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Pulmonary Hypertension and ATP-sensitive Potassium Channels: Paradigms and Paradoxes

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The clinical picture and genetic basis of PH

Pulmonary Hypertension (PH) is a rare but progressive and devastating clinical problem, associated with 6.5 in 100,000 deaths and 131 per 100,000 hospitalizations in the United States of America in 2010[1,2]. PH can arise from a diverse range of etiologies, all of which lead to increased pulmonary arterial pressure. This elevated arterial pressure consequently increases right ventricular afterload and wall stress, which results in maladaptive cardiac remodeling, and ultimately right heart failure. Additional symptoms include dyspnea, fatigue, heart palpitations and lower limb edema. PH is classified into 5 groups by The World Health Organization[3]. Mechanistically precise sub-classification has been provided by continuing advances in clinical genetics, with mutations of multiple genes implicated in PH. This is most clearly evident for Group 1 disease, also often referred to as Pulmonary Arterial Hypertension (PAH), which can arise from mutations in multiple genes, amongst other causes. The most commonly associated gene, *BMPR2*, which encodes bone morphogenic protein receptor type 2 (a member of the TGFβ super family of receptors) is mutated in ~70% of patients with hereditary PAH[4–7]. Mutations are also found in other TGFβ super-family genes including *ALK1* and *ENG*[8], in addition to the gene encoding Smad9[9], a downstream effector of BMPR2 signalling, *GDF2*[10] – a BMPR2 ligand, and *CAV1*[11] which codes for caveolin-1 - a scaffolding protein capable of regulating TGFβ-SMAD signalling[12]. These genetic pathways present new potential therapeutic targets.

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None.

Decreased potassium channel activity has long been recognized as a potential pathological substrate for PH[13–16], and recent genetic evidence for decreased potassium (K^+) channel function in discrete subsets of PAH patients has been provided by the identification of loss-of-function (LoF) mutations in *KCNK3*, which encodes TASK-1[17,18], and in *ABCC8*[19], a regulatory subunit of ATP-sensitive (K_{ATP}) potassium channels. Curiously, pulmonary hypertension is also a common feature of the rare genetic disorder Cantu Syndrome[20–24], which arises from *gain*-of-function (GoF) mutations in the K_{ATP} channel subunit genes *KCNJ8* and *ABCC9*. This begs the question, how can both *decreased* and *increased* potassium channel activity in the cardiovascular system result in the same clinical endpoint?

K^+ channel loss of function in PAH

PAH is characterized by progressive vascular remodeling, involving endothelial proliferation and medial hyperplasia, which together result in narrowing of medium-to-small pulmonary arterioles and the formation of plexiform lesions in the most severe cases[25]. Potassium channel activity controls the membrane potential of vascular smooth muscle cells. Decreased K^+ conductance will result in membrane depolarization and activation of L-type voltage-gated calcium channels (LTCCs), calcium influx, cellular contraction, and ultimately vasoconstriction. In addition to this canonical role in regulating vascular tone, K^+ channel activity can also influence the balance of proliferation and apoptosis. For example, pharmacological activation or overexpression of voltage-gated potassium channels in pulmonary artery smooth muscle cells (PASMCs) increases apoptosis, whilst K^+ channel downregulation has the opposite effect[26–28]. Furthermore, mechanical forces in PASMCs during vasoconstriction also promote proliferation[13,29,30]. Therefore, K^+ channel activity can play distinct roles in determining vessel diameters, both by regulating vascular contractility and cellular growth.

Extensive studies have identified voltage-gated K^+ channels (most notably Kv1.5) as key regulators of PASMC excitability, and multiple stimuli associated with PAH, including hypoxia, anorexigenic drugs, serotonin (5-HT) and thromboxane A2 (TXA2) decrease PASMC Kv currents[13,16]. In addition, LoF mutations in the 2-pore domain potassium (K2P) channel TASK-1 (*KCNK3*), which is expressed in the lungs and regulates PASMC resting membrane potential, have recently been identified as causal factors in familial and idiopathic PAH pathogenesis[17,18,31–34]. This demonstrates that decreased K^+ currents are not a mere epiphenomenon during PAH development, and support the general hypotheses that (1) decreased K^+ conductance in PASMC can cause PAH and (2) that this could potentially arise from downregulation of multiple molecularly diverse K^+ channels.

LoF mutations in the K_{ATP} channel ABCC8 gene in PAH

ATP-senstive potassium (K_{ATP}) channels represent a sub-family of potassium channels that link metabolic state to electrical activity in tissues throughout the body. K_{ATP} channel activity in vascular tissues controls vascular tone and regulates systemic blood pressure[35,36]. Uniquely, K_{ATP} channels are assembled as octameric complexes of pore-forming (Kir6.1 or Kir6.2) subunits associated with regulatory SUR1 or SUR2 subunits (Fig. 1). SUR1 is encoded by *ABCC8*, located on human chromosome 11, immediately preceding the gene

encoding the Kir6.2 subunit (*KCNJ11*), whilst the paralogous *ABCC9* (SUR2) and *KCNJ8* (Kir6.1) gene pair are immediately adjacent to each other on chromosome 12. Several LoF mutations in *ABCC8* were recently identified in two cohorts of pediatric- and adult-onset PAH patients[19].This association is initially surprising for a number of reasons: First, Kir6.2/SUR1 channels are critical regulators of pancreatic β-cell excitability and LoF mutations in *ABCC8* are an established cause of congenital hyperinsulinism (CHI)[37], yet *ABCC8*-variant PAH patients do not exhibit, or report any history of, hyperinsulinism[19]. Second, extensive molecular characterization of K_{ATP} channels in smooth muscle and endothelial cells of various tissues in multiple species demonstrates a predominance of *ABCC9* (SUR2) expression, not *ABCC8* (SUR1) which is instead highly expressed in the pancreas and neurons[35,38–44].

Remarkably, four functionally-confirmed missense LoF mutations have been identified both in patients with either PAH or CHI, yet no patients have been reported with any clinical overlap between these pathologies[19]. Limited penetrance of disease-associated mutations is commonly observed in heritable PAH. This suggests that causal gene variants may only predispose patients to disease which requires a “second-hit” genetic, developmental, or environmental insult to fully manifest, which might then explain why CHI patients with such variants do not exhibit PAH[7,19,45]. Three of the variants associated with both PAH and CHI are found in homozygous or compound heterozygous CHI patients (G111R, L135V and D1472N)[19,46–48], whilst D1472N is also observed as a heterozygous variant in focal CHI (where the imprinting of the maternal allele in specific pancreatic regions unmasks paternally inherited K_{ATP} LoF mutations)[49,50]. The fourth (D813N) was reported in a heterozygous patient with the variant inherited from the father[51]. Interestingly, imprinting of the maternal allele of chromosome 11p15, near the *ABCC8* locus, has been reported in focal CHI, which may explain how paternally inherited variants have effects in specific cases[52].

Intriguingly, whilst SUR2 (*ABCC9*) is likely the predominant SUR isoform expressed in human lung tissues[42,53], *ABCC8* expression was reported to be upregulated in lung tissue samples from PAH patients carrying *BMPR2* mutations[19]. Furthermore, antibody staining identified SUR1 expression in proximal pulmonary arteries and, prominently, in alveolar macrophages[19]. These data may point to currently unknown roles for SUR1-containing K_{ATP} channels in the lung, and the possibility that SUR1-dependent K_{ATP} function is somehow necessary to counter PAH triggers. Detailed studies of recombinant channels show that SUR1 and SUR2 can co-assemble in functional K_{ATP} channels in vitro[54–56], and both genes are expressed in certain smooth muscle tissues[42,57]. It is therefore also conceivable that SUR1 may be functionally expressed together with SUR2 in various cells in the human lung, and that *ABCC8*/SUR1 expression may be upregulated in PAH, perhaps as a protective response. Consistent with such lability, SUR1 upregulation has been documented in response to hypoxia in cerebral vascular endothelial cells via hypoxia-inducible factor 1 α (HIF1)[58], a transcription factor which is also highly activated in cultured PASMCs from human PAH patients[59]. If SUR1 is expressed in PASMC, either in normal physiology or in disease states, then LoF variants - resulting in decreased K_{ATP} activity - would be predicted to have a depolarizing effect on the membrane potential and thus to functionally converge with the effects of LoF mutations in *KCNK3*.

SUR1 has also been reported to co-assemble with TRPM4 non-selective pore-forming subunits to form SUR1-TRPM4 (Sur1-$NC_{Ca\text{-}ATP}$) complexes, in cerebral microvessels, neurons, and microglia[60–62]. TRPM4 is also expressed in vascular smooth muscle[63], pulmonary smooth muscle[64] and rat airway smooth muscle[63] and thus it is possible that SUR1-TRPM4 co-assembly may occur in the lung. However, the validity of the TRPM4-SUR1 association has been questioned[65], no study to date has reported SUR1-$NC_{Ca\text{-}ATP}$ channels in the lung, and the function of any such channel in PAH pathophysiology is unknown. Importantly, TRPM4 channels are non-selective cation channels and thus would underlie depolarizing conductances. How the loss of a SUR1-dependent TRPM4 mediated depolarizing current would result in PAH is thus not clear at this time.

In vitro, SUR1 expression can also mediate apoptosis induced by the SUR ligands glibenclamide, resveratrol, and 17β-estradiol[66–68]. This effect does not require K_{ATP} channel function. Therefore, it is possible that PAH-associated *ABCC8* mutations may reduce a K_{ATP}-independent effect of SUR1 on induction of apoptosis, which could promote the medial hyperplasia or intimal overgrowth observed in PAH.

Gain-of-function mutations in ABCC9 and KCNJ8 cause PH

Autosomal dominant mutations in *ABCC9* (SUR2) and *KCNJ8* (Kir6.1) cause the complex heritable disorder, Cantu Syndrome (CS)[69–74], characterized by hypertrichosis, distinct facies, and multiple cardiovascular abnormalities, including cardiomegaly, dilated and tortuous vasculature, pericardial effusion, and edema. Since mutations in both genes converge in a common pathophysiology, the underlying defect is gain-of-function (GoF) mutations in SUR2/Kir6.1-dependent K_{ATP} channels, and the primary cellular dysfunction is likely to be in a tissue in which both Kir6.1 and SUR2 are expressed. We have recently demonstrated that K_{ATP} channel activity in vascular SMC is markedly increased by CS-associated mutations in both *KCNJ8* and *ABCC9* in two novel CRISPR/Cas9 engineered mouse models which recapitulate the low systemic blood pressures and cardiac hypertrophy observed clinically[75]. As both Kir6.1 and SUR2 are also expressed in the pulmonary vasculature[40–42] it is a simple prediction that CS patients will exhibit pulmonary vasodilation and hence lower pulmonary blood pressures – as is observed in the systemic circulation[21,75,76]. However, CS patients present with the opposite effect, frequently demonstrating elevated pulmonary artery pressures and potentially fatal PH[22–24].

How could PH arise from K_{ATP} channel over-activity?

A clue as to how potassium channel over-activity in CS may paradoxically cause PH is provided by studies of the effects of vasodilatory K_{ATP} channel openers (KCOs), including diazoxide and minoxidil. Adverse effects of these drugs overlap strikingly with the clinical features observed in CS - edema, pericardial effusion, hypertrichosis, reopening of the ductus arteriosus, and PH all being reported both as side effects of KCO treatment and common in CS[77–82]. It has been proposed that KCOs will trigger compensatory feedback mechanisms in response to their potent systemic blood pressure lowering effect in patients[83]. Such feedback includes elevated sympathetic activity, and upregulation of renin-angiotensin-aldosterone axis signalling (RAAS) due to decreased renal perfusion. Activation of RAAS

leads to elevated salt and water retention, and blood plasma volume expansion (hypervolemia) which helps to normalize systemic blood pressure. However, it is also recognized that elevated RAAS can contribute to the development of PH, and that inhibition of this action via angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers can reverse hypoxia- and monocrotaline-induced PH in rats[84–87]. In animal models, chronic minoxidil treatment results in blood volume expansion and cardiac hypertrophy in spontaneously hypertensive[88] and in normotensive rats[89]. Left and right ventricular hypertrophy are observed in parallel with increased plasma renin activity[90], and prevented by administration of the angiotensin-receptor blocker losartan. This suggests that RAAS is a critical factor in the cardiac hypertrophy induced by chronic KCO administration. We therefore hypothesize that KCO-induced PH arises due to volume-overload of the pulmonary circulation, downstream of RAAS upregulation. Notably, diazoxide, which is used to treat hyperinsulinism by activating pancreatic K_{ATP} channels, also promotes vasodilation via vascular K_{ATP} activation and has been reported to cause PH in patients[78,79]. For this reason, diazoxide is often co-administered with diuretic drugs to counteract adverse effects associated with fluid retention[91–93].

Congenital defects in CS may contribute to PH.

Left heart disease can lead to Group 2 pulmonary hypertension. Chronic left ventricular systolic dysfunction, left sided valvular disease, or congenital heart defects, can all cause PH, and it is possible that in certain CS patients various structural cardiovascular abnormalities may contribute to PH. Reported CS abnormalities include patent ductus arteriosus (PDA) and persistence of other fetal circulation, aorto-pulmonary collaterals, aortic root dilation, and aortic valve defects, stenosis and regurgitation[21,22,72]. Constitutive dilation of the aortic root is observed in both CS patients and ‘Cantu mice’, which results in aortic regurgitation and aortic valve defects which can cause Group 2 PH[75]. Additionally, if not corrected in a timely manner, PDA can lead to PH and progress irreversibly to Eisenmenger’s Syndrome[94–96].

Many CS patients are born prematurely[21]. Extreme prematurity may also lead to bronchopulmonary dysplasia and cause Group 3 hypoxia-induced PH[23,97]. Pulmonary venous occlusion (PVO) was reported in a single CS case[22]. The highly tortuous vasculature in CS is suggestive of abnormal development, which may result in malformed vessels such as the PVO reported by Kobayashi and colleagues[22]. Furthermore, CS patients frequently present with “high-output” hypertrophic hearts[69]. As discussed above, we hypothesize that these structural and functional changes arise secondary to K_{ATP} GoF–induced vasodilation to compensate for lowered systemic blood pressure[75]. Elevation of stroke volume results in increased pulmonary artery pressures, as is observed in healthy individuals in exercise[98,99], and may therefore also contribute to the chronically elevated pulmonary pressures in CS patients.

Thus there are multiple potential structural, hemodynamic, and neurohumoral factors which may contribute to PH in CS patients, all of which may be secondary to GoF of K_{ATP} channels and consequent vasodilation in the systemic vasculature.

K_{ATP} dysfunction and PH: smooth muscle and endothelial contributions?

There are key roles for both smooth muscle and endothelial K_{ATP} channels in regulating vascular function. Unlike in excitable vascular smooth muscle cells, where K_{ATP} channel activation results in decreased calcium influx via voltage-gated calcium channels, , K_{ATP} activation causes hyperpolarization in non-excitable endothelial cells, increasing the driving force for Ca^{2+} influx through receptor- and store-operated channels, and thereby increases intracellular calcium[100]. As intracellular calcium critically regulates endothelial function, including mediator release, K_{ATP} activity could clearly affect endothelial physiology and the vasodilatory effects of sheer stress, adenosine, and hypo-osmolarity have been attributed in part to activation of endothelial K_{ATP} channels[101–103].

K_{ATP} expression has been demonstrated in pulmonary artery endothelial cells, where it is regulated by sheer stress[104,105], but endothelial K_{ATP} function has mostly been studied outside of the pulmonary vasculature. Interestingly, coronary vasospasm has been reported in both Kir6.1 and SUR2 null mice[106,107]. This phenotype reportedly persists in SUR2 KO mice even when SUR2B is transgenically overexpressed specifically in smooth muscle – suggesting that vasospasm may arise from non-smooth muscle dysfunction[108]. Consistent with this, endothelial specific expression of dominant-negative K_{ATP} subunits results in increased coronary perfusion pressure due to increased endothelin-1 secretion from ECs[109]. This was not observed following conditional deletion of Kir6.1 in endothelial cells (where Kir6.2 expression may remain) which did however impair hypoxia-induced vasorelaxation in the coronary circulation[43].

If these features are conserved in the pulmonary vasculature, it is conceivable that decreased pulmonary endothelial K_{ATP} activity could promote pulmonary vasoconstriction. In addition, the KCO nicorandil has recently been shown to reduce lipopolysaccharide-induced inflammation (via decreased reactive oxygen species generation), and monocrotaline-induced damage in pulmonary artery endothelial cells, pointing to a protective role of K_{ATP} activity in the pulmonary endothelium[110,111]. However, as Kir6.2, Kir6.1 and SUR2B are the major subunits expressed in vascular endothelial cells[112], there is no simple rationale for why either endothelial SUR1 LoF or SUR2 GoF mutations should be associated with PH. Studies of the effects of GoF in pulmonary endothelium (and vascular endothelium in general) are lacking and could provide telling novel insights.

Linking K_{ATP} channel dysfunction to PAH and CS-associated PH

Clearly much remains to be elucidated about how LoF mutations in *ABCC8* result in PAH whereas GoF mutations in *KCNJ8* and *ABCC9* cause PH in CS. In the case of *ABCC8* LoF, insights may be gleaned from studies of knockout mice[113]. *ABCC8* null and LoF transgenic mice exhibit abnormalities in insulin secretion and glucose intolerance[113,114], but to date there is little insight to cardiovascular dysfunction or remodelling. There are many examples of murine models providing novel insights into PAH pathophysiology (reviewed in[115–117]), but in some cases, species specific differences in pulmonary physiology can result in failures of mouse models to recapitulate human disease. For example *KCNK3* knockout mice do not exhibit RV hypertrophy or pulmonary vasculature remodelling despite strong genetic

evidence for the role of *KCNK3* LoF in human disease[7,17,32,33,118,119]. Recently, we demonstrated that knock-in of CS-causing mutations into the endogenous *KCNJ8* and *ABCC9* loci in mice results in vasodilation, decreased systemic blood pressure, and pronounced cardiac hypertrophy – mirroring clinical observations[75]. These "Cantu mice" therefore provide a faithful model of key cardiovascular abnormalities in patients and allow for investigation of pathophysiological mechanisms. The effects of K_{ATP} GoF on pulmonary vascular physiology in mice remain to be established. Based on the studies of K_{ATP} channel activating drugs in rodents, we hypothesize that K_{ATP} GoF will trigger RAAS activation and blood volume expansion, which may precipitate volume-overload of the pulmonary circulation in Cantu mice.

In addition to global knockout mice, insights to the role of K_{ATP} in cardiovascular system have been provided by mouse models either expressing dominant-negative K_{ATP} channel subunit transgenes or floxed alleles, which allow for inducible and tissue-specific downregulation of KATP channel activity[35,36,106,107,109,120]. Meanwhile, overexpression of GoF Kir6.1 mutant subunits in both vascular smooth muscle and cardiomyocytes has been shown to recapitulate certain features of Cantu Syndrome[36,121]. Most recently, we demonstrated that the introduction of Cantu Syndrome-associated point mutations into the endogenous *KCNJ8* and *ABCC9* mouse genes recapitulates the decreased systemic vascular resistance and high-output hypertrophic hearts observed in CS[75].

While the hypertensive effect of K_{ATP} knockdown in the systemic vasculature is well described[36,106,107], we are unaware of parallel *in vivo* studies in pulmonary vessels. The different mouse models described above provide valuable tools for future experiments to define the role of K_{ATP} dysfunction in various tissues in PH. Global SUR2 and Kir6.1 knockout mice would be expected to exhibit increased pulmonary vasoconstriction via loss of either smooth muscle or endothelial K_{ATP} function. Knockdown of over-active K_{ATP} channels in the Cantu mice in smooth muscle or endothelial cells using dominant-negative or floxed Kir6.1 alleles would establish the tissue in which K_{ATP} GoF causes PH in CS. The effect of loss of SUR1 on pulmonary physiology could be tested in global or tissue specific SUR1 knockout[122]. Together, such experiments have the potential to provide mechanistic explanations for how both loss- and gain-of-function of K_{ATP} channels can ultimately result in PH.

K_{ATP} channels as therapeutic targets in PH

Because K_{ATP} activators cause vascular smooth muscle hyperpolarization resulting in vasodilation, they present an interesting potential target for PAH therapy[83,123–125]. However, as noted above, classical KCOs effectively dilate pulmonary vessels but their powerful systemic vasodilatory effects may provoke counter-productive hypervolemia and exacerbate PH with long-term administration. Thus an important feature of an ideal vasodilatory drug for PH would be specific targeting of the pulmonary vasculature to avoid secondary compensation for associated systemic vasodilation. Vasodilators with more pulmonary-specific action, such as endothelin receptor antagonists or PDE5 inhibitors may be preferable to currently available KCOs. Intriguingly, one newer K_{ATP} channel activator, iptakalim, has been reported to be a selective vasodilator acting specifically on resistance

vessels in hypertensive patients, without effects on normotensive patients[126]. Iptakalim has been reported to reduce hypoxia- or endothelin-induced proliferation in PASMCs[127,128] and to protect endothelial function in rats[129], but whether these properties can be translated to benefit PAH patients without activation of potentially confounding secondary consequences in the long-term has not been established.

Why KCOs can cause PH yet other vasodilatory drugs do not is intriguing. KCOs have long been recognized as particularly powerful vasodilatory agents, capable of reducing systemic blood pressure in patients in which other therapies have been ineffective[82,83,130,131]. Therefore, perhaps the magnitude of the reflex sympathetic/RAAS activation is greater for KCOs than for other vasodilatory agents. Additionally, diazoxide and minoxidil have been shown to produce only weak venodilation (in contrast to many other vasodilatory drugs)[131–133]. Marked arteriolar dilation coupled with minimal venodilation, together with sympathetic/RAAS activation results in increased venous return and cardiac output, leading to increased cardiopulmonary blood volume and pulmonary arterial pressures[134]. Notably, this vasoactivity profile is shared by hydralazine, another vasodilator with weak venodilatory effects that can also induce increased pulmonary pressures[134,135].

Whether the specific dysfunction of SUR1 can be precisely targeted in the *ABCC8*-variant PAH patient population remains to be seen. Diazoxide activates SUR1-containing K_{ATP} channels, but exerts its vasodilatory effects via activation of SUR2B-dependent VSMC K_{ATP} channels[126], which would have undesirable systemic effects. A SUR1-specific activator might therefore be desirable, to avoid systemic vasodilation. A recently identified novel SUR1-selective activator, reported by Raphemot and colleagues, may prove a useful experimental tool for dissecting SUR1-specific dysfunction, without targeting SUR2-containing channels[136]. Importantly, however, any SUR1-selective activator would also activate pancreatic KATP channels, potentially decreasing β-cell excitability and insulin secretion, and thus hyperglycemic effects would have to be carefully monitored.

Conversely, directly targeting K_{ATP} GoF using inhibitors represents a potential strategy for treating cardiovascular pathologies in CS or related pathologies. The potent second-generation sulfonylureas (SUs), including glibenclamide, and glinidies, such as repaglinide, inhibit both pancreatic and cardiovascular K_{ATP} channels[137]. As their name suggests, the SUR domain contains the binding site for SUs, which was recently resolved in cryo-EM structures of Kir6.2/SUR1 channels bound by glibenclamide[138]. The sensitivity of pancreatic/neuronal channels (Kir6.2/SUR1) for SU inhibition is significantly higher than SUR2-containing channels *in vitro*[137,139,140]. Thus, it would be expected that higher doses than are used in the treatment of diabetes might be required to effectively target CV K_{ATP} channels in CS. Furthermore, certain disease-causing GoF mutations in K_{ATP} channels can reduce SU sensitivity, and thus the drugs may not be efficacious in specific patients[141,142]. However, significant sensitivity is retained for multiple other CS mutations and thus K_{ATP} inhibitors may serve as effective therapies for many CS patients[143].

As detailed above, the complex cardiopulmonary abnormalities in CS seem to arise from a primary dysfunction of vascular smooth muscle channels which could therefore represent the ideal target for a pharmacotherapy[75]. We predict that inhibiting VSMC K_{ATP} GoF in the

systemic circulation will attenuate the primary systemic vasodilation, which will in turn inhibit the secondary RAAS activation, predicted hypervolemia and PH. ‘Cantu mice’ represent a key tool for investigating the pathophysiological mechanisms underlying PH in CS and for determining the pre-clinical efficacy of potential therapies.

Summary

Recent advances in medical genetics have demonstrated that both loss-of-function and gain-of-function mutations in genes encoding K_{ATP} channel subunits can result in pulmonary hypertension. Just how loss-of-function mutations in *ABCC8* result in PAH is currently poorly understood but, in general, decreased K^+ channel activity is associated with vasoconstriction and proliferation of pulmonary artery smooth muscle and endothelial cells. Conversely, gain-of-function mutations in *ABCC9* and *KCNJ8* cause Cantu Syndrome, which is associated with multiple cardiovascular abnormalities including PH, which potentially arises as a secondary consequence of systemic vasodilation. While there are currently no directed therapies for these pathologies, mechanistic insights to the precise consequences of K_{ATP} channel dysfunction will be provided by appropriate animal models, and novel insights to channel-dependent PH pathophysiology will then facilitate targeted therapies for distinct patient subsets.

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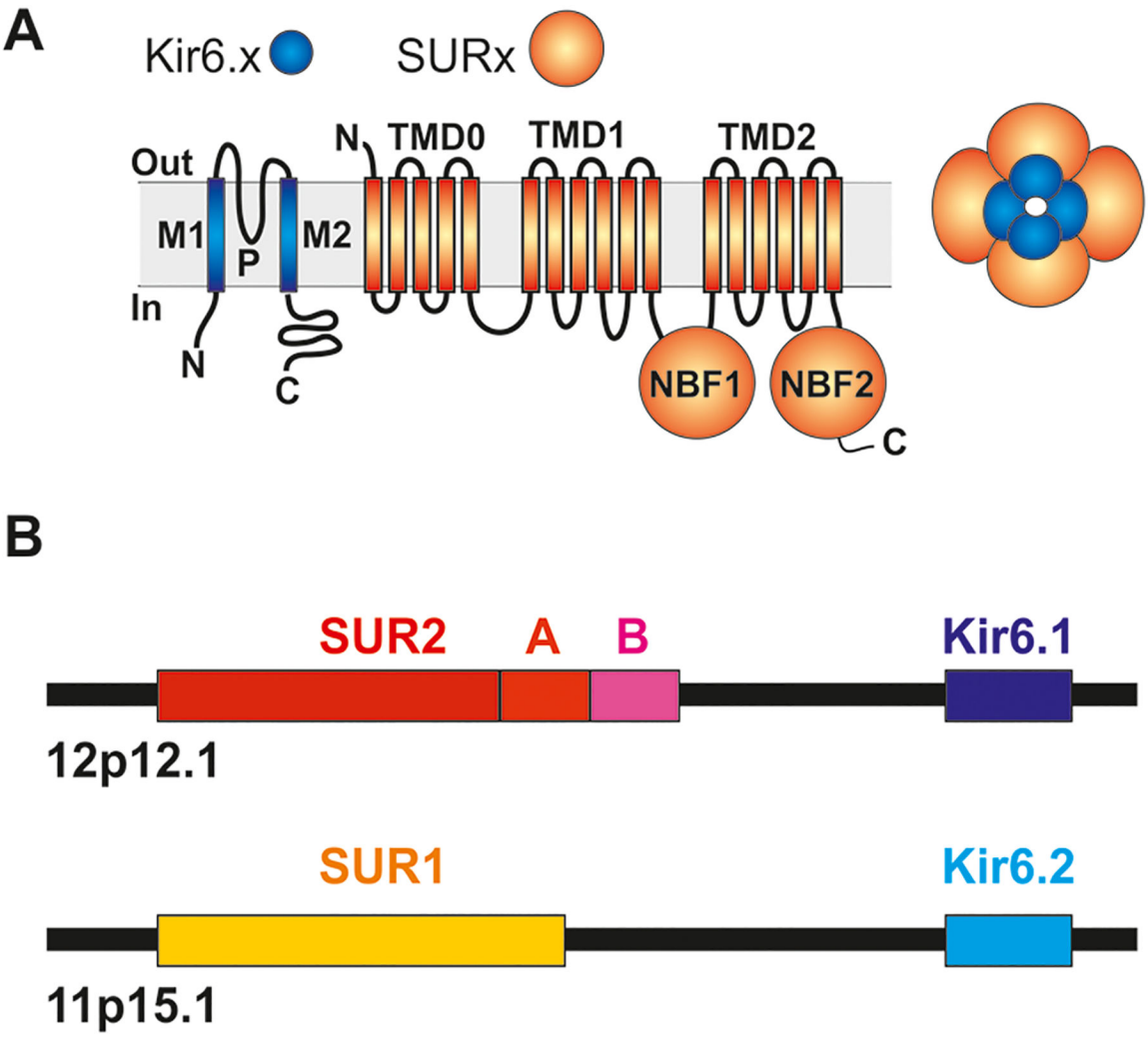

Fig. 1. Molecular basis of K_{ATP} channel activity

(**A**) K_{ATP} channels are generated as octamers of 4 pore-forming Kir6.x (Kir6.1 or Kir6.2) and 4 regulatory SURx (SUR1 or SUR2) subunits. (**B**) Two pairs of genes located on human chromosome 12 (*ABCC9, KCNJ8*) and chromosome 11 (*ABCC8, KCNJ11*) encode SUR2 (C-terminally spliced to SUR2A or SUR2B) and Kir6.1, or SUR1 and Kir6.2 subunits, respectively.

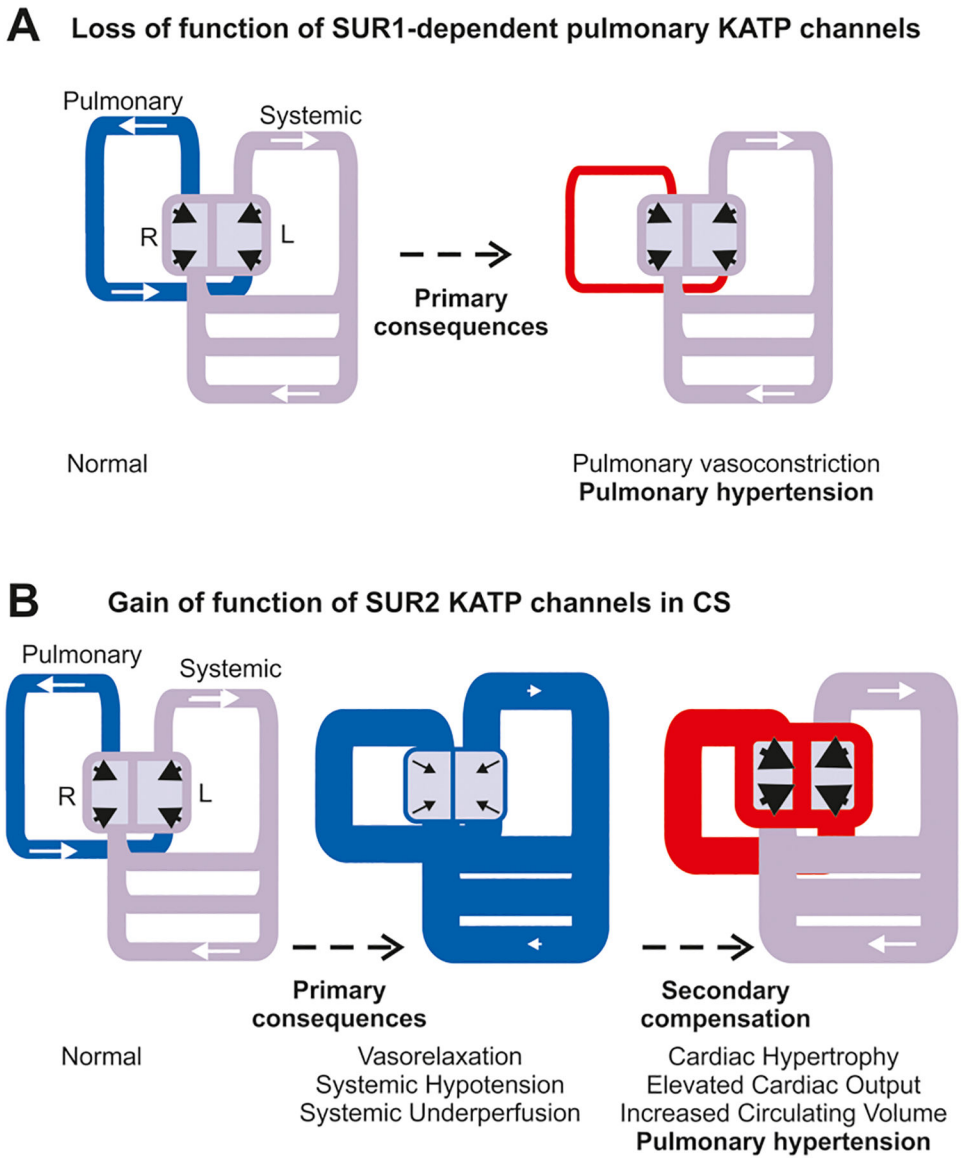

Fig. 2. Hypothesized mechanisms of K_{ATP} induced PH

(A) Schematic of cardiovascular system indicates normal pressures (grey) in systemic circulation and low pressures (blue) in pulmonary circulation resulting from normal pumping from the left (L) and right (R) heart, respectively. Loss-of-function of SUR1-dependent K_{ATP} (or other K) channels in pulmonary circulation may directly result in inappropriate pulmonary vasoconstriction and hypertension (red). **(B)** Gain-of-function of SUR2-dependent K_{ATP} (or other K) channels results primarily in inappropriate vasorelaxation and systemic hypotension (blue). Secondary compensatory mechanisms drive enlarged, hypercontractile hearts, raising pressures in the systemic circulation (to normal, grey) and in the pulmonary circulation (to hypertension, red).