# Adenosine triphosphate-sensitive potassium channels and cardiomyopathies (Review)

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**Abstract.** Cardiomyopathies have been indicated to be one of the leading causes of heart failure. Though it was indicated that genetic defects, viral infection and trace element deficiency were among the causes of cardiomyopathy, the etiology has remained to be fully elucidated. Cardiomyocytes require large amounts of energy to maintain their normal biological functions. Adenosine triphosphate-sensitive potassium channels ($K_{ATP}$), composed of inward-rectifier potassium ion channel and sulfonylurea receptor subunits, are present on the cell surface and mitochondrial membrane of cardiac muscle cells. As metabolic sensors sensitive to changes in intracellular energy levels, $K_{ATP}$ adapt electrical activities to metabolic challenges, maintaining normal biological functions of myocytes. It is implied that malfunctions, mutations and altered expression of $K_{ATP}$ are associated with the pathogenesis of conditions including c hypertrophy, diabetes as well as dilated, ischemic and endemic cardiomyopathy. However, the current knowledge is only the tip of the iceberg and the roles of $K_{ATP}$ in cardiomyopathies largely remain to be elucidated in future studies.

## Contents



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## 1. Introduction

Adenosine triphosphate-sensitive potassium channels ($K_{ATP}$), which are distributed throughout the body in tissue types including smooth muscle, brain, skeletal muscle and cardiac muscle, have been known for decades (1). The basic biological function of $K_{ATP}$ is to adjust cell activities to the metabolic status, and $K_{ATP}$ is situated at the crosstalk site between cell metabolism and membrane excitability. When encountering insufficient energy levels, the inwardly rectifying potassium channels of $K_{ATP}$ are activated by nucleotides in the presence of magnesium ions. Opening of the channels would result in hyperpolarization of the membrane, which was found to be cytoprotective under various pathophysiological conditions. Cardiomyopathy is among one of the leading causes of deterioration of cardiac function and even heart failure; however, to date, knowledge regarding the etiology and underlying mechanisms has remained limited. As cardiomyopathies are associated with metabolic disorders, studies on $K_{ATP}$ may provide novel basic knowledge and treatment strategies for cardiomyopathies. The present review briefly summarized the functions of $K_{ATP}$ with a focus on the current understanding of its role in cardiomyopathies.

## 2. Molecular structural properties of $K_{ATP}$

$K_{ATP}$ is generally accepted as a hetero-octameric complex composed of inward-rectifier potassium ion channel (Kir)6 and sulfonylurea receptor (SUR) subunits. Kir6 is a pore-forming unit, and is encoded by the *KCNJ8* (for Kir6.1) (2) and *KCNJ11* (for Kir6.2) genes (3). The regulatory SUR subunits belong to the family of the ATP binding cassette (ABC), which are encoded by genes including *ABCC8* (for SUR1) and *ABCC9* (for SUR2) (4). Post-transcriptional modification by RNA splicing generates mainly two molecular variants of SUR, namely SUR2A and SUR2B, whose biophysiological characteristics vary distinctly (5,6).

Biochemical and physiological studies suggested that the normal functional $K_{ATP}$ is supported and maintained by a 4:4 stoichiometric co-assembly of Kir6.2 and SUR1, or Kir6.2 and SUR2A (SUR2B) subunits (7,8). This octamer arrangement

implies that the genes of Kir and SUR may be co-regulated (9). Indeed, it was found that *KCNJ11* and *ABCC8* share neighboring locations on human chromosome 11p15.1 (10); similarly, *KCNJ8* and *ABCC9* were located on human chromosome 12p12.1 adjacently (11).

The understanding of the structure of $K_{ATP}$ is mainly based on crystallographic studies on bacteria and eukaryotic cells (12). It was demonstrated that the main structure of the Kir channel was composed of two transmembrane M1 and M2 helices, which were connected by a bridge-like loop, favoring ion selection control and the generation of a narrow porous architecture (13). TMD1 and TMD2, which are six-helix transmembrane domains, put up the primary structure of the SUR sub-units (14). An accessory five-helix transmembrane TMD0 domain was found at the N-terminus of SURs, having a role in gating and trafficking of the Kir6 sub-unit (15). Between TMD1 and TMD2, nucleotide binding fold (NBF), comprising NBF1 and NBF2, was identified in previous studies (16). An octameric structure composed of four Kir6.x and four SUR subunits was proposed (17); however, the specific physical contact, connection and interaction of the sub-units have remained to be fully elucidated.

## 3. Biological function and regulation of $K_{ATP}$

The signature sequence of potassium ion ($K^+$) channels, which is ubiquitous among the $K^+$ channel family, is highly conserved in Kir sub-units, eliciting $K^+$-selective properties (18). Rapid and reversible closure and activation accommodating to the metabolic status is the characteristic biological property of $K_{ATP}$ (19). In the presence of ATP, non-hydrolysable ATP analogues or even adenosine diphosphate (ADP) with the absence of magnesium ions ($Mg^{2+}$), the channel activity is blocked and the channel is closed (20,21), suggesting that the inactivation of $K_{ATP}$ does not rely on phosphorylation and the binding relies on the gamma-phosphate of the ATP molecule (22). A binding pocket is formed by the C- and N-termini residues in the plasma with three-dimensional folding (23,24). There are four binding pockets for the octameric structure - one for each channel at each kir6 sub-unit (25,26). Channel gating and ATP binding are linked via a helical structure, which was proposed to lie parallel to the interface of the membrane (27). The location of the contact point was suggested at the junction of the inner helix bundle (28,29) (Fig. 1).

The SUR sub-unit regulates $K_{ATP}$ activity by interacting with $Mg^{2+}$ adenosine nucleotides: ATP and ADP stimulate channel opening in the presence of $Mg^{2+}$, while the nucleotides deactivate channel activity in the absence of $Mg^{2+}$ (30). In the cytoplasm, composed of nucleotide-binding motifs, the NBFs (NBF1 and NBF2) have the main regulatory effect on $K_{ATP}$ function. It was suggested that the dimerization of two NBFs was required for $Mg^{2+}$-dependent ATP hydrolysis by SUR (31). The inhibition induced by ATP on the Kir6 sub-unit may be overcome by the hydrolytic activity of dimeric NBFs on ATP in the presence of $Mg^{2+}$ (32). These regulatory effects of SUR on Kir6 gating are supported by a connecting structure named L0 linker, which is situated between the SUR TMD0 domain and the Kir6.2 cytoplasmic N-terminus (33).

Briefly, $K_{ATP}$ regulation is characterized by fast and reversible deactivation and closure induced by cytoplasmic nucleotide diphosphates and triphosphates. In intact cells, the $K_{ATP}$ is almost permanently inhibited by ATP, whose concentration is steadily maintained at a millimolar level (1-5 mmol/l), even while the cells undergo metabolic changes (34). Under such circumstance, by interaction with the SUR subunit, the channel is effectively activated by exogenous $Mg^{2+}$ nucleotides, particularly MgADP (19). Nucleotide regulation is currently considered the key mechanism in controlling $K_{ATP}$ opening, though several other regulators were also proposed in certain $K_{ATP}$-associated diseases.

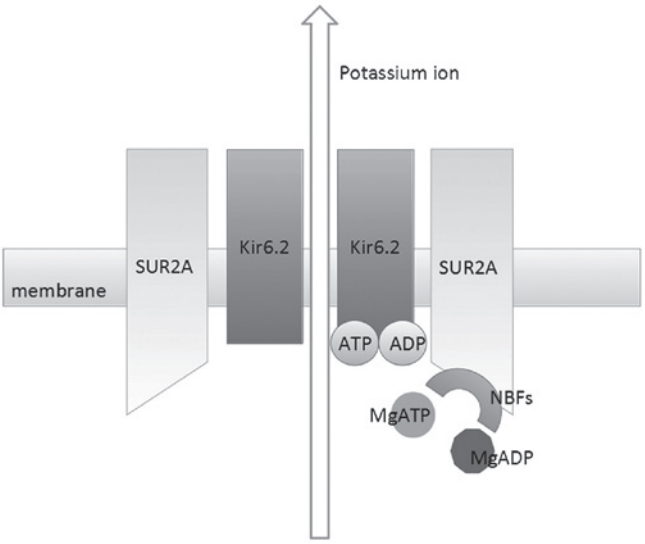


Figure 1. Schematic demonstration of the molecular structure and function of cardiac $K_{ATP}$ channels. 4 Kir6.2 subunits and 4 SUR2A subunits constitute the heterooctameric complex. $K_{ATP}$ activity is inhibited by ATP by direct binding to Kir6.2. In the absence of magnesium ions, ADP also inhibits channel activity even with lower binding affinity to Kir6.2. However, in the presence of magnesium ions, cytoplasmic ADP and ATP serve to stimulate channel activity by binding to NBF domains, which are located on SUR2A subunits. ATP, adenosine triphosphate; ADP, adenosine diphosphate; $K_{ATP}$, ATP-sensitive potassium channels; NBF, nucleotide binding fold; Kir, inward-rectifier potassium ion channel; SUR, sulfonylurea receptor.

## 4. Distribution of $K_{ATP}$ in cardiac muscle

*$K_{ATP}$ in cardiac sarcolemma*. Previous studies confirmed that in hearts of rodents, SUR1 and Kir6.2 constitute atrial sarcolemmal $K_{ATP}$ (35), while ventricular sarcolemmal $K_{ATP}$ is mainly composed of SUR2A and Kir6.2 (36). Variants of SUR1 and SUR2A were identified in atrial as well as ventricular cardiac muscles in humans. Generally, under normal physiological conditions, the sarcolemmal $K_{ATP}$ remains a static status unless it encounters severe metabolic challenges, including anoxia, ischemia and metabolic toxic drugs (37,38). Activated sarcolemmal $K_{ATP}$ serves a cardioprotective role by inhibiting calcium overload, recovering contractility, preserving energy supply and stabilizing the membrane potential (39). Treatment with $K_{ATP}$ openers, such as diazoxide, resulted in a decrease in the incidence of arrhythmias, including tachycardia and ventricular fibrillation (40).

*$K_{ATP}$ in cardiac mitochondria*. Except for the sarcolemmal $K_{ATP}$, $K_{ATP}$ distributed in cardiac mitochondria (mito$K_{ATP}$) are also considered important in cardiac pathophysiology. To date,

the molecular composition of mito$K_{ATP}$ has remained elusive. It was proposed that the heterogenous integration of SUR1 and Kir6.1 properly represents the properties of mito$K_{ATP}$ (41); however, in Kir6.1 and Kir6.2 knockout animals, the activity of mito$K_{ATP}$ remained unaffected (42). Several studies have assessed the canonical composition of SUR and Kir6 molecules in the mito$K_{ATP}$ structure. In mitochondrial extracts, protein detected with anti-Kir6.1 antibody was proved not to be Kir6.1 by subsequent mass spectrometric analysis (43). In another study, an NBF1 domain, which was specifically localized to mitochondria, and the lack of a SUR2 sub-unit protein were identified in myocytes (44).

Unlike the indeterminacy of its structure, the basic function of mito$K_{ATP}$ is relatively clear in the heart, though it is not completely understood. Under stress induced by multiple stimuli, efficient energy transfer from mitochondria to cytosol is guaranteed by mito$K_{ATP}$ activation. Extrinsic stressful signals, including reactive oxygen species, transduced across the cytosol to the mitochondria, may induce the activation of mito$K_{ATP}$, whose opening would decrease opening of the mitochondrial permeability transition (MPT) pore, which would result in myocyte death (45).

## 5. $K_{ATP}$ and cardiomyopathies

Cardiomyopathy was defined by the World Health Organization as cardiac diseases accompanied by cardiac dysfunction. Dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy and secondary cardiomyopathy are accepted as types of cardiomyopathy. It is considered that energetic and metabolic disorders are involved in pathophysiological processes of cardiomyopathy, which is highly associated with cardiac $K_{ATP}$ as mentioned above.

*$K_{ATP}$ and HCM*. HCM is characterized by unexplained and asymmetric left ventricular hypertrophy without explicit causes and includes coronary heart disease, arterial stenosis, hypertension, valvular heart disease and further systemic diseases that induce left ventricular hypertrophy (46). Heart failure, sudden cardiac death (SCD) and stroke are the common clinical manifestations in patients with HCM, which is often diagnosed by echocardiography showing a maximal left ventricular wall thickness of ≥15 mm. Myocyte malalignment, myocyte hypertrophy and myocardial interstitial fibrosis are the main histological features of HCM (47).

Imbalances in energy metabolism were suggested to be the underlying cause of the occurrence and development of HCM, corresponding with mitochondrial dysfunction and biophysical disorganization in HCM. In response to energetic metabolic deficiency, myocyte hypertrophy may be the compensatory consequence. As $K_{ATP}$ are highly involved in energy metabolism, they may be implicated in HCM development (48).

Mechanistic assays using $K_{ATP}$ antagonists or activators were performed to testify the role of $K_{ATP}$ in HCM. Hypertrophic myocytes were acquired from spontaneously hypertensive rats (SHR) by Sodder *et al* (49). Trypsin, which was able to re-activate $K_{ATP}$, only increased $K_{ATP}$ channel activity by 29% in hypertrophic myocytes as opposed to 63% in the control, indicating that $K_{ATP}$ activity loss was involved in the pathogenesis of cardiac hypertrophy. In another study by Rajesh *et al* (50), ischemic pre-conditioning (IP) was demonstrated to have protective effects against supra-renal transverse abdominal aortic constriction-induced cardiac hypertrophy. 5-hydroxydecanoic acid (5-HD), a specific $K_{ATP}$ antagonist, was applied to animals after IP. The results showed that 5-HD pre-treatment impaired the protective effects of IP during sustained cardiac ischemia in hypertrophied hearts (50). In another study, the induction of hypertrophy in cultured ventricular myocytes by alpha1 adrenoceptor agonist phenylephrine (PE) was evidenced by increased cell size, elevated expression of myosin light chain-2 and atrial natriuretic peptide (51). Diazoxide, as one of the canonical mito$K_{ATP}$ openers, almost completely prevented the hypertrophic inductive effects of PE.

Numerous previous studies provided direct evidence for the protective role of $K_{ATP}$ in cardiac hypertrophy. By partial ligation of the ascending aorta, Yuan *et al* (52) created an animal model of left ventricular hypertrophy. Responsiveness of $K_{ATP}$ to ATP (exogenous as well as locally generated ATP) in isolated myocytes from hypertrophic hearts was found to be markedly decreased in a patch clamp assay (52). In a study investigating hearts from SUR2-knockout mice, a significantly greater heart size and ventricular mass were identified (53). Shimokawa *et al* (54) found that in endocardial cells isolated from hypertrophied hearts of SHR, the $K_{ATP}$ channel currents were significantly smaller and the time required to reach peak currents after the onset of $K_{ATP}$ channel opening was significantly longer than that in the control group. Furthermore, the dysfunctional $K_{ATP}$ failed to respond rapidly to exogenous ATP. These results indicated that biophysiologically dysfunctional $K_{ATP}$ may contribute to cardiac hypertrophy.

The possible underlying mechanisms of $K_{ATP}$ impairment and HCM were investigated by several studies. Heart hypertrophy was achieved in a rat model of pressure overload, which was achieved by abdominal aortic banding (55). A $K_{ATP}$ opener, iptakalim, was applied orally to rats, which reversed the deteriorating cardiac function hemodynamically and histologically, as well as the serum content of B-type natriuretic peptide. After $K_{ATP}$ activation, the potassium efflux facilitated calcium influx to increase calcium concentration, which activated endothelial nitric oxide synthase (eNOS) via the calcium-calmodulin pathway. eNOS then catalyzed the biological synthesis of endogenous NO. Thus, indirectly, the activation of $K_{ATP}$ led to the maintenance of cardiac function and hemodynamic homeostasis by modulation of NO production (55). In chronic transverse aortic constriction-induced cardiac hypertrophied $K_{ATP}$-disrupted rats, the expression of PPAR gamma co-activator-1 alpha (PGC-1alpha) was significantly decreased (56). It was thought that PGC-1alpha had an important role in regulating energetic metabolism through mitochondrial enzymes during exposure to cardiac pressure overload. The transcription of PGC-1 alpha was activated by phosphorylated forkhead box protein O1 (FOXO1), whose phosphorylation was reported to proceed through activation of Akt. In addition, it was observed that the $K_{ATP}$ channel dysfunction induced by SUR1 disruption and Kir6.2 knockout resulted in an overall decrease in FOXO1 expression (56). The study indicated that FOXO1/PGC-1alpha signaling was one of the possible mechanisms of sarcolemmal $K_{ATP}$-associated cardiac hypertrophy.

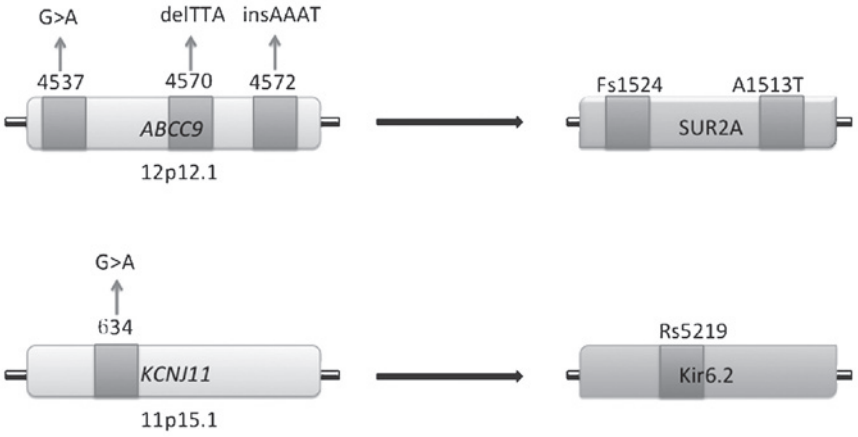


Figure 2. Mutations of $K_{ATP}$ sub-unit genes correlated with dilated cardiomyopathy. Mutations in *ABCC9* gene comprise a mis-sense mutation at site 4,537, a three-base pair deletion at site 4,572 and a four-base pair insertion mutation at site 4,570-4,572. These mutations lead to a frameshift at site 1,524 and amino acid substitution at site 1,513 of the SUR2A sub-unit. In the *KCNJ11* gene, a non-synonymous mutation at site 634 causes amino acid replacement at site 5,219 of the Kir6.2 sub-unit. Fs, frameshift; A, amino acid substitution; Rs, acid replacement; Kir, inward-rectifier potassium ion channel; SUR, sulfonylurea receptor.

*$K_{ATP}$ and dilated cardiomyopathy*. As another important type of cardiomyopathy, DCM is clinically characterized by ventricular dilation and impaired contractility, often leading to heart failure and SCD (3). As myocardial mass and volume increase, the ventricular wall often becomes thin and stretched (57). To date, the etiology of DCM has remained to be fully elucidated. DCM may occur secondary to heart diseases, including congenital heart disease, valvular heart disease, ischemic heart disease, viral myocarditis and Chagas disease (58). Of note, it is now widely accepted that DCM is highly genetic. Mutations of $K_{ATP}$-associated genes were confirmed to be involved in the etiology of DCM.

Bienengraeber *et al* (59) identified two mutations in the *ABCC9* gene encoding the $K_{ATP}$ sub-unit SUR2A by genomic DNA scanning in patients with dilated cardiomyopathy with tachycardia (DCM10). One mutation was described as a three-base pair deletion and a four-base pair insertion mutation (4,570-4,572delTTAinsAAAT), which introduced four abnormal terminal residues followed by a premature stop codon and caused a frameshift at Leu1524 (Fs1524) after translation. Another mutation was suggested as a missense mutation (4,537G>A), causing an A1,513T amino acid substitution as occurring at the C terminus of SUR2A and leading to a disruption of the normal organization of the NBD2 pocket. Reduced $K_{ATP}$ channel trafficking, aberrant $K_{ATP}$ channel gating and an anomalous intrinsic ATP hydrolysis cycle were observed when the SUR2 sub-unit was defective and co-expressed with the Kir6.2 sub-unit (59). Thus, the mediation between energetic and electrical signals by $K_{ATP}$ is impaired in DCM. Patients with the abovementioned genetic mutations may therefore be considered to have an increased susceptibility to DCM.

A study using Langendorff hearts extracted from patients diagnosed with DCM revealed that the expression of the Kir6 sub-unit (Kir6.1 as well as Kir6.2) changed correspondingly with that of the SUR sub-unit (SUR1 as well as SUR2A) in the endocardium and epicardium (60). This result indicated that the other sub-unit, Kir6, may also have a role as one of the etiological factors of DCM. The results of a study on *KCNJ11* gene knockout hearts exposed to hemodynamic overload showed that these hearts were more susceptible to maladaptive remodeling and congestive heart failure (59). When under imposed overload stress, *KCNJ11*-null mutant hearts were markedly dilated and inefficient regarding their contractility, sharing common features with CMD10 (61). Indeed, after the deficiency of Kir6.2 was compensated by embryonic stem cell therapy, the cardiac function was partially restored (62). Recently, *KCNJ11* gene mutation was also suggested to be one of the causes of DCM. A gene polymorphism called E23K, which is a non-synonymous mutation occurring at codon 23 of the *KCNJ11* gene (634G>A), led to the replacement of a glutamic acid residue by a lysine at this polymorphic site (rs5219) at the Kir6.2 sub-unit (63). By analyzing the blood of patients with DCM, Xi *et al* (64) discovered that this mutation was highly associated with the left ventricular end diastolic dimension (LVEDD) and left atrial dimension (LAD), which markedly increases in DCM (64) (Fig. 2).

## 6. $K_{ATP}$ and secondary cardiomyopathies

*$K_{ATP}$ and ischemic cardiomyopathy (ICM)*. Due to the high and increasing morbidity of coronary heart disease, ICM is now considered to be one of the most common underlying causes of heart failure in modern-day society (65). As a result of sustained myocardial ischemia, ICM is characterized by marked loss of contractile units in the myocardium. Ischemia and accompanied re-perfusion injury may lead to myocyte apoptosis and myocardial necrosis.

Several previous studies have examined the correlation between myocyte apoptosis and $K_{ATP}$ under ischemia/re-perfusion conditions. They posed the hypothesis that $K_{ATP}$ exerts its anti-apoptotic effects upon activation. Indeed, the role of $K_{ATP}$ in cellular calcium signal regulation may have a preventive effect against cardiac apoptosis (66). Calcium overload, which refers to the accumulation of calcium ions in the cell matrix, is one of the mechanisms triggering apoptosis. As the concentration of calcium ions rises in the mitochondria, the opening of the MPT pore becomes irreversible. Pro-apoptotic proteins, such as cytochrome C, are subsequently released to

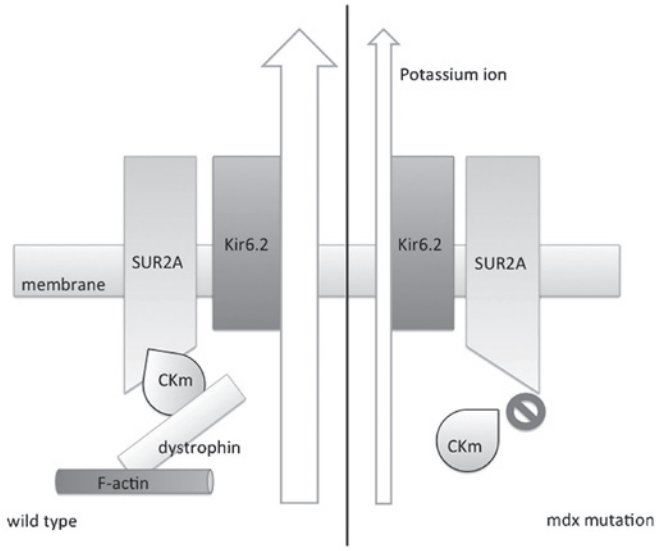


Figure 3. Possible mechanism of cardiomyopathy in Duchenne muscular dystrophy. The left part of the figure shows the activation of $K_{ATP}$ in the heart of normal controls. With the regulation of CKm, normal activity and function of $K_{ATP}$ are maintained. The right part of this figure shows the inhibition of $K_{ATP}$ in hearts of mdx-mutant mice deficient of dystrophin, probably leading to loss of activity of $K_{ATP}$. CKm, creatine kinase muscle isoform; Kir, inward-rectifier potassium ion channel; SUR, sulfonylurea receptor.

induce apoptosis. However, after being activated, $K_{ATP}$ opens to allow potassium ion influx into the cell matrix to depolarize the inner membrane, thus reducing the calcium uptake of the matrix (67).

Furthermore, previous studies implied that inflammation is involved in coronary artery disease and myocardial ischemia. During this process, inflammatory cytokines, including interleukin-1 (IL-1), IL-6 and tumor necrosis factor-alpha (TNF-alpha) were released (68). Through interacting with TNF receptors, TNF-alpha potently induced cell apoptosis through death receptor- or caspase cascade-mediated apoptotic pathways (69). Zhou *et al* (70) reported that the opening of $K_{ATP}$ reduced TNF-alpha production by inhibiting its downstream protein mitogen-activated protein kinase (70). Thus, the anti-apoptotic effects of cardiac $K_{ATP}$ in ICM may be based on its abilities to modulate inflammation.

*$K_{ATP}$ and cardiomyopathy in Duchenne muscular dystrophy (DMD).* It is generally accepted that DMD is an X-linked progressive neuromuscular disorder with the manifestation of generalized muscular weakness and wasting. Patients with DMD are often diagnosed at 6-8 years of age and die of respiratory or cardiac failure by the age of 30 years in most cases (71). The dystrophin gene, which is located at the short arm of the X chromosome at cytogenetic band 21 (Xp21), was suggested to be the leading cause of DMD. Mutations of this gene lead to the expression of mutant dystrophin protein within myofibers throughout all types of muscle cell, including smooth, skeletal and cardiac muscle cells. A lethal form of cardiomyopathy occurs in the majority of DMD patients, which is characterized by ventricular wall thickness reduction and cardiac chamber enlargement (72).

Graciotti *et al* (73) reported that cardiac $K_{ATP}$ has an important role in cardiomyopathy in DMD and proposed a possible regulatory mechanism. Importantly, the study reported that in myocytes from normal mice, $K_{ATP}$ sub-unit Kir6.2 and dystrophin were physically connected, sharing the same location on the t-tube. Furthermore, a metabolic enzyme, creatine kinase muscle isoform (CKm), which was described as a regulator of $K_{ATP}$ activity, was also in physical contact with dystrophin. In mdx mutant mice, which were deficient of the full length of dystrophin, CKm membrane localization was disrupted (73). This result suggested that dystrophyin may act as a scaffold allowing $K_{ATP}$ and its regulatory proteins to form a complex, coordinating metabolic regulation. Thus, when dystrophin was absent in DMD, loss of CKm interaction led to the disruption of its modulation of $K_{ATP}$ channel activity, resulting in a disability of $K_{ATP}$ in sensing the intracellular ATP concentration (Fig. 3).

*$K_{ATP}$ and diabetic cardiomyopathy (DbCM).* In patients with diabetes mellitus, almost every tissue type is affected by metabolic disorders, resulting in vital organ dysfunctions. It was reported that cardiovascular diseases take responsibility for ~65% of diabetes-associated mortality (74). Myocardial dysfunction occurring without evidence of any other primary heart disease, including coronary artery disease and valvular heart disease, is now generally defined as DbCM.

The association between diabetes and $K_{ATP}$ has been known for several years. Gloyn *et al* (75) launched a case-control study on 2,486 diabetes patients in the United Kingdom, showing that *KCNJ11* gene polymorphism E23K was associated with type 2 diabetes. In addition, in the Walker B motif of NBD2 of SUR sub-units, a mutation of the conserved glutamate catalytic residue (E1506) to lysine (E1506K) resulted in reduced $K_{ATP}$ channel activation in beta cells, which was detected in patients with neonatal diabetes. This mutation was therefore thought to be one of the causes of neonatal diabetes (76).

Based on these results, studies on $K_{ATP}$ in cardiomyocytes may be of potential significance to reveal the underlying mechanisms of DbCM. To date, only a few studies on this association are available; however, the results are of importance. Fancher *et al* (77) evaluated the function and expression of mito$K_{ATP}$ in the hearts of mice with type 1 diabetes. The expression of Kir6.1 and SUR1 was found decreased in interfibrillar mitochondria, while the expression of Kir6.1 was found to be reduced in sub-sarcolemmal mitochondria in diabetic rat hearts (77). Furthermore, the expression of Kir6.2 and SUR2A was significantly decreased in diabetic rats, which could be restored by correction of hyperglycemia. Of note, diazoxide, a $K_{ATP}$ opener, showed cardioprotective effects (78).

*$K_{ATP}$ and Keshan disease (KD).* KD initially drew attention in 1930s by its outbreak in Keshan County in northeast China. The heart is the primary target organ of KD (79). Enlarged heart, cardiac arrhythmia, cardiogenic shock and congestive heart failure are the clinical manifestations of KD. It was recognized as a form of cardiomyopathy, which was histologically characterized by multifocal necrosis and cardiac fibrosis (80). KD is endemic as it is limited to certain geographical areas and with seasonal variations. Though the etiology of KD still remains to be fully elucidated, selenium deficiency is considered the major cause, as selenium deficiency in local residents and food were significantly associated with the geographical distribution of KD (81).

A previous study by our group reported that cardiac function was significantly impaired in selenium-deficient rats (82). At the same time, the expression of the two sub-units of $K_{ATP}$, Kir6.2 and SUR2A, was inhibited in myocytes, accompanied by a decrease of glutathione peroxidase, which indicated the occurrence of oxidative stress (82). After introduction of oxidative stress, the activity of mito$K_{ATP}$ was upregulated according to a study by Pereira *et al* (83). They concluded that $K_{ATP}$ acted as a molecular sensor for oxidative stress, whose activation helped to reduce free-radical generation in the mitochondrial respiratory chain. However, the study did not continue to observe the activity of mito$K_{ATP}$ during sustained and severe oxidative stress, which may have induced significant mitochondrial dysfunction, and the activity and expression of mito$K_{ATP}$ may have been jeopardized under these conditions. Further study regarding oxidative stress, $K_{ATP}$ and cardiac dysfunction in KD is still required.

## 7. Summary and perspectives

As a mediator in cellular metabolism, $K_{ATP}$ couples the energetic status to the excitability of the cell membrane, sensing metabolic changes and leading to morphological changes as well as secondary signaling. $K_{ATP}$ channels are distributed in the cytosol and mitochondria of cardiomyocytes. As one of the leading causes of heart failure, cardiomyopathy is characterized by metabolic challenges, which could be alleviated by activation of $K_{ATP}$. Dysfunction and deficiency of cardiac $K_{ATP}$ were suggested to have important roles in primary cardiomyopathies, including hypertrophic cardiomyopathy and dilated cardiomyopathy, as well as secondary cardiomyopathies, including ischemic cardiomyopathy, diabetic cardiomyopathy, endemic cardiomyopathy and cardiomyopathy in Duchenne muscular dystrophy.

Due to the lack of sufficient knowledge regarding $K_{ATP}$ in cardiomyopathies, numerous questions remain: Do $K_{ATP}$ channels share unitary features in the occurrence and development of different types of cardiomyopathies? Are there any unique changes of $K_{ATP}$ specific for each type of cardiomyopathy? What are the polymorphisms of the gene encoding $K_{ATP}$ in other primary cardiomyopathies, including restrictive cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy? Is $K_{ATP}$ involved in gene-environmental interactions in endemic cardiomyopathies? To address these questions, further studies on $K_{ATP}$ in cardiomyopathies should be implemented in the future.

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