

Human K_{ATP} channelopathies: diseases of metabolic homeostasis

Timothy M. Olson · Andre Terzic

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Abstract Assembly of an inward rectifier K^+ channel pore (Kir6.1/Kir6.2) and an adenosine triphosphate (ATP)-binding regulatory subunit (SUR1/SUR2A/SUR2B) forms ATP-sensitive K^+ (K_{ATP}) channel heteromultimers, widely distributed in metabolically active tissues throughout the body. K_{ATP} channels are metabolism-gated biosensors functioning as molecular rheostats that adjust membrane potential-dependent functions to match cellular energetic demands. Vital in the adaptive response to (patho)physiological stress, K_{ATP} channels serve a homeostatic role ranging from glucose regulation to cardioprotection. Accordingly, genetic variation in K_{ATP} channel subunits has been linked to the etiology of life-threatening human diseases. In particular, pathogenic mutations in K_{ATP} channels have been identified in insulin secretion disorders, namely, congenital hyperinsulinism and neonatal diabetes. Moreover, K_{ATP} channel defects underlie the triad of developmental delay, epilepsy, and neonatal diabetes (DEND syndrome). K_{ATP} channelopathies implicated in patients with mechanical and/or electrical heart disease include dilated cardiomyopathy (with ventricular arrhythmia; CMD10) and adrenergic atrial fibrillation. A common Kir6.2 E23K polymorphism has

been associated with late-onset diabetes and as a risk factor for maladaptive cardiac remodeling in the community-at-large and abnormal cardiopulmonary exercise stress performance in patients with heart failure. The overall mutation frequency within K_{ATP} channel genes and the spectrum of genotype–phenotype relationships remain to be established, while predicting consequences of a deficit in channel function is becoming increasingly feasible through systems biology approaches. Thus, advances in molecular medicine in the emerging field of human K_{ATP} channelopathies offer new opportunities for targeted individualized screening, early diagnosis, and tailored therapy.

Keywords ATP-sensitive K^+ channels · *ABCC8* · *ABCC9* · *KNCJ8* · *KCNJ11* · E23K · Channelopathy · Genetics · Mutation · Polymorphism · Kir6.1 · Kir6.2 · SUR1 · SUR2A · SUR2B · Insulin · Diabetes · Disease · Atrial fibrillation · Cardiomyopathy · Heart failure

Throughout the lifespan, environmental challenges pose threats to organismal integrity [78, 108]. Decoding stress signals is vital to the initiation and execution of the adaptive response that secures stress tolerance and promotes evolutionary survival [23, 31]. To this end, molecular biosensors are essential in distress resolution, matching demand, and ensuring the safeguard of organ function [15, 132]. Failure to respond to stress load, in the context of a genetic defect and malfunction in sensor proteins, results in maladaptation and poor outcome highlighting the centrality of processes responsible for the maintenance of ecogenetic homeostasis in disease avoidance and species preservation [11, 83, 134]. A case in point, the adenosine triphosphate (ATP)-sensitive K^+ (K_{ATP}) channel—widely represented in metabolically active tissues throughout the body—controls

T. M. Olson · A. Terzic (✉)
Marriott Heart Disease Research Program, Division
of Cardiovascular Diseases, Department of Internal Medicine,
Department of Molecular Pharmacology & Experimental
Therapeutics, Department of Medical Genetics, Mayo Clinic,
200 First Street SW,
Rochester, MN 55905, USA
e-mail: terzic.andre@mayo.edu

T. M. Olson (✉)
Division of Pediatric Cardiology,
Department of Pediatric and Adolescent Medicine, Mayo Clinic,
200 First Street SW,
Rochester, MN 55905, USA
e-mail: olson.timothy@mayo.edu

energy expenditure [6] and serves as a molecular coordinator of metabolic well-being [133]. This homeostatic function identifies K_{ATP} channels in the hierarchy of molecular events underlying propagation of the general adaptation syndrome in both health and disease.

K_{ATP} channels: prototype biosensors

The K_{ATP} channel complex, a unique combination of an inward rectifier K^+ channel and an ATP-binding cassette protein, is a prototypic metabolism-gated biosensor [81, 84, 132]. K_{ATP} channels operate as high-fidelity molecular rheostats adjusting membrane potential-dependent functions to match cellular energetic demands [5, 117]. Under-scoring the critical role for K_{ATP} channels in coupling metabolic dynamics with transmembrane electrical activity is the emerging recognition that disruption of channel function is associated with increased susceptibility to a range of life-threatening diseases [10, 100, 125].

In humans, dysfunction in K_{ATP} channel gating has been most commonly linked to insulin secretory disorders (Table 1), namely, congenital hyperinsulinism and neonatal diabetes [11, 13, 36, 41, 74, 93, 119, 125]. Beyond isolated failure of pancreatic β -cells, mutations in *KCNJ11*, the gene encoding the pore-forming Kir6.2 subunit of K_{ATP} channels [3, 53], are also pathogenic in the developmental delay, epilepsy, and neonatal diabetes (DEND) syndrome (Table 1) [11, 42, 49, 95]. An even broader role in disease pathogenesis has been realized with the discovery of K_{ATP} channel malfunction in human myopathies. K_{ATP} channels have been reported essential in sustaining endurance [6, 26], and deficit in Kir6.2 of the skeletal muscle K_{ATP} channel has been reported in patients diagnosed with muscle weakness (Table 1), known as hypokalemic periodic paralysis [60, 121].

In the heart, Kir6.2 is integral in the make-up of myocellular K_{ATP} channels [54], and targeted disruption of *KCNJ11* generates a Kir6.2-deficient state characterized by lack of functional K_{ATP} channels in ventricular myocytes [112]. Intact Kir6.2 is required in cardiac adaptation to physiological and pathophysiological stressors [45, 63, 120, 127, 133, 134], and K_{ATP} channel malfunction has been implicated in the development and progression of heart disease in both model systems and in patients [51, 66]. In fact, K_{ATP} channels were originally discovered in cardiomyocytes [86] where they assemble as heteromultimers of the Kir6.2 pore and SUR2A, the regulatory ATP-binding cassette sulfonyleurea receptor subunit [20, 37, 54, 68, 76, 84]. Integrated with cellular metabolic pathways [1, 21, 33, 38, 59, 107], SUR2A contains nucleotide-binding domains and intrinsic ATPase activity, endowing this regulatory K_{ATP} channel subunit with the ability to process energetic

Table 1 Human disorders associated with genetic variation in K_{ATP} channel genes

Pathogenic mutations	
Congenital hyperinsulinism	
<i>ABCC8</i>	Hyperinsulinemic hypoglycemia, familial, 1; HHH1 (OMIM #256450)
<i>KCNJ11</i>	Hyperinsulinemic hypoglycemia, familial, 2; HHH2 (OMIM #601820)
Permanent neonatal diabetes (OMIM #606176)	
<i>ABCC8</i> and <i>KCNJ11</i>	Diabetes mellitus, permanent neonatal; PNDM
<i>KCNJ11</i>	DEND syndrome
Transient neonatal diabetes	
<i>ABCC8</i>	Diabetes mellitus, transient neonatal, 2; TNDM2 (OMIM #610374)
<i>KCNJ11</i>	Diabetes mellitus, transient neonatal, 3; TNDM3 (OMIM #610582)
Dilated cardiomyopathy	
<i>ABCC9</i>	Cardiomyopathy, dilated, 10; CMD10 (OMIM #608569)
Adrenergic atrial fibrillation	
<i>ABCC9</i>	
Risk-conferring <i>KCNJ11</i> /Kir6.2 E23K polymorphism	
Noninsulin-dependent diabetes mellitus (NIDDM; T2DM)	
KK genotype	Over-represented
Maladaptive cardiac remodeling	
KK genotype	Increased left ventricular size under hypertensive stress load
Heart failure	
KK genotype	Over-represented; blunted heart rate response to exercise

ABCC8 ATP-binding cassette, subfamily C, member 8 (*SUR1*); *ABCC9* ATP-binding cassette, subfamily C, member 9 (*SUR2*); *DEND* developmental delay, epilepsy, and neonatal diabetes; *KCNJ11* potassium channel, inwardly rectifying, subfamily J, member 11 (*Kir6.2*); *T2DM* adult-onset type 2 diabetes mellitus

signals of distress under conditions of increased workload [5, 16, 91, 131]. The tandem function of nucleotide-binding domains confers Kir6.2-gating competence to SUR2A [135], leading to regulation of pore opening in response to stress challenge [75, 84, 134]. A deficit in K_{ATP} channels impairs tolerance to sympathetic surge [134], endurance challenge [64], and hemodynamic load [63, 65, 127]. Genetic disruption of K_{ATP} channels compromises the protective benefits of ischemic preconditioning [46, 113], while overexpression of channel subunits generates a protective phenotype [35, 61, 62]. Mutations that perturb K_{ATP} channel proteins have been linked to increased susceptibility to cardiac pathology in humans. In particular,

dilated cardiomyopathy and adrenergic atrial fibrillation are now recognized as cardiac K_{ATP} channelopathies [17, 66, 89]. Thus, molecular medicine has advanced our understanding of K_{ATP} channels as conserved regulators of homeostasis [11, 84, 104, 132]. Recognizing the molecular basis of a K_{ATP} channelopathy provides opportunities for targeted individualized screening, early diagnosis, and tailored therapy to address the root cause of a malady.

Molecular identity of K_{ATP} channels

The biogenesis of K_{ATP} channel complexes expressed in the plasma membrane relies on co-assembly of the pore-forming subunit consisting of the inward rectifier K^+ channels, Kir6.2 or Kir6.1 [53], with the regulatory sulfonylurea receptors SUR1, SUR2A, or SUR2B, members of the ATP-binding-cassette transporter family [3]. The human Kir6.2 and Kir6.1 genes—*KCNJ11* and *KCNJ8*—map to chromosome bands 11p15.1 [53] and 12p11.23 [56], respectively. SUR genes, *SUR1* (or *ABCC8*) at locus 11p15.1 and *SUR2* (or *ABCC9*) at locus 12p12.1 [25, 119] each have 39 exons with the last two exons of SUR2 alternatively used as the terminal exon of the two main SUR2 isoforms, SUR2A and SUR2B [2].

K_{ATP} channels are obligatory heteromultimers, which adopt an octameric conformation demonstrated through functional analysis [27, 55, 111, 130] and validated by direct imaging [79] or quaternary structure resolution [92]. Stoichiometry is enforced by intracellular quality-control checkpoints that keep incomplete channel complexes from reaching the plasma membrane [125]. To this end, each Kir6 protein possesses a stretch of three residues, RKR, within the C-terminus, which acts as a retention signal [130]. Unless a SUR protein is bound to the Kir6 protein, this signal is exposed, keeping the channel protein from exiting the endoplasmic reticulum/Golgi network [125]. Substantial diversity among K_{ATP} channels has been reported given multiple possible octameric combinations. Yet, primary biophysical properties common to K_{ATP} channels include ion selectivity, rectification mediated through interaction with cytosolic multivalent cations, and the trademark inhibition by intracellular ATP imparted by the Kir6 protein. SUR confers the more complex physiological regulations, including gating by the cellular energetic state [125].

Adenine nucleotide modulation of channel function is a defining property of K_{ATP} channels. The interface between Kir6.2 subunits, constituted by residues from the N-terminal of one subunit and from the C-terminal of its neighbor [7, 34, 94], is critical for ATP-mediated pore inhibition. SUR-less Kir6.2 channels are blocked, non-cooperatively, by ATP. Association with SUR decreases the

IC_{50} by an order of magnitude [29]. Activation by intracellular adenosine diphosphate (ADP) is conferred by the SUR subunit and is essential to the function of K_{ATP} channels as metabolic sensors [85]. ADP, in the presence of Mg^{2+} , stimulates channel activity. It is thought that MgADP binds preferentially to the nucleotide NBD2 site within SUR [122], stabilizing a post-hydrolytic conformation of the SUR catalytic cycle associated with reduced ATP-induced channel inhibition and promotion of channel opening [131]. Activation requires Mg^{2+} and relies on the integrity of both NBD domains of SUR as it is abolished by mutations in the conserved folds of NBD1 or NBD2 [32, 44, 110, 135].

K_{ATP} channels in health

K_{ATP} channels are widely expressed in tissues of the body. They have been most characterized in pancreatic β -cells, skeletal muscle, and cardiac muscle, where they are present at high density [125]. They are also present less prominently in smooth muscle and brain. Functional measurements, tissue mRNA and protein expression data, and analyses of transgenic animal models have identified SUR1+Kir6.2, SUR2A+Kir6.2, SUR2B+Kir6.1, and SUR2B+Kir6.2 as the major β -cell, cardiac muscle, vascular smooth muscle nucleotide-diphosphate-dependent (K_{NDP}), and non-vascular smooth muscle channels, respectively [12, 53, 54, 57, 106, 126]. Neuronal K_{ATP} channels are predominantly SUR1+Kir6.2, although SUR2B+Kir6.1 and SUR2B+Kir6.2 are also found. K_{ATP} channel subunits have been reported as well within intracellular membranes [125]. This is the case for the pancreatic β -cell insulin secretory granules (Kir6.2 and SUR1) [90, 123] and nuclei [99], and the pancreatic acinar cell zymogen granules (Kir6.1) [69]. Moreover, the presence of SUR/Kir6 subunits in mitochondria further highlights the contribution of K_{ATP} channel-related structures in metabolic homeostasis [8, 47, 52, 109, 116].

K_{ATP} channels are involved in the maintenance of normoglycemia mediated by the pancreas and the central nervous system through complementary mechanisms [125]. The role of K_{ATP} channels is best understood in pancreatic β -cells that release insulin as a function of glucose levels [10, 11]. The SUR1+Kir6.2 K_{ATP} channels provide the dominant resting K^+ conductance and set the membrane potential in pancreatic β -cells. Glucose is shuttled in the cytosol by the GLUT-2 transporter, enters the glycolytic cycle, and triggers ATP production from ADP. When plasma glucose levels increase, the concomitant increase in ATP (a Kir6.2 inhibitor) and decrease in ADP (a SUR1 activator) lower K_{ATP} channel activity and depolarize the membrane [125]. Depolarization triggers action potential trains during which voltage-dependent L-type Ca^{2+} chan-

nels open, increasing internal Ca^{2+} and initiating exocytosis of granules comprised of insulin-zinc co-crystals [125]. Zinc is a potent activator of SUR1+Kir6.2 channels, and its release could provide a negative feedback mechanism to limit excessive insulin secretion [97]. Leptin, the product of the obese (*ob*) gene, activates K_{ATP} channels [70] possibly through phospholipid-dependent cytoskeleton disruption [48]. The metabolic-sensing capacities of K_{ATP} channels are also used by the brain to titrate glucose levels. In severe hypoglycemia, food intake is stimulated, and secretion of counter-regulatory hormones like glucagon is augmented under autonomic input [114]. This response is initiated in hypothalamic glucose-responsive neurons where K_{ATP} channels, as in β -cells, couple glucose levels to electrical activity [80].

K_{ATP} channels regulate vascular tone, and thereby the delivery of metabolic resources to match demand [28]. This is accomplished by K_{ATP} channel-dependent membrane hyperpolarization, causing reduction in Ca^{2+} influx through voltage-gated Ca^{2+} channels and intracellular Ca^{2+} mobilization in smooth muscle [98]. Knockout of K_{ATP} channel subunits promotes vasospasm and hypertension [24, 82]. Conversely, activation of K_{ATP} channels controls blood pressure under conditions of systemic hypertension [58].

Myocardial K_{ATP} channels function as high-fidelity metabolic sensors through tight integration with the cellular energetic network [5]. This vital function is facilitated via phosphotransfer enzyme-mediated transmission of controllable energetic signals [107]. By virtue of cellular energetic network coupling and metabolic signal decoding, K_{ATP} channels set membrane excitability to match energy demand [1, 21]. K_{ATP} channels serve a cardioprotective role against ischemia through channel-mediated shortening of the cardiac action potential and control of potentially deleterious calcium influx into the cytosol [45, 84]. Sarcolemmal K_{ATP} channel activation is responsible for the electrical current that underlies the characteristic ST-segment elevation of transmural ischemic injury [73] and has been implicated in the endogenous protective mechanism of ischemic preconditioning [46, 113]. Genetic ablation of the metabolic-sensing K_{ATP} channel disrupts the integrated homeostatic mechanism required in maintaining energetic myocardial stability under ischemic stress [66]. More recent experimental data support a wider interpretation of this channel as a guarantor of metabolic and ionic homeostasis to diverse stressors [66, 133]. K_{ATP} channels, harnessing the ability to recognize alterations in the metabolic state of the cell and translate this information into changes in membrane excitability, provide the link necessary for maintaining cellular well-being in the face of stress-induced energy-demanding augmentation in performance. Conditions of sympathomimetic challenge [75, 134], physical exertion [6, 64], mineralocorticoid-induced

hypertension [63, 136], transverse aortic banding [9, 127, 128], and septic shock [65] result in cardiac decompensation in the absence of myocardial K_{ATP} channel-mediated protection. Moreover, stress challenge is pro-arrhythmic in the K_{ATP} channel-deficient myocardium provoking early afterdepolarizations, triggered activity, and ventricular dysrhythmia [75].

K_{ATP} channels in disorders of insulin secretion

Diseases of glucose handling that arise from mutations in *KCNJ11* and *ABCC8*, the genes encoding the Kir6.2 and SUR1 subunits of the pancreatic K_{ATP} channel, respectively, are well documented [42, 125] (Table 1). Loss-of-function mutations are the most common cause of the rare disease hyperinsulinemia of infancy (HI), also known as persistent hyperinsulinemic hypoglycemia of infancy (PHHI) or congenital hyperinsulinism (CHI). Mutations in *ABCC8* (SUR1) are the most frequent cause of HI and are responsible for familial hyperinsulinemic hypoglycemia type 1 (HHF1, OMIM #256450) [10]. Class I mutations reduce the number of channels at the plasma membrane by disrupting a step (e.g., synthesis, addressing, and trafficking) in biogenesis of the channel complex, whereas class II mutations reduce the open probability of correctly formed and localized channels mainly by abrogating MgADP activation [10, 85]. Mutations in *KCNJ11* (Kir6.2), a less frequent cause of HI, also result in lower channel activity recognized in familial hyperinsulinemic hypoglycemia type 2 (HHF2, OMIM #601820) [10]. In rare HI cases where channels remain functional and responsive to K_{ATP} channel openers, pharmacological treatment with diazoxide-type openers may partially restore channel activity and reduce insulin release [36]. Sulfonylureas can also act as chemical chaperones and correct trafficking deficiencies of SUR1 mutants [129]. Gain-of-function mutations tend to keep channels open, hyperpolarize β -cells, and reduce insulin secretion [41]. These mutations are responsible for rare forms of diabetes mellitus in neonates (NDM, OMIM #606176). In these conditions, channels are overactive, and normal activity can be restored with sulfonylurea blockers [72]. NDM mutations cluster near the presumed ATP-binding site of Kir6.2 and reduce the apparent blocking affinity of ATP [10]. Functionally equivalent mutations in SUR1 have also been identified [13, 96]. Clinical severity correlates with the magnitude of shift in ATP affinity and ranges from mild, in the case of transient NDM, to severe, for permanent NDM. The later can lead to developmental and neurological complications and the syndrome of DEND. Clarification of the molecular etiology has led to refinement of pharmacogenomic approaches for individualized patient care [93, 104]. Specifically, therapeutic

management has changed from insulin injections to better-suited oral sulfonylureas. There are also indications that K_{ATP} channel gene single nucleotide polymorphisms are associated with the widespread adult-onset type 2 diabetes (T2DM). In particular, although this has been disputed, the K allele of the common E23K Kir6.2 gene variant (c.67G>A; rs5219) has been linked to increased T2DM susceptibility [43, 71]. Functional studies have revealed that K23 increased channel open probability, leading to a slightly reduced sensitivity to inhibition by ATP [105] and abnormal gating by long chain acyl CoA esters [103].

Atrial fibrillation: a K_{ATP} channelopathy

Atrial fibrillation is an electrical disorder characterized by chaotic atrial activation, defined on the electrocardiogram as replacement of sinus P waves by rapid oscillations or fibrillatory waves associated with an irregular ventricular response. A growing epidemic in the aging population with structural heart disease, atrial fibrillation also presents as an earlier-onset, apparently idiopathic (lone) condition in a subset of patients and is increasingly recognized as a heritable disorder [30, 39] attributable to monogenic defects. The paradigm of a genetic 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 [40, 77]. In these cases, channel malfunction creates an arrhythmogenic milieu of re-entry or triggered activity caused by reduced electrical refractoriness or after-depolarization, respectively. A case in point was the identification of a loss-of-function mutation in *KCNA5*, encoding the voltage-dependent Kv1.5 channel [88]. In contrast to initially identified mechanisms for channelopathy-based atrial fibrillation, predicted to shorten action potential duration and cause proarrhythmogenic reduction in refractory period [22, 40], Kv1.5 channelopathy provided an alternative mechanism for atrial fibrillation. Namely, increased propensity for prolongation of action potential duration provides a substrate for triggered activity in the human atrium.

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 [89] (Table 1). The mutation was identified in a middle-aged patient with long-standing atrial fibrillation in the absence of identifiable risk factors, which was 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

[89]. 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 venoatrial 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.

Molecular genetic investigation demonstrated a missense mutation in *ABCC9*, encoding the regulatory subunit of cardiac K_{ATP} channels [89] (Table 1). 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.

Patch-clamp recording demonstrated that the T1547I substitution compromised adenine nucleotide-dependent induction of K_{ATP} channel current [89]. Mutant T1547I SUR2A, coexpressed with the *KCNJ11*-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. 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 previously unrecognized 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 [89]. 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.

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 [14, 19]. Moreover, metabolic and mechanosensitive gating of K_{ATP} channels [118] might become compromised with structural heart disease and atrial dilation, precipitating suboptimal repolarization reserve, and providing a substrate for the more common acquired form of atrial fibrillation.

Dilated cardiomyopathy with tachycardia (CMD10): a ventricular K_{ATP} channelopathy

Cardiomyopathy is an intrinsic, progressive disorder of the myocardium with a spectrum of underlying pathological presentations, resulting in impaired function of the heart as a circulatory pump and increased propensity to electrical instability. The clinical entity of dilated cardiomyopathy is characterized by ventricular dilation and reduced contractile function, precipitating congestive heart failure, arrhythmia, and death. Age-dependent onset of symptoms typically portends advanced myocardial disease and end-stage organ failure, accounting for dilated cardiomyopathy as the most common indication for cardiac transplantation [115]. Idiopathic dilated cardiomyopathy is increasingly recognized as a heritable disorder, exhibiting Mendelian inheritance in 25–50% of cases [87]. This has provided the impetus for human genetics investigations to uncover the molecular basis and corrupted pathways in disease and ultimately improves prediction, prevention, and treatment for each individual patient [125]. Advances in high-throughput DNA analysis applied to phenotypically well-characterized patient cohorts, families, and populations have led to discovery of mutations in over 25 distinct genes linked to the pathobiology of dilated cardiomyopathy [4, 50]. The ontological spectrum of dilated cardiomyopathy-associated mutant gene products has encompassed the fundamental components of excitation-contraction coupling such as contractile, cytoskeletal, and myocellular ion regulatory proteins. More recently, human molecular genetic studies have linked K_{ATP} channel defects and aberrant homeostatic stress response in the pathogenesis

of the disease. These defects, identified in the regulatory K_{ATP} channel subunit, disrupt catalysis-dependent gating and impair metabolic decoding, establishing a previously unrecognized mechanism of channel malfunction in human cardiomyopathy.

The cardiomyopathic-arrhythmia syndrome characterized by the triad of dilated cardiomyopathy, ventricular arrhythmia, and *ABCC9* K_{ATP} channel mutations has been designated CMD10 (OMIM #608569; Table 1). This entity was reported in middle-aged patients with marked left ventricular enlargement, severe systolic dysfunction, and ventricular tachycardia [17]. 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). 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 [17] (Table 1).

The identified missense and frameshift mutations were mapped to domains bordering the catalytic ATPase pocket within SUR2A. Structural molecular dynamics simulation showed that the 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 [17]. 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. 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 [17]. 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. Indeed, salient phenotypic traits of malignant dilated cardiomyopathy are reproduced in K_{ATP} channel knockout models under imposed stress load [127] and rescued following stem cell therapy [128].

K_{ATP} channel polymorphism predisposes to altered cardiac structure and function

Susceptibility or resistance to heart failure, despite apparently similar risk load, is attributable to individual variation in homeostatic reserve [18]. Following identification of mutations within a K_{ATP} channel gene in patients with dilated cardiomyopathy [17], the relationship between the common Kir6.2 E23K polymorphism (rs5219) and subclinical heart disease was investigated [102] (Table 1). 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 [103]. 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. 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 [67, 124]. 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. These findings, consistent with previous human and animal studies [63, 89], 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.

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 [101] (Table 1). 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 testing. 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 [101]. 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 stress performance and underscoring the essential role of K_{ATP} channels in human cardiac physiology.

Systems biology and K_{ATP} channels: role in predictive medicine

Beyond discrete molecular defects underlying disease pathobiology, the modern approaches of systems biology and network medicine enable comprehensive resolution of proximal and distal interactive pathways on a global scale. Decoding maladaptive signatures prior to onset of overt disease permits a rational forecast of individual susceptibility. Indeed, the tenets of predictive medicine offer a paradigm shift from managing symptoms toward proactive interventions tailored to prevent disease progression or even cure the root cause of disease.

To this end, subclinical signatures predictive of heart disease manifestation have been most recently unmasked in a model system of K_{ATP} channel deficit using an unbiased profiling approach for large-scale identification [9, 136]. Although K_{ATP} channel coupling with cellular metabolism is known to contribute to stress tolerance, a broader understanding of the channel's relationship with the intracellular milieu and its implication on disease predisposition was revealed through high-throughput proteomic cartography and network analysis. In the absence of stress, ontological annotation stratified the K_{ATP} channel-

dependent protein cohort into a predominant bioenergetic module, with additional focused sets ranging from signaling molecules, oxidoreductases, chaperones, to proteins involved in catabolism, cytostructure, transcription, and translation. Protein interaction mapping, in conjunction with expression level changes, localized a K_{ATP} channel-associated subproteome within a non-stochastic scale-free network. Global assessment of the K_{ATP} channel-deficient environment demonstrated a primary impact on metabolic pathways and revealed overrepresentation of markers associated with cardiovascular disease at an otherwise asymptomatic state [9].

Experimental imposition of stress precipitated exaggerated structural and functional myocardial defects in the K_{ATP} channel knockout, decreasing survivorship and validating the forecast of disease susceptibility [9]. Further iterative systems interrogation of the proteomic web extracted from K_{ATP} channel knockouts under stress prioritized adverse outcomes, exposing cardiomyopathic traits [136]. Phenotyping documented aggravated myocardial contractile performance, massive interstitial fibrosis, and exaggerated left ventricular size, all prognostic indices of poor outcome. Proteomic profiling-enabled bioinformatic forecasting is thus a powerful tool to predict the consequences of a deficit in K_{ATP} channel function.

Conclusions

Much progress has been made in the understanding of the structure and function of K_{ATP} channels catalyzing the most recent advances in molecular medicine that increasingly recognized the vital homeostatic role of this metabolic sensor in health and disease. Indeed, life-threatening human conditions ranging from disorders of insulin secretion to cardiomyopathies are now classified as bona fide K_{ATP} channelopathies. Future research will be required to determine the overall mutation frequency within K_{ATP} channel genes and the spectrum of genotype–phenotype relationships in individual patients and populations. Beyond constitutive K_{ATP} channel subunits, patient stratification and forecast of outcome in the setting of K_{ATP} channel dysfunction will facilitate a personalized approach to diagnosis and individualized management.

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