benefit.[62,63] Both ischemic and pharmacologic preconditioning are abolished in the absence of Kir6.2-containing K_{ATP} channels.[64,65] Absence of sarcolemmal K_{ATP} channel activity has negative effects on cardiac relaxation and contractility under acute ischemic stress. In parallel, knockout of Kir6.2 negates protection afforded by ischemic preconditioning on myocardial energy generation, transfer and utilization.[66] Total ATP turnover, a global parameter of energy demand, fails to increase in the ischemic-preconditioned K_{ATP} channel knockout as opposed to the wild-type, correlating with failure of preconditioned hearts lacking K_{ATP} channels to functionally recover.[66] The K_{ATP} channel-dependent cardioprotective potential is underscored by improved myocardial function during post-

ischemic reperfusion following introduction of the SUR2A transgene into the SUR2 null cardiomyocyte.[67]

Fight-or-flight response

Beyond protection against the insult of ischemia, K_{ATP} channels serve as guarantors of metabolic and ionic homeostasis, appearing central to cardiac participation in the general adaptation syndrome.[57] In the "fight-or-flight" response, metabolic adaptations in bodily functions achieve a superior level of performance necessary to cope with the demands of imposed stress. The sustenance of augmented performance requires energy-controlling mechanisms, such as the K_{ATP} channel, ensuring that the reaction to stress itself does not become harmful, i.e., "stress without distress".[57] A common trigger of the general adaptation syndrome is systemic sympathetic stimulation that augments cardiac contractility and heart rate, and thereby provides the necessary higher cardiac output to meet demand. Enhanced cardiac output imposes a significant metabolic load on the heart. A compensatory increase in outward K^+ current activates when the sustained augmentation of heart muscle performance competes with the ability of cellular energetics to maintain contractile and electrical stability. The K_{ATP} channel-mediated action potential shortening limits actomyosin ATP consumption by reducing Ca^{2+} influx, thereby restraining energy utilization to ensure functional and structural cellular integrity.[68] Under sympathetic distress, hearts without K_{ATP} channels lack stress-induced cardiac action potential shortening predisposing to cytosolic Ca^{2+} overload associated with development of contractile dysfunction, and possibly death.[68] On autopsy, contraction bands, pathognomonic of cytosolic Ca^{2+} loading, are visible throughout the myocardium of the Kir6.2-knockout but not wildtype.[68] Measurement of oxygen consumption has revealed that increased workloads produce only moderate elevation of energy expenditure, in line with K_{ATP} channel-dependent shortening of action potential duration.[56] Conversely, absence of K_{ATP} channel-driven action potential shortening in K_{ATP} channel-deficient hearts precipitates significant elevation in oxygen consumption.[56]

Under catecholamine challenge, action potential prolongation remains uncompensated in the absence of K_{ATP} channel function predisposing the myocardium to early afterdepolarizations.[69] This deficit in repolarization reserve translates into a high risk for induction of triggered activity and ventricular dysrhythmia.[69] Intact K_{ATP} channel function appears thus mandatory for adequate repolarization under sympathetic stress providing electrical tolerance against triggered arrhythmia. Proarrhythmogenic features and lack of adaptation to stress in transgenic mice with cardiac myocyte-specific ablation of K_{ATP} channels verifies that these features are intrinsic to the myocardium, and that K_{ATP} channel function has an essential role in protecting the heart from lethal arrhythmias ensuring stress adaptation.[70] Moreover K_{ATP} channels may provide a vital feedback element for cardiovascular tolerance in sepsis, where the systemic inflammatory response to infection imposes a high demand for bodily adaptation.[71] In a model of acute septic shock, induced by endotoxin lipopolysaccharide challenge, knockout of the *KCNJ8* gene encoding the typically vascular Kir6.1 K_{ATP} channel pore predisposes to an early and profound survival disadvantage. The exaggerated susceptibility provoked by disruption of Kir6.1-containing channels was linked to progressive deterioration in cardiac activity, ischemic myocardial damage, and contractile dysfunction.[71] K_{ATP} channels, harnessing the ability to recognize alterations in the cellular energy state and to translate this information into changes in membrane excitability, provide therefore a link necessary for maintaining myocardial well being in the face of stress-induced energy demanding augmentation in performance.

Chronic exertion

Exercise training elicits an array of metabolic responses that underlie fitness. Mice lacking K_{ATP} channels when challenged with a regimented training protocol failed to manifest improved exercise capacity.[72] Repetitive exercise-stress unmasks a survival disadvantage in the Kir6.2-knockout associated with cardiac damage, implicating K_{ATP} channel activity in achieving physiologic benefits of exercise training without accumulating deficits.[72] Even modest stress following a repetitive physical exertion program provokes significant mortality in the Kir6.2-knockout with death occurring during or suddenly in the immediate post-exercise period,[72] perhaps representing manifestation of stress-induced dysrhythmia, to which Kir6.2-knockout are predisposed.[69,70] Exercise intolerance has also been documented in the setting of ablation of the regulatory SUR2 subunit,[73] underscoring the role of K_{ATP} channels in ensuring optimal performance. Beyond physical exercise, in distinct hyperadrenergic states exemplified by cocaine abuse, K_{ATP} channel deletion amplifies poor cardiovascular outcome while promotion of channel activity by potassium channel opening drugs improves survival.[74,75]

Experimental heart failure

Intact K_{ATP} channels prevent the transition from a state of disease risk to that of overt organ failure. In experimental hypertension, induced by volume overload, knockout of Kir6.2 K_{ATP} channel predisposes to heart failure and death.[76] Defective decoding of hypertension-induced metabolic distress signals in the K_{ATP} channel knockout sets in motion pathological Ca^{2+} overload and aggravates cardiac remodeling through a calcium/calcineurin-dependent cyclosporine-sensitive pathway, implicating intact channel activity as a required safety element preventing hypertension-induced heart failure.[76] Similarly, in experimental models of pressure overload, such as that imposed by transverse aortic constriction, compromised K_{ATP} channel function renders the heart vulnerable to poor outcome.[77] The constricted K_{ATP} channel knockout displays fulminant biventricular congestive heart failure, characterized by exercise intolerance, cardiac contractile dysfunction, hepatopulmonary congestion and death. Surviving K_{ATP} channel knockouts develop sequelae, including exaggerated fibrotic myocardial hypertrophy associated with nuclear up-regulation of calcium-dependent pro-remodeling MEF2 and NF-AT pathways, precipitating chamber dilatation.[77] Moreover, it has been documented that disease-induced K_{ATP} channel metabolic dysregulation, even in the absence of channel gene defect, is a contributor to the pathobiology of heart failure, illustrating a mechanism for acquired channelopathy.[78] Thus, operational K_{ATP} channels appear mandatory in securing cardiac adaptation and protecting against heart failure.[12]

Human cardiac K_{ATP} channelopathies

Genetically-determined K_{ATP} channel malfunction has been originally linked to insulin secretory disorders, namely congenital hyperinsulinism and neonatal diabetes.[4,17-19,79,80] Beyond isolated failure of pancreatic β-cells, K_{ATP} channel mutations are also pathogenic in the DEND syndrome, characterized by varying degrees of delayed speech/motor development, epilepsy, neonatal diabetes, muscle hypotonia, and balance issues.[17-19] An even broader role in disease pathogenesis has been realized with the discovery of K_{ATP} channel malfunction in human skeletal myopathies.[81,82] In cardiovascular medicine, K_{ATP} channelopathies have been associated with atrial fibrillation and dilated cardiomyopathy with tachycardia, as well as phenotypic modifiers of preclinical and overt heart disease (Fig. 2).[19]

Adrenergic atrial fibrillation

Atrial fibrillation is increasingly recognized as having genetic underpinnings.[83,84] A case in point are the early onset cases in a subset of patients attributable to monogenic defects. The paradigm of a heritable basis for atrial fibrillation is exemplified by reports of familial disease attributed to gain-of-function or loss-of-function mutations in ion channel genes predicted to accelerate or slow repolarization. In these cases, channel malfunction creates an arrhythmogenic substrate of re-entry or triggered activity caused by reduced electrical refractoriness or after-depolarization, respectively. Initially, channelopathy-based atrial fibrillation predicted shortening of the action potential duration and proarrhythmogenic reduction in refractory period as mechanisms of arrhythmia.[85,86] An alternative mechanism for atrial fibrillation, namely increased propensity for prolongation of action potential duration and triggered activity in the human atrium, was identified for a loss-of-function mutation in *KCNA5*, encoding the voltage-dependent Kv1.5 channel.[87] A possibly equivalent mechanism has been reported in the case of a K_{ATP} channel mutation conferring risk for adrenergic atrial fibrillation originating from the vein of Marshall.[20] The mutation was identified in a middle-aged patient who, in the absence of identifiable risk factors, presented with long-standing atrial fibrillation precipitated by activity and refractory to medical therapy. In this patient with early-onset atrial fibrillation and an overtly normal heart, adrenergic stress as a possible trigger was investigated using a candidate gene approach and invasive electrophysiologic testing under sympathomimetic challenge.[20] The focal source of rapidly firing electrical activity was mapped to the vein of Marshall, a remnant of the left superior vena cava rich in sympathetic fibers and a recognized source for adrenergic atrial fibrillation. Although this potentially arrhythmogenic veno-atrial interface is present in the population at large, it does not trigger arrhythmia in the majority of individuals despite comparable environmental stress exposure. It was postulated that the patient was vulnerable to adrenergic atrial fibrillation due to an inherent defect in electrical stability.[20]

Molecular genetic investigation demonstrated a missense mutation in *ABCC9*, encoding the regulatory subunit of cardiac K_{ATP} channels (Fig. 2).[20] Identified in exon 38, specific for the cardiac splice variant of SUR2A, this heterozygous c.4640C>T transition caused substitution of the threonine residue at amino acid position 1547 with isoleucine (T1547I). Protein alignments revealed that the missense substitution altered the amino acid sequence of the evolutionarily conserved carboxy-terminal tail. Homology modeling mapped the defect adjacent to the signature Walker motifs of the nucleotide binding domain, required for coordination of adenine nucleotides in the nucleotide binding pocket. Removal of the polar threonine (T1547) and replacement with the larger aliphatic and highly hydrophobic isoleucine, as would occur in this patient, predicted compromised nucleotide-dependent K_{ATP} channel gating.[20]

Patch-clamp recording demonstrated that the T1547I substitution compromised adenine nucleotide-dependent induction of K_{ATP} channel current.[20] Mutant T1547I SUR2A, co-expressed with the *KCNJ*11-encoded Kir6.2 pore, generated an aberrant channel that retained ATP-induced inhibition of potassium current, but demonstrated a blunted response to ADP. A deficit in nucleotide gating, resulting from the T1547I mutation, would compromise the homeostatic role of the K_{ATP} channel required for proper readout of cellular distress and maintenance of electrical stability.

The pathogenic link between channel malfunction and adrenergic atrial fibrillation was verified, at the whole organism level, in a murine knockout model deprived of operational K_{ATP} channels. Compared with the normal atrium, resistant to arrhythmia under adrenergic provocation, vulnerability to atrial fibrillation was recapitulated in the setting of a K_{ATP} channel deficit.[20] Thus a lack of intact K_{ATP} channels, either due to a naturally occurring

mutation affecting channel regulation or a targeted disruption of the channel complex, is a substrate for atrial electrical instability under stress, and a molecular risk factor for adrenergic atrial fibrillation.

Once the vein of Marshall had been isolated by radiofrequency ablation, atrial fibrillation could no longer be provoked by programmed electrical stimulation and burst pacing with or without isoproterenol infusion.[20] This case demonstrates that vulnerability to arrhythmia can be caused by an inability of mutant K_{ATP} channels to safeguard against adrenergic stress-induced ectopy. The apparently curative outcome was achieved by disrupting the gene-environment substrate for arrhythmia conferred by the underlying K_{ATP} channelopathy.[19]

Risk factor for electrical instability

While the case underscores heritable channel dysfunction in lone atrial fibrillation, K_{ATP} channel deficit could play a broader role in the pathogenesis of electrical instability. Gene expression and electrophysiological studies in patients with atrial fibrillation demonstrate altered atrial ion channel mRNA transcription and post-translational activity, including downregulation of the K_{ATP} channel pore and associated current.[88,89] Moreover, structural heart disease and/or atrial dilation may compromise metabolic and mechanosensitive gating of K_{ATP} channels,[90-92] precipitating a suboptimal repolarization reserve and providing a substrate for the more common acquired form of atrial fibrillation.

K_{ATP} channel alteration may also impact predisposition towards ventricular vulnerability to arrhythmia. In this regard, a case of ventricular fibrillation with prominent early repolarization was recently reported in a young patient who was resuscitated following an episode of sudden death. Subsequent, unrelenting ventricular fibrillation was unresponsive to several classes of antiarrhythmics prior to rhythm restoration with quinidine.[93] Myopathic and coronary heart disease were excluded, and a K_{ATP} channel subunit amino acid substitution, namely the S422L variant of the *KCNJ8* gene encoding Kir6.1, identified (Fig. 2).[93] The gain-of-function K_{ATP} channel variant was further linked to the pathogenic substrate of pleiotropic J-wave abnormalities, in single Brugada syndrome and early repolarization syndrome cases.[94]

Dilated cardiomyopathy with tachycardia

Beyond isolated arrhythmias, K_{ATP} channelopathy has been implicated in a syndrome of cardiomyopathy with ventricular arrhythmia. The ontological spectrum of cardiomyopathy-associated mutant gene products has encompassed the fundamental components of excitation-contraction coupling such as contractile, cytoskeletal, and myocellular ion regulatory proteins.[95] Human molecular genetic studies have also linked K_{ATP} channel defects and aberrant homeostatic stress response in the pathogenesis of dilated cardiomyopathy.[19] These defects, identified in the regulatory K_{ATP} channel subunit, impair channel-dependent decoding of cellular metabolic state, establishing a previously unrecognized mechanism in human heart failure.[18]

The cardiomyopathic-arrhythmia syndrome characterized by the triad of dilated cardiomyopathy, ventricular arrhythmia, and *ABCC9* K_{ATP} channel mutations has been designated CMD1O (OMIM #608569; Fig. 2),[21] and salient phenotypic traits were reproduced by K_{ATP} channel knockout under imposed stress.[77] Clinically, this entity was reported in middle-aged patients with marked left ventricular enlargement, severe systolic dysfunction, and ventricular tachycardia. In these patients, heterozygous mutations were identified in exon 38 of *ABCC9*, which encodes the C-terminal domain of the SUR2A channel subunit, specific to the cardiac splice variant. DNA sequencing of a mutated allele identified a 3-bp deletion and 4-bp insertion mutation (c.4570-4572delTTAinsAAAT),

causing a frameshift at L1524 and introducing four anomalous terminal residues followed by a premature stop codon (fs1524).[21] Another mutated allele harbored a missense mutation (c. 4537G>A) causing the amino acid substitution A1513T. The identified frameshift and missense mutations occurred in evolutionarily conserved domains of SUR2A, and neither mutation was present in unrelated control individuals.[21]

The identified missense and frameshift mutations were mapped to domains bordering the catalytic ATPase pocket within SUR2A. Structural molecular dynamics simulation showed that residues A1513 and L1524 flank the C-terminal β-strand in close proximity to the signature Walker A motif, required for coordination of nucleotides in the catalytic pocket of ATP-binding cassette proteins.[21] Replacement of A1513 with a sterically larger and more hydrophilic threonine residue or truncation of the C terminus caused by the fs1524 mutation would disrupt folding of the C-terminal β-strand and, thus, the tertiary organization of the adjacent second nucleotide binding domain (NBD2) pocket in SUR2A (Fig. 2). Indeed, ATP-induced K_{ATP} channel gating was aberrant in channel mutants, suggesting that structural alterations induced by the mutations A1513T and fs1524 of SUR2A distorted ATP-dependent pore regulation.[21] Thus, the mutations A1513T and fs1524 compromise ATP hydrolysis at SUR2A NBD2, generating distinct reaction kinetic defects. Aberrant catalytic properties in the A1513T and fs1524 mutants translated into abnormal interconversion of discrete conformations in the NBD2 ATPase cycle. Alterations in hydrolysis-driven SUR2A conformational probability induced by A1513T and fs1524 perturbed intrinsic catalytic properties of the SUR2A ATPase, compromising proper translation of cellular energetic signals into K_{ATP} channel-mediated membrane electrical events. Traditionally linked to defects in ligand interaction, subunit trafficking or pore conductance, human cardiac K_{ATP} channel dysfunction provoked by alterations in the catalytic module of the channel complex establishes a new mechanism for channelopathy.

Risk factor for cardiac remodeling

Susceptibility or resistance to heart failure, despite apparently similar risk load, is attributable to individual variation in homeostatic reserve. Following identification of mutations within a K_{ATP} channel gene in patients with dilated cardiomyopathy,[21] the relationship between the common Kir6.2 E23K polymorphism (rs5219) and subclinical heart disease was investigated (Fig. 2).[23] A community-based cross-sectional cohort of 2,031 predominantly Caucasian adults was utilized, for which detailed clinical and prospective echocardiographic data were available. Genotype frequencies were in Hardy–Weinberg equilibrium (EE = 44%; EK = 47%; KK = 9%) and similar to previously reported control populations. In the group at large, there was no significant association between genotypes and measures of cardiac structure/function (left ventricular dimensions, mass, and ejection fraction), electrical instability (atrial and ventricular arrhythmias), or metabolism (fasting glucose, diabetes, and body mass index) at enrollment. However, among individuals with documented hypertension at the time of echocardiography (n = 1,187), the KK genotype was significantly associated with greater left ventricular dimension and volume in both diastole and systole.[23] A synergistic effect on left ventricular size of KK genotype and left ventricular mass, a marker of chronic cardiac stress load, further validated the impact of Kir6.2 E23K on cardiac structure in hypertension. From a public health perspective, hypertension is the most common risk factor for congestive heart failure, and left ventricular enlargement is an established precursor of symptomatic ventricular dysfunction. The Kir6.2 K23 allele, present in over half the population, is thus implicated as a risk factor for transition from hypertensive stress load to subclinical maladaptive cardiac remodeling.[23] These findings, consistent with previous human and animal studies,[19,76] uncover an interactive K_{ATP} channel gene-environment substrate that confers cardiac disease risk. Determining the overall impact of Kir6.2 E23K across ethnic groups and on long-term

clinical outcome, i.e., progression to left ventricular enlargement and clinical heart failure, will require further study.

Biomarker for impaired stress performance

The translational significance of the Kir6.2 E23K polymorphism in human cardiac physiology was more recently explored in a cohort of patients with heart failure who underwent comprehensive exercise stress testing.[22] The frequency of the minor K23 allele was found over-represented in the 115 subjects with congestive heart failure compared to the 2,031 community-based controls described above (69 vs. 56%, $P < 0.001$). Moreover, the KK genotype, present in 18% of heart failure patients, was associated with abnormal cardiopulmonary exercise stress test results.[22] In spite of similar baseline heart rates at rest among genotypic subgroups, subjects with the KK genotype had a significantly reduced heart rate increase at matched workloads. Molecular modeling of the tetrameric Kir6.2 pore structure revealed the E23 residue within the functionally relevant intracellular slide helix region.[22] Substitution of the wild-type E residue with an oppositely charged, bulkier K residue would potentially result in a significant structural rearrangement and disrupted interactions with neighboring Kir6.2 subunits, providing a basis for altered high-fidelity K_{ATP} channel gating, particularly in the homozygous state. Blunted heart rate response during exercise is a risk factor for mortality in patients with heart failure, establishing the clinical relevance of Kir6.2 E23K as a biomarker for impaired performance under exercise stress underscoring the essential role of K_{ATP} channels in human cardiac physiology.[22]

Association with myocardial infarction

Experimental evidence has also suggested that K_{ATP} channels could be involved in the pathogenesis of coronary vasomotor dysfunction and ischemic heart disease.[96,97] The potential clinical significance of such a premise was documented in a cohort of patients with myocardial infarction at an early age, whereby a rare missense variant V734I in the *ABCC9* SUR2A K_{ATP} channel gene was found overepresented (Fig. 2).[98] Statistical significance was demonstrated after controlling for multiple established risk factors for coronary artery disease.[98]

Summary

Deficient cellular energetics set by aberrant K_{ATP} channel function is increasingly implicated in a spectrum of conditions underlying metabolic imbalance and electrical instability.[5] Indeed, cardiac K_{ATP} channelopathies are emerging as a recognized disease entity underlying heart failure and arrhythmia.[19] Understanding the molecular structure and function of K_{ATP} channel subunits,[8] and their relationship to cellular metabolic signaling,[99] has been instrumental in interpreting the pathophysiology of channel malfunction associated with heart disease predisposition (Fig. 3).[12] From individual patients to populations, variants in K_{ATP} channel genes have now been documented in human dilated cardiomyopathy[21], atrial fibrillation,[20] and as risk factors for electrical instability,[93,94] adverse cardiac remodeling,[23] impaired performance under stress[22] or myocardial infarction.[98] Beyond the initial deciphering of genotype-phenotype relationships, development and application of high-throughput platforms to screen for disrupted coding and/or regulatory sequences in cardioprotective K_{ATP} channel genes, as well as diagnose corrupted interactions within the cellular milieu, would advance current knowledge regarding this homeostatic channel complex and its implications in cardiovascular medicine. In particular, deconvolution of altered metabolic pathways and signaling cascades associated with pathogenic K_{ATP} channel mutation may offer unique opportunities to pinpoint lesions that stratify the consequences of genetic variation on disease traits.[18] In this regard, it can be anticipated that systems biology and network medicine strategies will be increasingly deployed to resolve the K_{ATP} channel

interactome.[11] Mapping of the systems integration of molecules and their respective biological networks in health versus disease will, in turn, guide the judicious development of prognostic discriminators of disease variability and selection of treatment response predictors.[100-102] Advances in the molecular medicine of K_{ATP} channelopathies are thus poised to offer new perspectives in the diagnosis and therapy of individuals and populations.[103-107]

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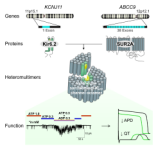

Figure 1. Structure and function of ventricular sarcolemmal K_{ATP} channel complexes

The pore-forming *KCNJ11*-encoded Kir6.2 subunit assembles with the regulatory *ABCC9*-encoded SUR2A protein to form heteromultimeric K_{ATP} channels abundantly expressed in the ventricular sarcolemma. The defining feature of K_{ATP} channel operation is adenine nucleotide-dependent gating, ensuring high-fidelity coupling between the cellular energetic state and membrane electrical activity. Intracellular ATP keeps K_{ATP} channels closed under normal conditions, while ADP promotes channel opening in response to metabolic challenge. K_{ATP} channel opening under stress translates into shortening of the cardiac action potential (↓APD) and accelerated repolarization (↓QT).

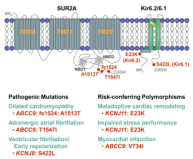

Figure 2. Pathogenic mutations and risk-conferring polymorphisms in K_{ATP} channel genes associated with human cardiac disorders

Topology of Kir6.2/Kir6.1 and SUR2A (with nucleotide binding domain NBD1/NBD2 and transmembrane domains TMD0-TMD1-TMD2) subunits, with mapped locations of variant sites underlying K_{ATP} channelopathies.

Figure 3. Advances in K_{ATP} channelopathies

Over the last three decades, science has increasingly defined K_{ATP} channel structure and function at molecular, cellular, organ and organism levels. Today, new knowledge in K_{ATP} channelopathies informs the practice of cardiovascular medicine expanding the understanding of cardioprotection in health and disease.