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The Role of Ion Channels in Pulmonary Hypertension: A Review

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ABSTRACT

Pulmonary hypertension (PH) constitutes a critical challenge in cardiopulmonary medicine with a pathogenesis that is multifaceted and intricate. Ion channels, crucial determinants of cellular electrochemical gradient modulation, have emerged as significant participants in the pathophysiological progression of PH. These channels, abundant on the membranes of pulmonary artery smooth muscle cells (PASMCs) and pulmonary artery endothelial cells (PAECs), pivotally navigate the nuanced interplay of cell proliferation, migration, and endothelial function, each vital to the pulmonary vascular remodeling (PVR) hallmark of PH. Our review delves into the mechanistic insights of potassium, calcium, magnesium, zinc, and chloride ion channels in relation to their involvement in PH. It not only emphasizes the notable advances and discoveries that cast these ion channels as underlying factors in the etiology and exacerbation of PH but also highlights their potential as innovative therapeutic targets.

1 | Pulmonary Hypertension

Pulmonary hypertension (PH) is a severe cardiopulmonary disorder primarily caused by persistent constriction of the pulmonary vasculature, concentric thickening of the pulmonary vessel walls, and sclerosis of the pulmonary artery (PA) walls [1], resulting in increased pulmonary arterial resistance. This, in turn, leads to increased right ventricular afterload and, ultimately, right heart failure and even death. The main features of PH include constriction and remodeling of the pulmonary vasculature. The diagnosis of PH is confirmed by a mean PA pressure ≥ 20 mmHg measured by right heart catheterization at sea level at rest, based on hemodynamic indices [2]. The World Health Organization classifies PH into five groups [3]: pulmonary arterial hypertension (PAH), which is mainly caused by mutations in various genes and other causes; PH associated with left heart disease, a very common form of PH; PH due to lung disease and/or hypoxia, such as chronic obstructive pulmonary disease; PH associated with PA obstruction; and PH of undetermined and/or multifactorial origin. In patients with severe PH, endothelial lesions and fibrosis of the pulmonary vasculature due to smooth muscle cell (SMC) migration [4], endothelial-to-mesenchymal transition (EndMT), and endothelial cell proliferation lead to partial or complete occlusion of the pulmonary vasculature; however, the exact pathogenesis remains not fully understood. Recent studies related to ion channels have demonstrated that calcium, potassium, magnesium, and zinc channels play a role in many vasoactive substances, inflammatory mediators, and transcription factors that regulate intra- and extracellular ion concentrations, thereby regulating vasoconstriction, cellular value-addition, migration, and apoptosis. Since the body is

unable to synthesize essential micronutrients such as zinc, potassium, and magnesium, these nutrients must be consumed daily in the diet to maintain cellular homeostasis. In mammals, ion channels in the cell membrane primarily regulate this homeostasis. Calcium-activated chloride channels (CACCs) play a crucial role in maintaining the balance of potassium, magnesium, and chloride ions across the membrane of vascular smooth muscle cells (VSMCs) and in regulating vascular smooth muscle (VSM) tone. Magnesium channels inhibit the proliferation and migration of pulmonary artery smooth muscle cells (PASMCs) and promote vasodilation by mediating magnesium diffusion. Hypoxia upregulates the expression of the zinc transporter solute carrier (SLC) family 39 member 12 (ZIP12), leading to intracellular zinc accumulation and PASMCs proliferation, which is a significant contributor to hypoxic PH-induced pulmonary vascular remodeling (PVR). Although pulmonary artery endothelial cells (PAECs) are considered nonexcitable cells, they express a diverse array of cation and anion channels in the plasma membrane. In addition to modulating membrane potential, PAECs may directly regulate vasoactive substances (such as endothelium-derived relaxing and contracting factors) via calcium and magnesium ions in these channels. This review summarizes the structure, function, and expression of several ion channels, providing a solid theoretical foundation for better elucidating the relationship between ion channels and PH and identifying potential therapeutic targets for improved PH treatment.

2 | Potassium Channels

2.1 | Voltage-Gated Potassium Channels

Voltage-gated potassium (Kv) channels are homotetrameric or heterotetrameric potassium channels composed of alpha subunits, each containing six transmembrane domains. Each subunit's six transmembrane domains comprise a voltage-sensitive domain and a pore domain. Kv channels are major regulators of VSMCs excitability and resting membrane potential. They are involved in the regulation of PASMCs proliferation and apoptosis, critical for the regulation of pulmonary vascular tone, and maintain resting membrane potential during activation. During VSMCs depolarization induced by further activation, Kv channels are regulated by the inhibition of voltage-gated calcium channels (VGCCs) in the plasma and sarcoplasmic membranes. Among the Kv channels expressed by mammalian VSMCs, Kv1.5, a key channel regulating vascular tone and atrial excitability, is 0regionally expressed in low-resistance PAs, attracting significant attention [5]. As shown in Figure 1, in PH, decreased Kv1.5 current leads to a shallower resting membrane potential, resulting in pulmonary vasoconstriction, PASMCs proliferation and migration, and reduced caspase expression, which confers resistance to apoptosis [6]. Additionally, mutations in the bone morphogenetic protein receptor 2 (BMPR2) gene, which cause PH, have a substantial impact on Kv channels. Fantozzi et al. found that in human PASMCs with BMPR2 mutations, Kv1.5 expression and current density were reduced, whereas recombinant BMPR2 reversed this effect, suggesting that BMPR2 mutations can lead to decreased Kv channel expression or function [7]. A recent study found that the activity and function of Kv1.5 channels are closely related to sigma-1 receptor (S1R) expression. S1Rs induce bimodal regulation of Kv1.5 channel expression/activity, and as S1R levels increase, S1Rs regulate Kv1.5 channel expression and activity in an S1R-dependent manner [8], attenuating pulmonary vasoconstriction and proliferation. These studies suggest that S1R may be a potential new pharmacologic target for PH associated with Kv1.5 injury.

2.2 | Adenosine Triphosphate-Sensitive Potassium Channels

The adenosine triphosphate (ATP)-sensitive potassium channel is an octameric complex composed of sulfonylurea receptor 1/2 (SUR1/2), encoded by the ATP-binding cassette subfamily C

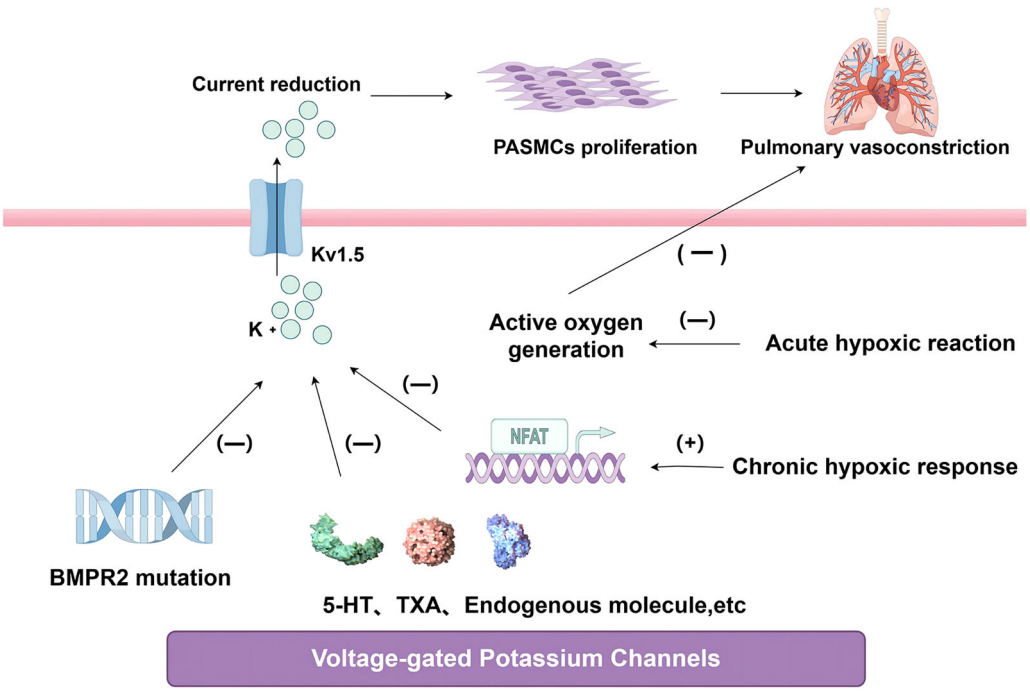

FIGURE 1 | The current of Kv1.5 in PH causes the resting membrane potential to become shallow and the pulmonary vasoconstriction.

member 8/9 (ABCC8/9) genes, and inwardly rectifying potassium channel 6 (Kir6), encoded by the potassium voltage-gated channel subfamily J member 8/11 (KCNJ8/11) genes. ABCC8/SUR1 and SUR2 can be coassembled in ATP-sensitive potassium channels in vitro, and both genes are expressed in various smooth muscle tissues. It is hypothesized that SUR1 may be functionally expressed alongside SUR2 in diverse cell types in the human lung and that upregulation of ABCC8/SUR1 expression in PH may be a protective response. As shown in Figure 2, the activity of potassium channels can influence the balance between PASMCs proliferation and apoptosis. Increased activity promotes PASMCs apoptosis, allowing potassium channels to affect PH by regulating PASMCs contraction and cell proliferation [9]. In a study combining biochemical, ex vivo, and in vivo approaches, SUR1/Kir6.2 and SUR2/Kir6.1 were found to be expressed in human PASMCs and human PAECs [10]. While activation of SUR1 with SUR1 activators (diazoxide, VU0071063, and NN414) was effective in relaxing PA tone, SUR2 activators not only induced PA relaxation but also inhibited the proliferation and migration of human PASMCs [11]. In addition, in vivo activation of SUR1/Kir6.2 and SUR2/Kir6.1 effectively restores and improves monocrotaline (MCT)-PH and chronic hypoxia-PH. Although diazoxide has been reported to have deleterious side effects in humans, SUR1/Kir6.2 and SUR2/Kir6.1 can still be regarded as novel pharmacological targets for PH. The CRISPR/Cas9 system is a widely used genome editing technology that uses specific sgRNA-guided endonuclease Cas9 to accurately generate mutations at sites of interest [12]. It has been increasingly used to discover cardiovascular diseases and other diseases. Genome-wide CRISPR screening of mammalian cells has also been widely used to identify new disease genes and functional modules [13]. McClenaghan et al. demonstrated in two novel CRISPR/Cas9-engineered mouse models that mutations in specific sites of KCNJ8 and ABCC9 in ATP-sensitive potassium channels lead to a significant increase in potassium channel activity in VSMCs, resulting in pulmonary vasodilation and decreased pulmonary blood pressure [14]. In excitable VSMCs, ATP-sensitive potassium channel activation reduces calcium influx through VGCCs, whereas in non-excitable endothelial cells, potassium channel activation leads to hyperpolarization. ATP-sensitive potassium channels can influence endothelial physiology by increasing the drive for calcium through receptors and storage channels, thereby increasing intracellular calcium content. Furthermore, the use of vasodilatory potassium channel openers triggers compensatory feedback mechanisms [15] that affect their potent blood pressure-lowering effect. This feedback includes increased sympathetic nervous system activity and enhanced signaling to the renin–angiotensin–aldosterone axis, which promotes PH development.

2.3 | Two-Pore Domain Potassium Channels

Potassium channel subfamily K member 3 (KCNK3), encoded by the KCNK3 gene, is also known as TWIK-associated acid-sensitive-K^+ channel (TASK-1). It consists of two subunits, each of which has two pore-structural domains and four transmembrane fragments. KCNK3 contributes to the regulation of resting membrane potential in cells, including PASMCs and cardiomyocytes [16]. In 2006, Olschewski et al. used KCNK3 inhibitors in human PASMCs [17], demonstrating that the KCNK3 channel is expressed in PASMCs and is oxygen-sensitive. In 2013, Ma et al. identified heterozygous missense mutations in the KCNK3 gene in patients with PH through whole-exome sequencing, with no identifiable mutations in other genes associated with PH, suggesting that KCNK3 plays a crucial role in PH [18]. Loss-of-function mutations in the KCNK3 gene cause KCNK3 dysfunction [19], leading to disruption of pulmonary endothelial integrity, resulting in perivascular edema, pulmonary arterial epicardial remodeling, and enhanced inflammatory signaling. This, in turn, leads to increased proliferation of PASMCs and promotes pulmonary

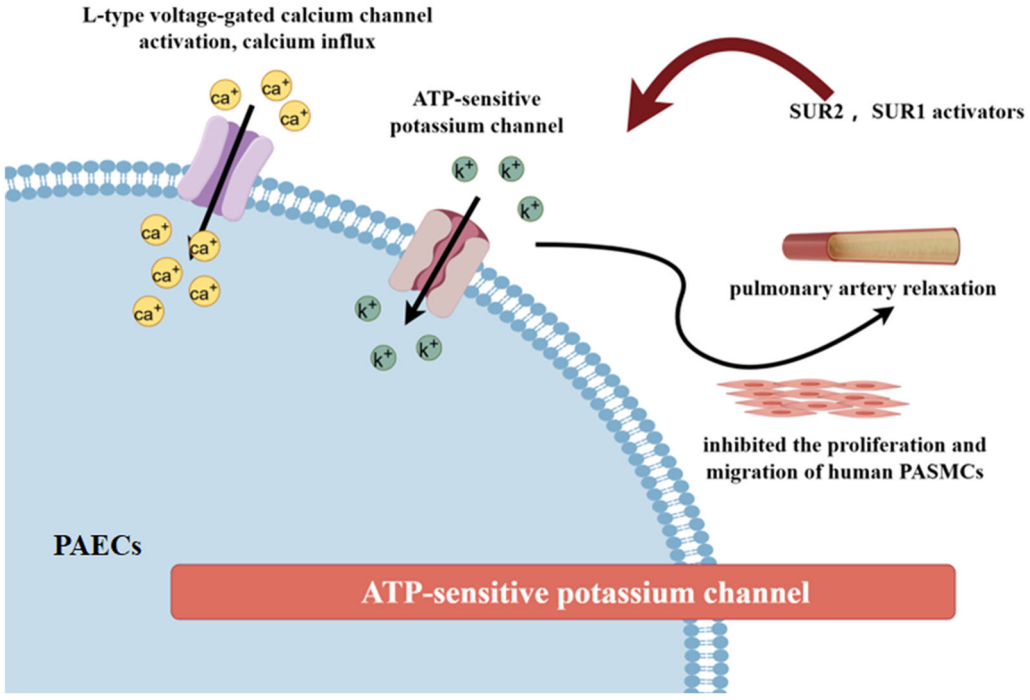

FIGURE 2 | ATP-type potassium channel causes pulmonary vasodilation and pulmonary blood pressure by affecting endothelial physiology.

vascular and parenchymal remodeling [20]. These findings suggest that KCNK3 deficiency is a key mechanism in the pathogenesis of PH. In 2016, Antigny et al. demonstrated reduced KCNK3 function in PH using KCNK3 loss-of-function rats and observing tissue specimens from 11 patients with PH [21]. As shown in Figure 3, decreased KCNK3 function resulted in increased proliferation and inflammation of PASMCs, PAECs, and ectodermal fibroblasts, leading to changes in hemodynamic indices and distal neomuscularization in rats. This suggests that downregulation or loss of KCNK3 channel function can result in a decrease in KCNK3 current, leading to increased proliferation and inflammation of pulmonary vascular cells and the development of PH. This may be related to micro-RNA and nuclear receptor-dependent mechanisms [22]. Upregulated miR-138-5p in MCT-treated rats repressed KCNK3 expression, and its inhibition restored KCNK3 mRNA expression levels in the lungs of this PH model [23]. In addition, vitamin D deficiency is widespread in PH patients [24, 25], and vitamin D deficiency decreases KCNK3 expression and activity, depolarizes PASMCs, and leads to dysfunction of PAECs [26]. In contrast, supplementation with appropriate levels of vitamin D ameliorates PA endothelial dysfunction and KCNK3 channel activity and restores some pathophysiologic features of PH. In addition, the reduced expression of KCNK3 in PH appears to be influenced by dasatinib. A recent study [27] revealed that in dasatinib-associated PH, a KCNK3 gene mutation was identified, which led to the loss of KCNK3 function, resulting in PA contraction and endothelial dysfunction. These findings indicate that dasatinib can downregulate the function and expression of KCNK3, thereby contributing to endothelial dysfunction in PH. These studies have confirmed that the lack of KCNK3 expression and function is an important mechanism in PH and that activation of KCNK3 channels may be a novel pharmacological target for PH. In addition, EndMT induced by transforming growth factor β1, a member of the transforming growth factor superfamily, has also been shown to be an important cause of endothelial cell proliferation and metastasis [13].

3 | Calcium Ion Channels

In PH PASMCs, the alteration of calcium homeostasis is a key feature of PH. During the development of PH, the increase in intracellular calcium concentration is a crucial factor in PASMCs contraction, proliferation, and migration [28], promoting chronic hypoxic PH remodeling. Calcium channels can be classified into VGCCs, Piezo-type mechanosensitive ion channel component 1 (Piezo1), store-operated Ca^{2+} entry (SOCE), and calcium-sensitive receptors (CaSRs) based on the factors that regulate channel opening. VGCCs are the primary route for calcium ion influx into PASMCs [29]. The VGCC family is further divided into L, T, N, P/Q, and R subtypes according to the distinct characteristics of calcium ion current gating. Among these, L-type voltage-gated calcium channels (L-VGCCs) and T-type voltage-gated calcium channels (T-VGCCs) are the most significant. Although both L-VGCCs and T-VGCCs are activated by depolarizing potentials, L-VGCCs are mainly activated by a larger degree of depolarizing potential, whereas T-VGCCs are activated and rapidly deactivated near the resting membrane potential [30]. In addition to this, there is a mechanically activated ion channel Piezo1, in the lung. In the presence of two inhibitors of sarcoplasmic calcium release, ryanodine (100 μM ryanodine receptor inhibitor) and thapsigargin (2 μM sarcoplasmic/endoplasmic reticulum calcium ATPase pump inhibitor), the increase in calcium concentration induced by Yoda1, which is the Piezo1, agonist did not decrease. Furthermore, the L-type calcium channel antagonist (1 μM nifedipine), T-type calcium channel blocker (CCB) (1 μM NC 55-0396), and purinergic receptor P2 antagonist (20 μM suramin) did not inhibit calcium influx, confirming calcium flow through Piezo1 channels. Piezo1 channels trigger the influx of Ca^{2+}, which then activates the release of nitric oxide (NO), causing VSM relaxation. Piezo1 in PAECs

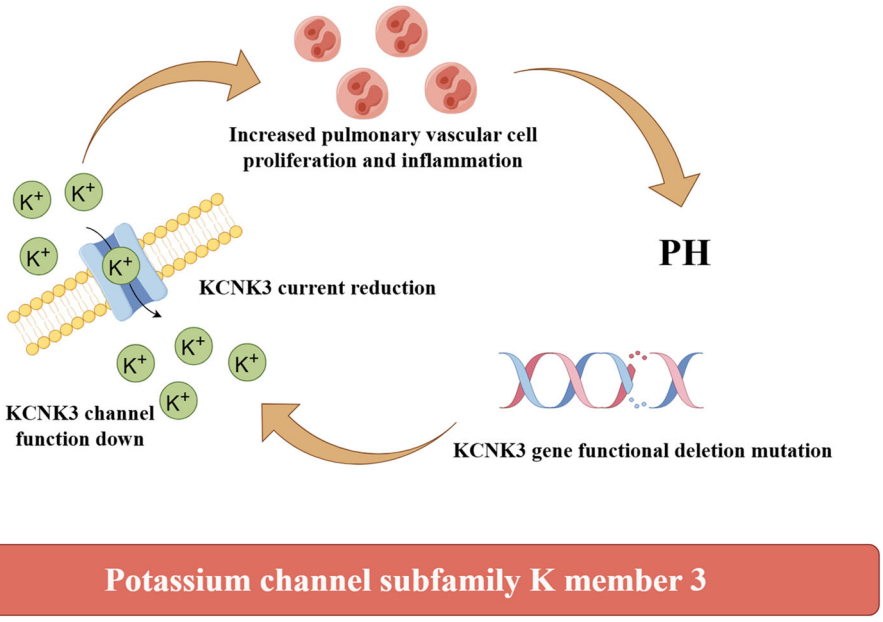

FIGURE 3 | Downregulation or loss of KCNK3 channel can lead to decrease in KCNK3 current, increased proliferation and inflammation of pulmonary vascular cells, which leads to the formation of PH.

controls pulmonary circulation tension in health and disease and has a potential relationship with the development of PH [31]. SOCE is ubiquitously expressed in mammalian cells and contributes to pathophysiological processes such as neovascularization, vasoconstriction, and remodeling by regulating intracellular Ca^{2+} concentration. CaSR, a member of the G protein-coupled receptor C family, is highly expressed in various organs and tissues. It can be activated by Ca^{2+}, Mg^{2+}, and amino acids, thus participating in the physiological and pathological processes of cardiovascular diseases [32].

3.1 | T-VGCCs

T-VGCCs are mainly expressed in neurons, cardiomyocytes, myocytes, osteocytes, and the thalamus and are composed of α1 (Cav3.1, CaV3.2, and CaV3.3) subunits. Compared to other types of calcium ion channels, T-type channels are activated at a lower voltage threshold (< -30 mV) and are inactivated at a lower voltage range. With the development of research on the molecular mechanisms and targets of T-VGCC activity, transgenic animal experiments have demonstrated that T-VGCCs are important drug targets for the treatment of many cardiovascular diseases, including cardiac hypertrophy. They may also be alternative therapeutic targets for PH, as they are involved in cell proliferation and vascular tone changes in PAs, and their activity is influenced by multiple hormones [33]. Studies have shown that T-VGCC protein expression increases in PH [34, 35]. Selective inhibition of Cav3.1 expression inhibited PASMCs proliferation in vitro [36, 37]. In addition to PASMCs, modulation of the Ca^{2+} signaling pathway in PAECs [38] is also important for the control of pulmonary vascular tone. In PAECs, acetylcholine triggers Ca^{2+} inward flow through Cav3.1 channels [39], which subsequently activates NO synthase and induces NO release, leading to vasorelaxation. This suggests a potentially beneficial effect of T-VGCC on pulmonary vascular reactivity at endothelial sites. In vivo administration of TTA-A2 (a T-VGCC blocker) reduced the hyperresponsiveness of pulmonary vessels to potassium chloride and serotonin in rats with hypoxia-induced PH [33]. This effect may be due to a sustained reduction in calcium influx through T-VGCCs, which limits vasoconstriction and elevated pressure. The decrease in intrapulmonary artery (IPA) calcium influx may also decrease the effect of calcium on PVR, which usually occurs during hypoxia-induced PH. Therefore, T-VGCCs may be related to the development of hypoxic PH, and specific blockers of T-VGCCs may be valuable therapies for hypoxia-induced PH.

3.2 | L-VGCCs

L-VGCCs, also called dihydropyridine (DHP) channels, are activated by strong depolarization and are mainly expressed in muscle, bone, ventricular myocytes, and dendrites of cortical neurons. They are composed of α1 (Cav1.1, Cav1.2, Cav1.3, and Cav1.4), α2, δ, β, and γ subunits. Abnormal L-VGCC expression may be involved in the development of hypoxia-induced PH. In newborn piglets, polymerase chain reaction and patch-clamp experiments have shown that hypoxic PH is associated with aberrant upregulation of L-VGCCs in small PAs in vivo, resulting in abnormal intracellular calcium concentrations that may induce the development of PH [40]. Earlier research using primarily rodent PH models [41–43] demonstrated that hypoxia acutely inactivates Kv channels in the PAs, subsequently inhibiting their expression in the plasma membrane, thereby leading to depolarization of PASMCs. This mediates L-VGCC opening and calcium influx, raising intracellular calcium concentration, which then causes VSMCs contraction and promotes PVR, ultimately leading to the occurrence of hypoxic PH. In conclusion, existing studies have linked the upregulation of L-VGCC expression in pulmonary arterioles to the development of hypoxic PH and have shown that during chronic hypoxia, drugs designed to inhibit the expression of L-VGCCs in pulmonary vessels may reduce abnormal calcium-dependent tension and the development of hypoxic PH. Clinically, CCBs that inhibit L-VGCCs may improve symptoms in some children with hypoxic PH [44]. However, CCBs are only suitable for patients who have a positive response to an acute pulmonary vasodilation test. They are contraindicated for patients who have not undergone this test, those who do not respond to it, and patients with right heart failure [45], as the use of CCBs in these cases may not only be ineffective but could potentially worsen the condition.

3.3 | Piezo1

Piezo1 is a stretch-activated calcium-permeable channel and a mechanical stress sensor in PAECs [46]. As shown in Figure 4, PAECs respond to mechanical stimuli by releasing NO, a signaling molecule that regulates vascular tone. Piezo1 channels exist in PAECs, and Piezo1 modulates endothelium-dependent tension. Compared to $Piezo1^{+/+}$ mice, the endothelium-dependent relaxation of PAs was significantly decreased in $Piezo1^{-/-}$ mice. Piezo1 agonists and mechanical stimulation can increase calcium concentration in mouse or human PAECs, both of which increase NO production and affect the occurrence and development of PH [47]. Increases in NO and calcium concentrations were significantly reduced in the PAECs of $Piezo1^{-/-}$ mice or in the presence of Piezo1 inhibitors. Piezo1 still mediates pulmonary arterial relaxation in chronically hypoxic PH mice, and loss of this channel does not impair disease development. Thus, Piezo1 promotes intrapulmonary vasodilation by controlling endothelial tension and NO production, and this effect is still present in PH [31]. Previous studies have shown that upregulation of Piezo1 protein expression is closely associated with the shift from a contractile to a proliferative phenotype and PVR in PASMCs [48]. Upregulated Piezo1 in PASMCs of patients with idiopathic PH mediates an increase in Ca^{2+} concentration by simultaneously triggering intracellular calcium release and extracellular calcium inflow, leading to the function and consequence of PASMCs, promoting contraction and proliferation of PASMCs [49, 50]. Subsequently, in a study by Chen et al. [51] exploring the function of Piezo1 in a rat model of shear stress-associated PH, it was found and concluded that upregulation of Piezo1 protein expression in PASMCs was associated with yes-related protein/TEA structural domain transcription factor 4. It was also found that the upregulation of Piezo1 protein expression might be related to RelA/p65 transcriptional regulation and lung inflammation.

3.4 | SOCE

SOCE starts from the emptying of intracellular calcium stores, which is one of the most common calcium flow pathways in

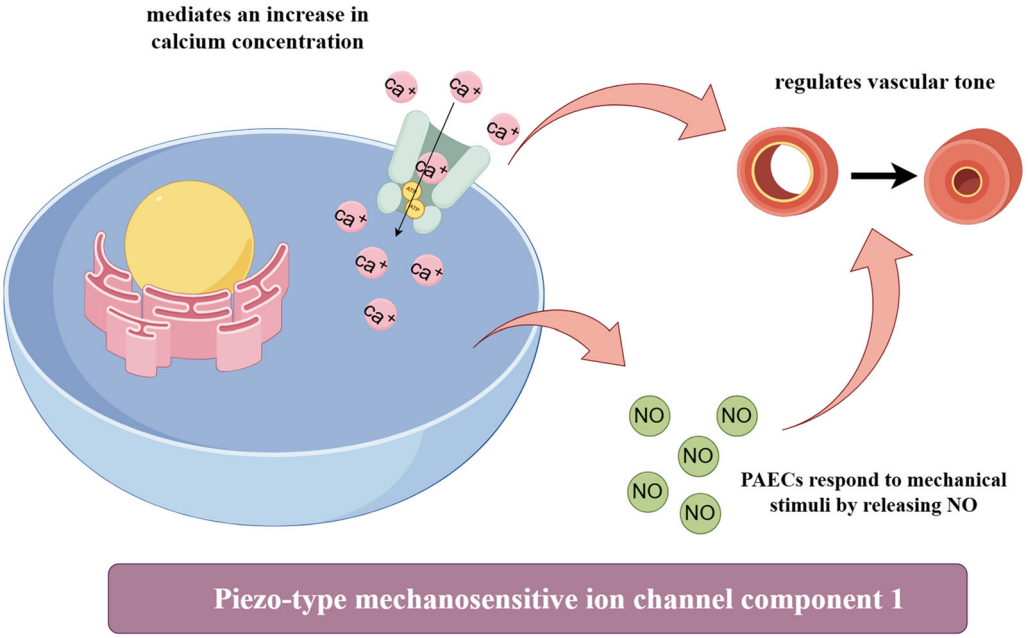

FIGURE 4 | Piezo1 promotes pulmonary vasodilation by controlling endothelial tension and NO production.

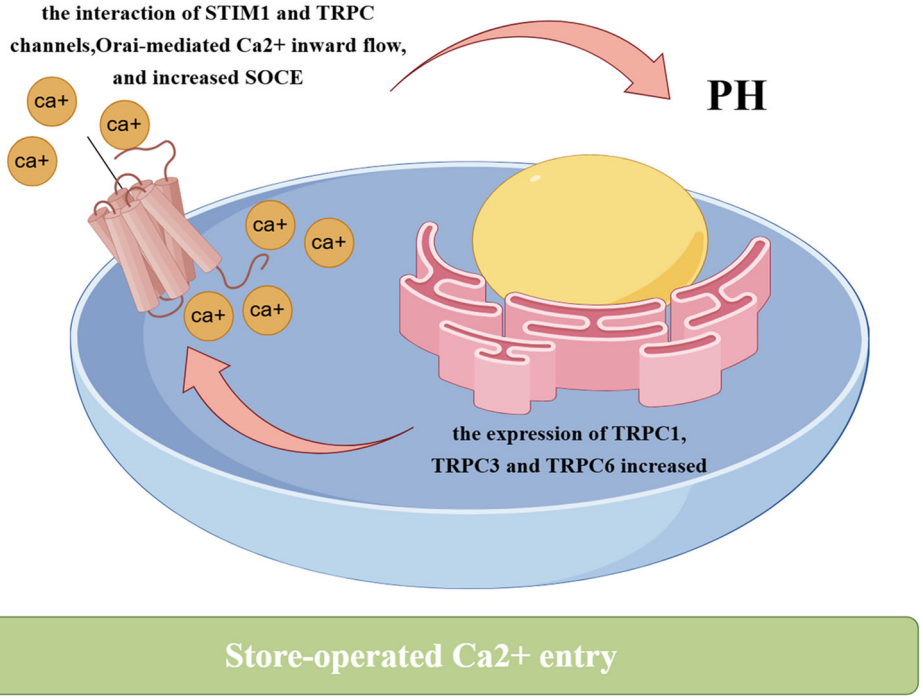

FIGURE 5 | The role of SOC channel in PAH.

nonstimulated cells [52] and may play a key role in regulating PASMCs function [10, 53]. Stromal interaction molecule 1 (Stim1) and calcium release-activated calcium regulatory protein 1 (Orai1) [53], as well as the transient receptor potential typical channels (Trpc family), comprise SOCE channels, are important calcium channel family members. The Trpc family is a Ca^{2+}-permeable channel consisting of seven members (Trpc1–7) that plays an important role in SOCE in different cell types, including PASMCs and PAECs, and is involved in the proliferation and migration of PASMCs and PAECs [54]. Among them, it has been demonstrated that the expression levels of Trpc1, Trpc3, and Trpc6 [55] are significantly elevated in hypoxia-induced PH, which may be associated with the interaction of Stim1 and Trpc channels, Orai-mediated Ca^{2+} inward flow, and increased SOCE [56] as shown in Figure 5. In contrast, triple knockdown of Trpc1/Trpc3/Trpc6 or administration of Trpc3 inhibitors decreased the proliferation of SOCE and human PASMCs, reduced hypoxia-induced pulmonary vasoconstriction [57], and attenuated the development of PH. The mechanism behind this may be related to reduced expression of the cystic fibrosis transmembrane regulator (CFTR) [20], a transporter that is functionally and physically coupled to

Trpc6 [58]. In the hypoxic mouse pulmonary vascular system, deletion of CFTR enhances Trpc6 expression and function, leading to vasoconstriction [59]. Another statement is that the markedly enhanced expression and activity of Orai1 in human and animal models of PH leads to upregulation of SOCE and promotes proliferation, migration, apoptosis resistance, and pulmonary vasoconstriction of PASMCs, which may be attributed, in part, to activation of the calmodulin-neurophosphatase/NFAT pathway and/or the activity of the calmodulin kinase II pathway or the NF-κB pathway [60], which affects ventricular remodeling. In a study in which an Orai1 inhibitor was given to inhibit the pharmacological activity of Orai1 in vivo, it was found that [61] both right ventricular fibrosis and hypertrophy in PH were ameliorated. This suggests that inhibition of Orai1 pharmacological activity may also be a relevant strategy to reduce PVR in PAH and influence the development of PAH.

3.5 | CaSR

CaSR is a member of the C family of G protein-coupled receptor cell membrane receptor superfamily. It is expressed in many tissues and organs and is also expressed in VSMCs of subcutaneous arteries, aorta, and PAs [62]. Increased calcium signaling in PASMCs is an important therapeutic target in PH. It has been demonstrated that both mRNA and protein levels of CaSR are significantly increased in hypoxia-induced PH [63, 64], which promotes Ca^{2+} inward flow to induce VSMCs proliferation and vasoconstriction and influences the development of PH. Calcilytics, an allosteric inhibitor of CaSR, reduce the sensitivity of CaSR to extracellular Ca^{2+} and shift the concentration–response curve of CaSR-expressing cells to the right after binding [65]. Studies have shown that the administration of calcilytics in an idiopathic PAH (IPAH) mouse model can prevent the development of PH and right ventricular hypertrophy. Additionally, there is a significant reduction in the thickening of pulmonary arterioles and right ventricular systolic pressure [64].

CCBs act as vasodilators by blocking calcium channels on the cell membrane, thereby reducing the inward flow of calcium in VSMCs. They work well in patients with acute vasodilator response sensitivity [66]. However, DHP CCBs potentiate CaSR-mediated increases in Ca^{2+} in IPAH, which further potentiates right ventricular systolic pressure, leading to increased right ventricular hypertrophy [67] and exacerbating symptoms in patients with IPAH. Chloroquine, a potent vasodilator, has also been shown to directly or indirectly inhibit calcium channels, decrease the increase of Trpc1, Trpc6, and CaSR proteins [62, 68], and inhibit Ca^{2+} inward flow, as well as prevent PVR, reduce medial wall thickness, and inhibit the development of PH [69]. These findings suggest that CaSR plays a crucial role in the pathogenesis of PH and may serve as a potential therapeutic target. Calcilytics, which are CaSR antagonists, can be employed as a novel pharmacological approach to ameliorate the pathophysiological alterations caused by CaSR or its intracellular coupling protein activation mutations. Furthermore, calcilytics may also have therapeutic potential in the treatment of nonbone metabolism-related diseases, such as PH.

4 | Magnesium Ion Channels

Magnesium ions are the abundant cations in cells and play a role in many physiological aspects, including intermediate metabolism, proliferation and repair, potassium and calcium ion transport, and cell proliferation and signal transduction [70]. ATP is involved in the reaction in the form of Mg^{2+}-ATP, so changes in intracellular magnesium directly affect mitochondrial function and energy metabolism [71]. There is plenty of evidence that magnesium deficiency can lead to oxidative stress and inflammatory reaction, which can accelerate PH. Magnesium homeostasis is coregulated by related transporters such as transient receptor potential melastatin (Trpm) protein, magnesium transporter (MagT) protein, cyclin and cystathionine β-synthase (CBS) domain divalent metal cation transport mediator (CNNM) protein, and SLC protein, but it is still unclear whether many magnesium ion transporters interact with each other to promote the occurrence and development of PH [72].

4.1 | Trpm7

In adult male rats with chronic hypoxia or MCT-induced PH, magnesium supplementation could alleviate the degree of right heart hypertrophy and pulmonary vascular wall thickening and regulate the mobilization, binding, and translocation of calcium ions in VSMCs [73], as well as reverse the changes in magnesium ion transporter expression. High concentrations of magnesium ions can also significantly inhibit the proliferation and migration of PASMCs and increase apoptosis, whereas low concentrations of magnesium ions have the opposite effect. As shown in Figure 6, in PASMCs, siRNAs targeting SLC41A1/2, CNNM2, and Trpm7 attenuated PASMCs proliferation and migration and promoted apoptosis. High magnesium ion incubation also inhibited hypoxia-induced upregulation and nuclear translocation of NFATC3 in PASMCs [74]. Magnesium ions, as natural calcium antagonists and cofactors of many enzymatic reactions, play a crucial role in regulating a variety of cellular functions, including many vascular functions [75]. It is concluded that PH affects the steady state of magnesium ions in PASMCs and the angiotensin II-triggered magnesium ion efflux [74]. However, high magnesium concentrations can decrease the proliferation and migration of PASMCs and promote their apoptosis [76–78]. In PASMCs, magnesium modulates calcium signal transduction through the Trpm7 channel [79].

4.2 | MagT1

In a rat model of MCT-induced PH, the effect of magnesium ions on the endothelium-dependent relaxation of PAs during PH was observed. As shown in Figure 7, it was found that high magnesium ions may inhibit the calcium ion influx mediated by three different types of calcium channel activators through competitive action with calcium ions or attenuate PAs contraction in PH rats by affecting agonist-contraction coupling and altering vascular responsiveness to vascular agonists [80, 81]. Thus, high magnesium concentrations can act directly on VSMCs and endothelial cells to induce vasodilation or promote endothelium-dependent vasodilation by modulating

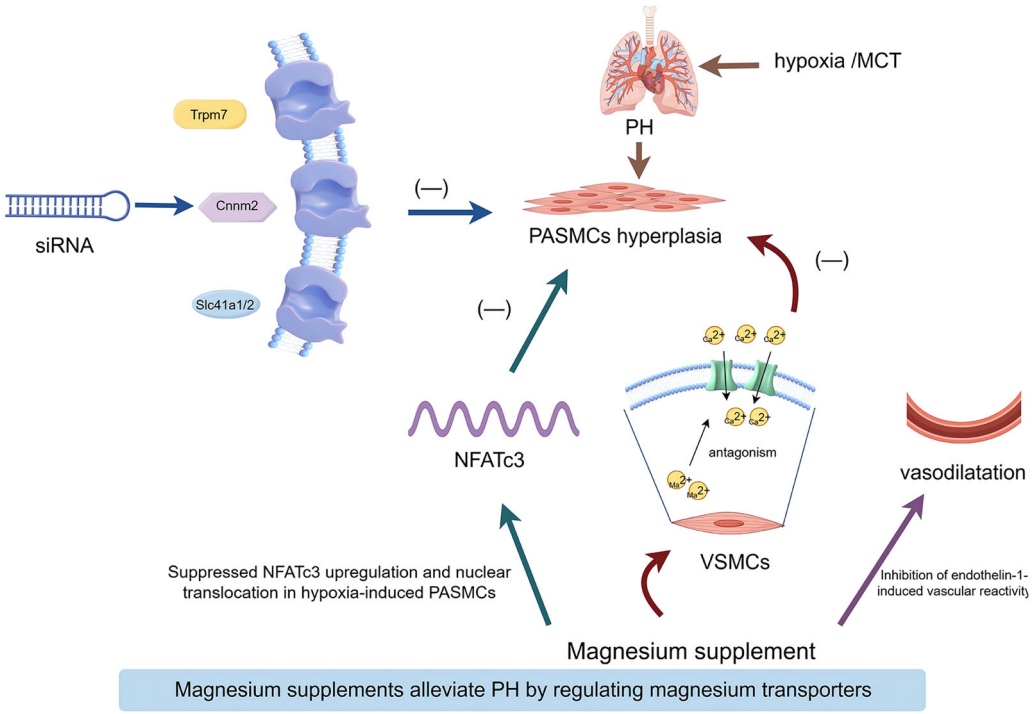

FIGURE 6 | Magnesium supplement reduces PH by regulating magnesium transporter.

vascular endothelial function. High magnesium concentrations are more sensitive to the endothelium-dependent vasodilation of PAs [82]. Meanwhile, in animal models of PH, magnesium ions have also been shown to reduce pulmonary arterial pressure and improve cardiac output [83]. Magnesium ions can attenuate endothelin-1-induced vasoreactivity and enhance PAs relaxation in mice. The increase in magnesium ion intake may attenuate the endothelin-1-induced contractile response and promote the release of NO from endothelial cells to improve vasodilation, potentially through the MagT1. Long-term exposure to hypoxic environments can cause endothelial dysfunction that inhibits magnesium-dependent vasodilation regulation [84]. Taken together, it follows that magnesium ions not only alter vascular responses to vasodilators and vasoactive agonists but also affect endothelin-1-induced endothelial disruption and intact mouse PAs contraction. This may be related to the fact that magnesium ion removal reduces the sensitivity of PAs to NO-mediated vasodilation, possibly through the downregulation of MagT1 [84].

5 | Zinc Ion Channels

Zinc is an essential micronutrient and a crucial cofactor for numerous enzymes, as well as a key component of zinc finger structures. It serves as a second messenger that activates various signaling pathways, including phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and extracellular signal-regulated kinase (ERK) [85]. The elevated expression of the zinc transporter ZIP12 in lung tissue, along with the activation of the PI3K/AKT and ERK pathways and the recently identified sphingosine-1-phosphate targets, may play significant roles in the initiation and progression of PH [86].

5.1 | SLC Family 39 Member 12

ZIP12 is a transmembrane protein mainly located in the cell membrane that transports zinc ions from the extracellular space or organelles to the cytoplasm. As shown in Figure 8, in hypoxic PH, the hypoxia-inducible factor-1α (HIF-1α) pathway upregulates the expression of ZIP12, induces an increase in intracellular free zinc ions, and promotes PASMCs proliferation [87]. MCT can directly cause endothelial injury and promote vascular remodeling [88]. ZIP12 expression was increased in PASMCs of MCT-induced PH rats, and the proliferation and migration of PASMCs were also significantly increased. All these effects were significantly reversed after silencing ZIP12. In contrast, overexpression of ZIP12 produced the opposite effect in PASMCs of control rats. As a lipid kinase, PI3K exists in the cytoplasm and is an important signaling molecule closely related to cell life activities. PI3K normally regulates its downstream effects by phosphorylating target proteins, including cell proliferation and migration. AKT is a pivotal component of the PI3K/AKT signaling pathway, where its activation plays a critical role in cell proliferation, antiapoptosis, and migration processes [89]. This pathway is activated by inflammatory factors, which stimulate the proliferation and hypertrophy of PASMCs, enhance cell migration, and downregulate the expression of α-smooth muscle actin and smooth muscle actin-22α, ultimately promoting PVR [90]. Selective inhibition of AKT phosphorylation by y294002, a PI3K/AKT pathway-specific inhibitor, abrogated the effect of ZIP12 overexpression on promoting cell proliferation and migration and partially inhibited ZIP12 overexpression-induced ERK1/2 phosphorylation. However, inhibition of ERK activity by U0126, an ERK pathway-specific inhibitor, partially reversed this effect and did not affect the ZIP12 overexpression-induced increase in AKT phosphorylation. In conclusion, ZIP12 is involved in PVR of PH and promotes PASMCs proliferation

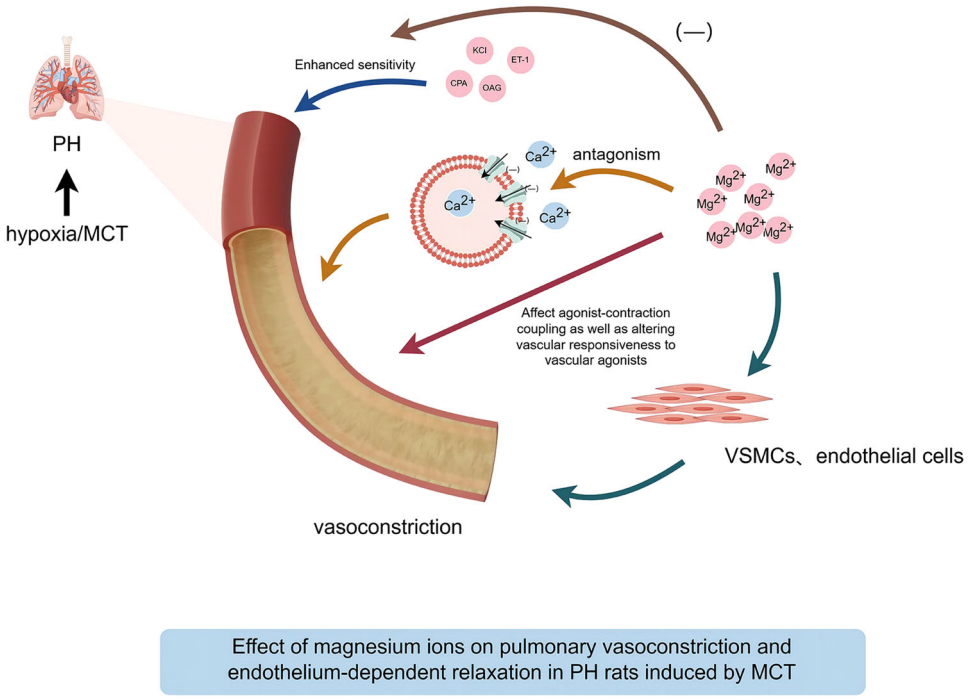

FIGURE 7 | Effect of magnesium ion on pulmonary vasoconstriction and endothelium-dependent relaxation induced by MCT in PH rats.

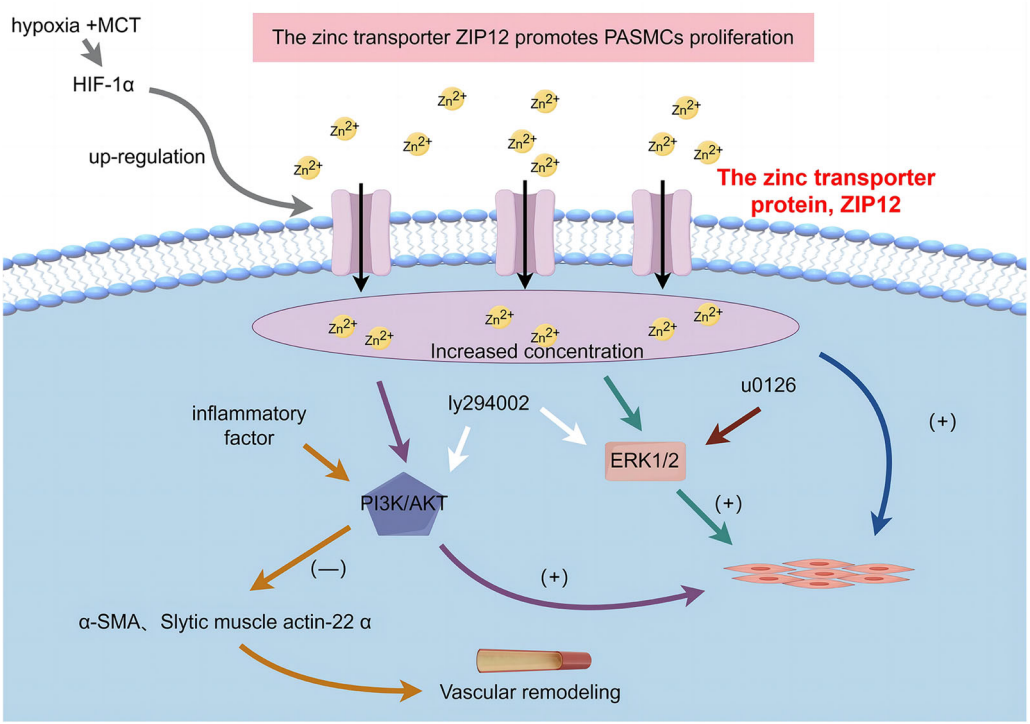

FIGURE 8 | Effect of zinc transporter ZIP12 on proliferation and migration of PASMCs.

and migration. The mechanism of these effects is mediated by enhancing the AKT/ERK signaling pathway [86].

6 | Chloride Ion Channels

In addition to persistent vasoconstriction, extensive remodeling of intrapulmonary arterioles, and right heart hypertrophy, which are hallmark features of PH, mitochondrial fission and metabolic switching from oxidative phosphorylation to glycolysis are also key features of vascular pathology in PH, associated with intense endothelial cell proliferation and apoptosis. In studies of mitochondrial dysfunction and energy metabolism in PAECs by two intracellular chloride channel proteins, recombinant chloride intracellular channel (CLIC)1 and CLIC4 proteins, it was found that both proteins are highly expressed in

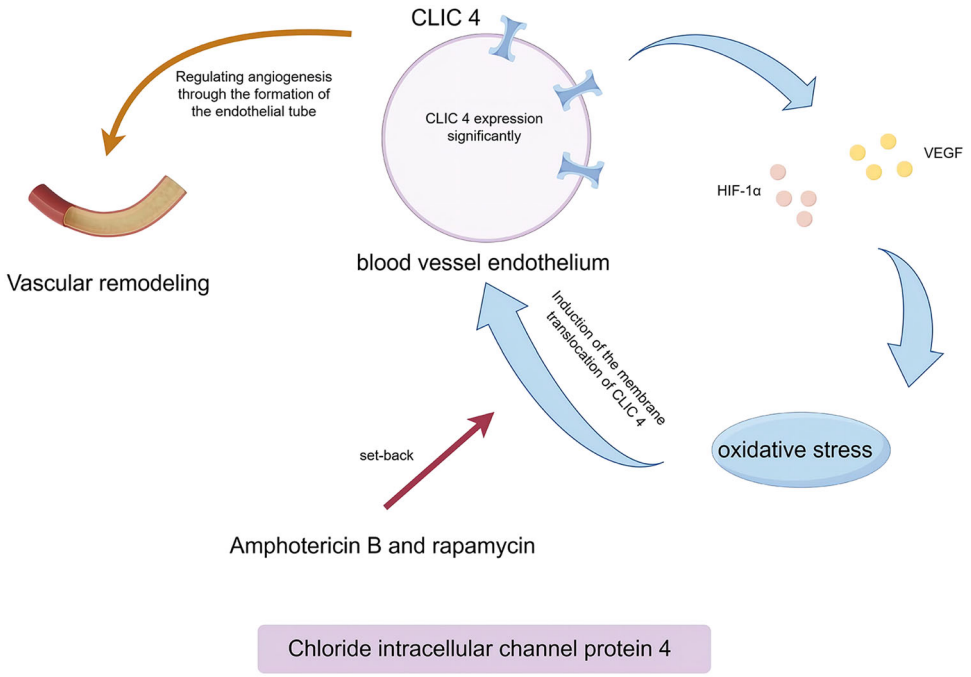

FIGURE 9 | Relationship between CLIC4 expression and vascular pathology of PH.

PH and cancer. The pathological overexpression of CLICs induced mitochondrial fragmentation, inhibited the formation of mitochondrial lysis, and induced the metabolic transition to glycolysis in human PAECs.

6.1 | Recombinant CLIC4 Protein

CLIC4 is a novel intracellular ion channel protein closely related to vascular biology and tumors. It can regulate cell proliferation, apoptosis, and angiogenesis and participate in many pathological signaling pathways. Compared to healthy lung tissue, CLIC4 is highly expressed in the pulmonary vascular endothelium of PH patients, especially in the occlusive and plexiform lesions caused by endothelial cell proliferation, apoptosis, and angiogenesis disorder. Increased expression of CLIC4 is an early manifestation and mediator of PH endothelial dysfunction [91]. CLIC4 can regulate multiple stages of angiogenesis by forming endothelial lumens and plays a role upstream of HIF-1α and vascular endothelial growth factor signaling, thereby driving the development of oxidative stress. Therefore, abnormal expression of CLIC4 may be associated with the vascular pathology of PH [92] (Figure 9). Structural discoveries of CLIC4 inhibitors are currently being actively explored, and nuclear magnetic resonance analysis has confirmed the binding and conformational disruption of amphotericin B and sirolimus. These compounds also reverse stress-induced translocation of CLIC4 to the membrane and inhibit migration of PAECs, making them novel targets for PH therapy.

6.2 | Chloride Channel 3

Chloride channel 3 (ClC-3) is a gene encoding a volume-activating channel candidate protein, and membrane ion channels are critical for cell proliferation, a concept first shown to apply to potassium channels and subsequently proposed for other cation and chloride channels [93, 94]. ClC-3 also seems to be involved in the formation and development of PH and plays a key role in the hyperproliferation of PASMCs. Previous studies have demonstrated that chloride current (ICl) inhibits the proliferation of PASMCs [95, 96], and ClC-3 mRNA was found to be most abundant after measuring ICl channel genes. This suggests that ClC-3 may be a new target for the prevention of PH.

6.3 | Transmembrane Protein 16A

CACCs play an important role in many physiological processes. As shown in Figure 10, when voltage-dependent calcium channels are activated, calcium ions flood into the cells and chloride ions rush out, causing blood vessels to constrict. Transmembrane protein 16 (TMEM16) is considered a CACC because of its high similarity in sequence and predictable transmembrane topology, but to date, only TMEM16A and TMEM16B have been definitively identified as CACCs, and TMEM16A has 10 subtypes. Moreover, it has 62% structural similarity with TMEM16B [97]. Ion channels in the PASMCs membrane play an important role in maintaining the tension of pulmonary vessels, with CACCs playing a crucial role in maintaining the chloride homeostasis inside and outside the membrane of VSMCs and regulating vascular tension [98]. In a study of an animal model using an aortic-caval shunt, pulmonary TMEM16A and PCNA expression were increased, and PASMCs proliferated in the shunt group after surgery. This may be related to the regulation of PASMCs proliferation by TMEM16A in high pulmonary blood flow-induced PH [99]. In addition, it has now been shown that TMEM16A also plays a crucial role in IPAH. In PASMCs from IPAH patients or animals, the expression and function of TMEM16A were significantly increased, which in turn led to the hyperproliferation of

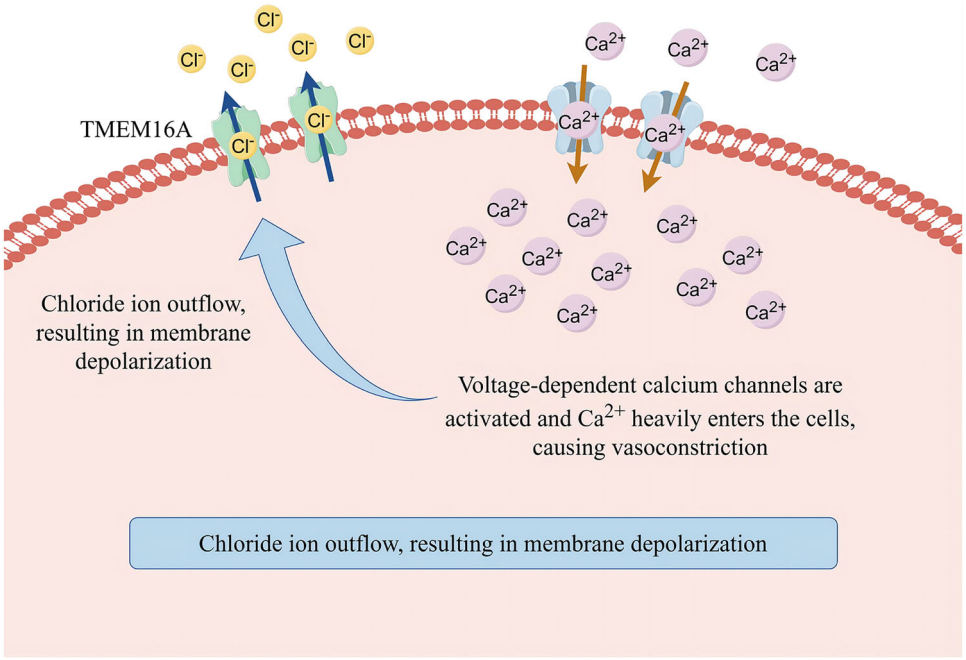

FIGURE 10 | Activation of TMEM16A promotes pulmonary vascular resistance in PH.

PASMCs [100], which may be related to the phosphorylation of c-fos. This was confirmed by the use of TMEM16A blockers as well as vasodilation after silencing TMEM16A and inhibition of proliferation of PASMCs. Similarly, the presence of active TMEM16A was found in the mitochondria [101] and plasma membrane of PAECs. A recent study on a mouse model reported that enhanced activity of TMEM16A promotes Nox2/p22phox expression and reactive oxygen species production [102], leading to PA endothelial dysfunction [103].

6.4 | Cystic Fibrosis Transmembrane Conductance Regulator

The CFTR is an ATP-gated Cl^- channel belonging to the ABC transporter protein superfamily, which is not only a secreted chloride channel but also extensively regulates the activity of other ion channels. An earlier study found that CFTR is expressed not only in cardiomyocytes and endothelial cells but also in tracheal SMCs [104, 105] and aortic SMCs in rats and mice. However, CFTR expression levels were significantly reduced in PASMCs and PAECs in PH patients and animal models [100], and in hypoxia-induced PH, upregulated HIF-1α suppressed CFTR expression [106], and prolonged suppression of CFTR led to the formation of RVSPs and distal neovessels and promoted PVR [20]. This suggests that part of the downregulation of CFTR may be due to overexpression of HIF-1α. In addition, there is clear evidence in several recent studies [107] that PA endothelial CFTR can affect vasodilation and that CFTR impairment leads to a series of overlapping endothelial dysfunctions [108], proliferation of PAECs and PASMCs, including increased endothelial cell activation due to leukocyte extravasation, oxidative stress, decreased cell viability, growth, delayed wound repair, and cessation of autophagy [109], and is accompanied by an EndMT, which may be a secondary event caused by endothelial dysfunction due to CFTR injury. However, CFTR modulators were able to reduce the expression of mesenchymal markers, EC activation, and their subsequent leukocyte adhesion [109, 110]. In a study involving rat IPA [111], it was found that CFTR in PASMCs can be activated by cyclic adenosine monophosphate (cAMP), leading to endothelium-independent pulmonary vasodilation. Overall, these results suggest that CFTR contributes to PA tension and plays a crucial role in the regulation of pulmonary vascular tension, making it a potentially powerful target for future research.

7 | Acid-Sensitive Ion Channels

The acid-sensing ion channel (ASIC), a novel and noteworthy ion channel in the development of PH, is a nonselective cation channel controlled by extracellular protons and is widely present in a variety of neuronal and nonneuronal tissues [110]. It has been shown that ASIC1 [112] channels may promote hypoxia-induced depolarization of pulmonary arterial tone, in addition to their role in promoting voltage-independent Ca^{2+} inward flow, which is involved in altering Ca^{2+} homeostasis and vasoconstriction in PASMCs. However, the regulation of ASICs in PAs is very complex, our knowledge of it is limited, and future efforts are still needed to explore it.

8 | Pannexins—A New Mechanical Stimulus-Sensitive Channel Protein

Pannexins are a family of glycoproteins, consisting of PANX1, PANX2, and PANX3, that are highly permeable to ATP and other signaling molecules [113]. All three pannexins are expressed in pluripotent stem cells, but PANX1 is the most abundant [114]. PANX1 channels are activated when there is a high extracellular concentration of K^+ or a high intracellular concentration of Ca^{2+} [115, 116], and the activation of PANX1 leads to the formation of channels in the cell membrane that release ATP, guanosine

triphosphate, K^+, Ca^{2+}, and so forth [117]. In a study by Grimmer et al. [118], Panx1 was identified as a novel pulmonary vasoconstriction regulator. Panx1 plays a role in modulating pulmonary vasoconstriction by acting as a direct or indirect modulator of the PASMCs Ca^{2+} response to hypoxia. In addition, Panx1 may indirectly regulate PASMCs Ca^{2+} homeostasis and signaling through other mechanisms and pathways, such as Panx1–P2X7 coupling through an ATP-independent mechanism. Panx1 may also indirectly regulate PASMCs Ca^{2+} homeostasis and signaling through other mechanisms and pathways, such as Panx1–P2X7 coupling through ATP-dependent mechanisms [118]. Therefore, studies on Panx1 clearly deserve further exploration.

9 | Conclusion

The proliferation and migration of PASMCs play a key role in the pathogenesis of PH [119] and are also targets of several current therapies, including prostacyclin analogs [120], endothelin receptor antagonists [121], and phosphodiesterase inhibitors [122, 123]. With further research and application of various techniques, it has been found that the ion channels on the cell membranes of PASMCs and PAECs are closely related to the occurrence and development of PH [124, 125]. Understanding how these channels affect the proliferation and migration of PASMCs and the dysregulation of PAECs has important implications for the clinical treatment of PH, particularly in the development of therapeutic strategies targeting ion channels.

This article reviews the structure, function, expression, pathogenesis, and potential therapeutic targets of several ion channels in the membranes of PASMCs and PAECs. However, they have not been fully studied, and this area has broad research prospects and is challenging in the field of life sciences. Ion channels not only play a role in the transport of ions but may also be involved in complex signal transduction processes. Research on the regulation mechanisms of ion channel steady state, activation and inhibition, and transmembrane transport can provide a solid scientific basis for the treatment of PH caused by ion channel dysfunction.

Author Contributions

Han-Fei Li: literature search, study screening, data curation, formal analysis, investigation, software, writing–original draft, preparation. **Xin-Yao Li:** literature search, conceptualization. **Yu-Qing Sun:** writing–review and editing, figure preparation. **Ze-Ying Zhi:** study screening, data curation. **Liao-Fan Song:** literature search, study screening. **Meng Li:** writing–review and editing. **Yi-Ming Feng:** weriting–review and editing. **Zhi-Hao Zhang:** writing–review and editing. **Yan-Feng Liu:** writing–original draft, preparation. **Yu-Jing Chen:** supervision, project administration, conceptualization, investigation, validation, writing–review and editing, funding acquisition. **Fan-Rong Zhao:** supervision, project administration, conceptualization. **Tian-Tian Zhu:** supervision, project administration, formal analysis, writing–review and editing, funding acquisition.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

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