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Hydrogen sulfide as a new therapeutic target of pulmonary hypertension: an overview with update on immunomodulation

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Pulmonary hypertension (PH) is a complex and progressive vascular disease characterized by elevated pulmonary arterial pressure (PAP) and vascular resistance, leading to right ventricular failure and, ultimately, death. Current therapies primarily focus on vasodilation and symptom management, but there remains a critical need for treatments that address the underlying pathophysiological mechanisms of PH. Numerous studies have identified hydrogen sulfide (H₂S) as a potential therapeutic target in PH. Traditionally recognized for its toxic effects at high concentrations, H₂S is now known to play crucial roles in various physiological processes, including vasodilation, anti-inflammation, and antioxidation, which are relevant to PH pathogenesis. Given its multifaceted roles in the pathophysiology of PH, H₂S represents a promising therapeutic target. Strategies to enhance endogenous H₂S production or administer exogenous H₂S donors are being explored as potential treatments for PH. These approaches aim to harness the vasodilatory, anti-inflammatory, antioxidant, and anti-remodeling properties of H₂S to mitigate disease progression and improve patient outcomes. Future research should focus on optimizing H₂S-based therapies and exploring their clinical efficacy and safety in PH patients.

KEYWORDS

hydrogen sulfide, pulmonary hypertension, oxidative stress, immunomodulation, organosulfur compounds

Introduction

Pulmonary hypertension (PH) has a prevalence of 11–26 cases per million adults, with a mortality rate of approximately 50% at 5 years despite targeted therapies (Thenappan et al., 2018). PH is a rare disorder marked by remodeling of small pulmonary arteries and increased pulmonary arterial pressure (PAP), leading to progressive right heart failure and death (Austin and Loyd, 2014; Zhang and Sun, 2020a; Zhang et al., 2023; Zhang et al., 2024). This remodeling involves interactions among various cell types, including endothelial cells, smooth muscle cells, and fibroblasts, across the distinct layers of the pulmonary arteries, resulting in histological alterations to the vessel wall (Zhang and Sun, 2021; 2022; Bian and Chen, 2024). Endothelial dysregulation and proliferation in the intima, smooth muscle cell

proliferation and resistance to apoptosis in the medial layer, and adventitial fibroblast activation collectively contribute to the narrowing of the vascular lumen, thus causing PH (Nie et al., 2020; Wołowicz et al., 2023). Consequently, strategies that inhibit cell proliferation or induce apoptosis to reverse pulmonary remodeling may offer therapeutic potential for PH. Emerging evidence suggests that PH shares numerous pathogenic mechanisms with cancers, positioning it as a proliferative disorder with cancer-like characteristics (Sun H. J. et al., 2022; He et al., 2023). This similarity presents opportunities to explore cancer-specific therapeutic approaches, including the use of anti-cancer agents, for the treatment of PH (Nicoleau et al., 2021; Li et al., 2022).

PH is classified into four groups, including pulmonary arterial hypertension (PAH), PH due to left heart disease, PH due to lung diseases or hypoxia, and PH due to pulmonary artery obstruction (Castillo-Galán et al., 2025; Hu et al., 2025). PAH is found to result from endothelial dysfunction, vasoconstriction, and vascular remodeling of the small pulmonary arteries. Elevated left atrial pressure due to systolic or diastolic dysfunction, valvular disease, or congenital defects leads to pulmonary venous hypertension and passive pulmonary artery pressure elevation. Chronic hypoxia causes pulmonary vasoconstriction, leading to vascular remodeling. Conditions include chronic obstructive pulmonary disease (COPD), interstitial lung disease, and sleep apnea. Chronic thromboembolic pulmonary hypertension (CTEPH) results from unresolved pulmonary emboli and thrombus organization, leading to mechanical obstruction and secondary remodeling. The etiopathogenesis of PH involves a complex interplay of genetic, molecular, and environmental factors, leading to vascular remodeling, increased pulmonary vascular resistance, and right ventricular dysfunction. Specifically, the pathogenesis of PH is driven by factors such as mutations in the type II bone morphogenetic protein receptor (BMPR2), chronic inflammation, fibrosis, immune activation, and mitochondrial metabolic dysfunction (Thenappan et al., 2018).

The current management of PH aims to improve symptoms, delay disease progression, and reduce mortality (Ge et al., 2024). Treatment strategies vary depending on the PH group and disease severity. Generally, oxygen therapy for hypoxia, diuretics for volume overload, physical activity, and pulmonary rehabilitation are routine methods for treating PH. In addition, endothelin receptor antagonists (Bosentan, Ambrisentan, and Macitentan), phosphodiesterase-5 inhibitors including Sildenafil, and Tadalafil, soluble guanylate cyclase (sGC) stimulator Riociguat, prostacyclin analogues and prostacyclin receptor agonists including Epoprostenol, Treprostinil, and Selexipag, calcium channel blocker including Nifedipine, and Amlodipine are commonly used drugs for treating PH (Azaredo Raposo et al., 2024; DeVughn et al., 2024; Madonna et al., 2024; Tangcharoen et al., 2024; Doktor et al., 2025; Yi et al., 2025). Overall, PH treatment requires a multidisciplinary approach and close monitoring to optimize outcomes.

The immune system plays a significant role in the pathogenesis of PH, with various immune cells, cytokines, and signaling pathways contributing to vascular remodeling, inflammation, and fibrosis in the pulmonary vasculature (Zhao et al., 2024). Overproduction of inflammatory cytokines and chemokines, immune cell infiltration,

and NLRP3 inflammasome activation are critically implicated in the pathogenesis of PH (Rudyk and Aaronson, 2021). Understanding the immune mechanisms in PH has led to the exploration of immunomodulatory therapies. Drugs targeting specific cytokines, chemokines, or immune cells, as well as those modulating the NLRP3 inflammasome, are being investigated for their potential to treat PH. PH exhibits heterogeneous and multifactorial pathophysiology, underscoring the importance of a comprehensive understanding of their underlying mechanisms. Despite existing treatments, including renin-angiotensin system blockers, calcium antagonists, steroidal mineralocorticoid receptor antagonists, and thiazide-type diuretics, nearly half of PH patients fail to achieve adequate control (Halimi et al., 2024). Thus, optimizing the prevention, treatment, and diagnosis of PH necessitates a deeper exploration of its pathogenic network.

The endogenous gasotransmitters, such as nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H₂S), and sulfur dioxide (SO₂), are characterized by their rapid generation, swift transmission, diverse functions, and short half-lives, playing pivotal roles in the pathogenesis of PH (Huang et al., 2022; Sun Y. et al., 2022; Liu et al., 2023; Gerges et al., 2024; Madonna et al., 2024; Kanemaru and Ichinose, 2025; Zhang et al., 2025). Significant progress has been made in elucidating the involvement of these gasotransmitters in PH development (Sun Y. et al., 2022; Song et al., 2024). Among them, H₂S, the third identified gasotransmitter after NO and CO, is particularly implicated in various cardiovascular diseases, including PH (Turhan et al., 2022; Wang and Tang, 2022). A downregulated endogenous H₂S pathway has been observed in pulmonary vascular diseases such as PH (Zhang et al., 2003; Chen et al., 2020; Roubenne and Marthan, 2021). However, exogenous H₂S donors can mitigate the progression of PH (Chunyu et al., 2003; Schiliro et al., 2021). H₂S is involved in the regulation of vascular tone, reduction of blood pressure and PAP, inhibition of vascular smooth muscle cell (VSMC) proliferation, modulation of endothelial inflammatory responses, induction of VSMC apoptosis, and prevention of vascular collagen remodeling (Figure 1) (Qingyou et al., 2004). Notably, H₂S exerts several immune regulatory mechanisms that influence cardiovascular health, including anti-inflammatory, antioxidant, and cytoprotective effects (Pan et al., 2017). H₂S regulates the activity of various immune cells, including macrophages, T Cells, and neutrophils. It can shift macrophages from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype, thereby promoting tissue repair and reducing inflammation in the cardiovascular system. H₂S is reported to decrease the adhesion of leukocytes to the endothelium, a critical step in the initiation of inflammation and atherosclerosis. By reducing leukocyte adhesion, H₂S prevents the infiltration of immune cells into the vascular wall and subsequent inflammatory responses. H₂S has been revealed to modulate the expression of chemokines and adhesion molecules (e.g., ICAM-1, VCAM-1) on endothelial cells, further controlling the recruitment and migration of immune cells into cardiovascular tissues.

This review will summarize recent advancements in understanding the functional and mechanistic roles of H₂S in the inflammatory and immunoregulatory processes underlying PH. We will also discuss the crucial role of H₂S in various PH subtypes, including hypoxic PH (HPH), monocrotaline (MCT)-induced PH,

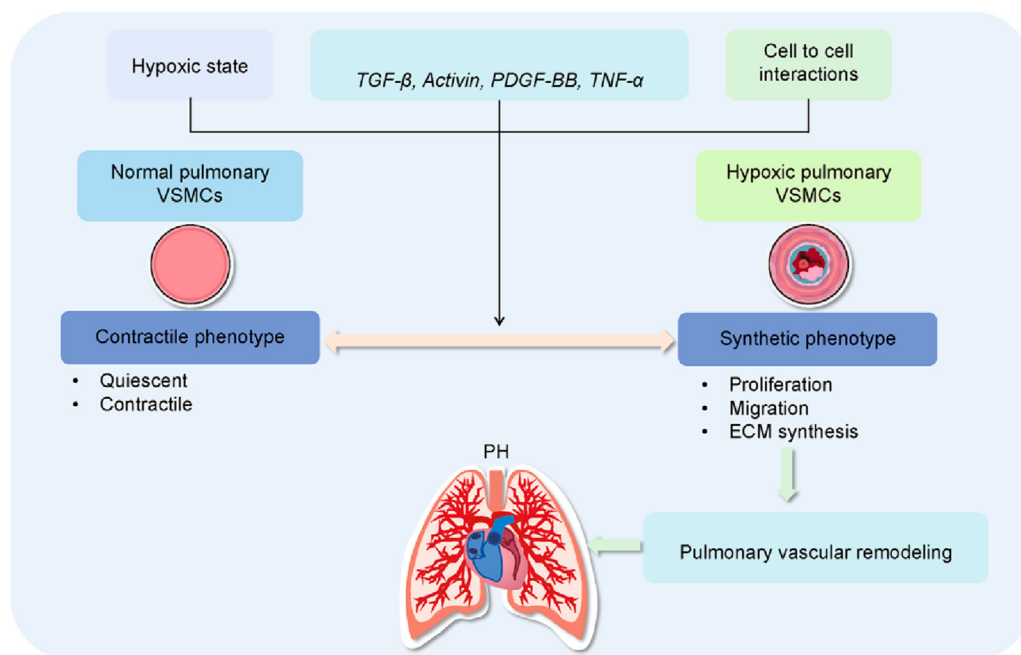


FIGURE 1

Role of VSMC dysfunction in pulmonary vascular remodeling and PH. In the pulmonary circulation, the heterogeneity and phenotypic plasticity of vascular smooth muscle cells (VSMCs) are crucial for maintaining vascular function in the lungs. Quiescent pulmonary VSMCs exhibit a contractile phenotype, characterized by low extracellular matrix (ECM) synthesis and a fusiform shape, representing their differentiated state. In response to hypoxia, growth factors, inflammatory mediators, pulmonary VSMCs transition from a contractile to a synthetic phenotype. This change is marked by increased proliferation, migration, and ECM synthesis, along with the development of PH.

high blood flow-induced PH, congenital heart disease (CHD)-associated PH, and COPD-associated PH. Additionally, we address the potential challenges in developing H₂S-based therapies to modulate pathological processes in PH. A deeper understanding of the immunomodulatory and biochemical functions of H₂S may pave the way for novel therapeutic strategies targeting PH.

H₂S biosynthesis and catabolism

H₂S is primarily produced endogenously through the enzymatic pathways, whereas the non-enzymatic pathways also contribute to its mobilization under physiological conditions (Olson, 2018; Yang et al., 2019). In physiological settings, approximately 28% of H₂S exists in its undissociated form, 72% as hydrosulfide anions (HS⁻), and a negligible amount as sulfide anions (S₂⁻) (Li and Lancaster, 2013). The effects of the undissociated and dissociated forms are collectively referred to as H₂S. Initial studies estimated H₂S concentrations at around 30 μM in lung tissue, increasing to over 200 μM in the heart, brain, and plasma (Furne et al., 2008). However, those methodological issues, such as variability in pH, temperature, and substrate concentration, indicated these levels might not reflect physiological reality (Vitvitsky et al., 2012). More accurate assessments suggest that steady-state H₂S concentrations are in the nanomolar range in most tissues and plasma (Vitvitsky et al., 2012). This lower concentration aligns with the high turnover rate of H₂S, characterized by significant production and rapid oxidation under physiological conditions (Vitvitsky et al., 2012). At

concentrations exceeding 50 μM, H₂S can have detrimental effects, including mitochondrial poisoning due to the inhibition of cytochrome c oxidase (complex IV) (Cooper and Brown, 2008; Libiad et al., 2019). Therefore, the dual effects of H₂S necessitate careful regulation of its production and clearance.

Traditionally, H₂S is generated endogenously through both enzymatic and non-enzymatic pathways (Chiku et al., 2009). The primary enzymatic production occurs in the cytoplasm, where L-cysteine (L-Cys) serves as the main substrate. Three key enzymes involved in this process include cystathionine-γ-lyase (CSE), cystathionine-β-synthase (CBS), 3-mercaptopyruvate sulfur transferase (3-MST), and cysteine aminotransferase (CAT) (Chiku et al., 2009). CSE and CBS catalyze the production of H₂S in the cytoplasm using L-cysteine and L-homocysteine as substrates (Majtan et al., 2018). Additionally, 3-MST, in conjunction with CAT, generates H₂S from L-cysteine in both the cytoplasm and mitochondria. 3-MST can also produce H₂S from D-cysteine in coordination with D-amino acid oxidase (Majtan and Kožich, 2023). The expression of these enzymes is tissue-specific: CSE is abundant in the thoracic aorta, liver, portal vein, ileum, and non-vascular tissues; CBS is predominantly found in the brain, kidney, and liver; and 3-MST is active in the aorta, kidney, brain, and liver (Li et al., 2011). CSE is particularly crucial for H₂S production in the cardiovascular system. Recent advances in the study of endogenous H₂S metabolism suggest that H₂S can be generated independently of CSE, CBS, and 3-MST/CAT coupling pathways. In contrast to the enzymatic pathways, non-enzymatic H₂S production is partially catalyzed by the synergistic action of vitamin B6 and iron, using cysteine as a substrate (Paul and Snyder, 2012). This non-

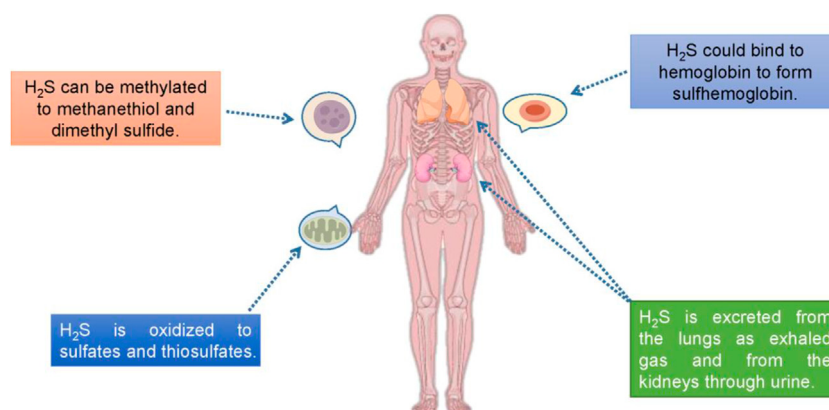


FIGURE 2

There are four known pathways for H₂S decomposition in mammal system.

enzymatic pathway is active in the heart, lungs, spleen, muscles, plasma, bone marrow, and especially in erythrocytes. Free H₂S can be oxidized in mitochondria by sulfhydryl reductase (SQR) or methylated in the cytoplasm by sulfhydryl-S-methyltransferase (Hu and Lukesh, 2023). Additionally, H₂S is excreted through biological fluids after binding with methemoglobin or other metal and disulfide-containing molecules (Figure 2). H₂S levels can be increased using inorganic sulfide salts, organic H₂S donors, or phosphodiesterase inhibitors. Common H₂S donors include sodium hydrosulfide, GYY4137, 4-carboxyphenyl-isothiocyanate acid esters (4CPI), SG-1002, cysteine analogs, S-propylcysteine, S-allylcysteine, N-acetylcysteine, and drug chimeras such as l-DOPA, NOSH-sulindac (AVT-18A), NOSH-aspirin, and ACS67 (a combination of latanoprost and an H₂S-releasing moiety) (Zhang L. et al., 2018). S-propargyl-cysteine (SPRC), also known as ZYZ-802, is a slow-releasing H₂S donor and an analog of S-allylcysteine (SAC), which is abundant in aged garlic (*Allium sativum*) extract (Wen and Zhu, 2015). N-acetylcysteine (NAC) is widely used as an antioxidant and cell protectant (Cerdeira and Pluth, 2018), and L-cysteine is a substrate for endogenous H₂S production (Salvi et al., 2016). Mitochondria-targeted compounds like AP39 and AP123 also play roles in H₂S regulation (Gerő et al., 2016). Correspondingly, it is crucial to understand the role of H₂S in the physiology and pathophysiology of pulmonary blood vessels by using exogenous H₂S donors or regulating endogenous H₂S. Although minor, non-enzymatic H₂S release occurs through the chemical reduction of reactive sulfur groups in thiosulfates or polysulfides. Benavides et al. demonstrated that dietary *A. sativum*-derived organic polysulfides, such as diallyl disulfide and diallyl trisulfide, can release H₂S in the presence of glutathione (GSH) and glucose metabolism (Benavides et al., 2007). Consequently, it has been suggested that basal circulating H₂S levels may result from this non-enzymatic process.

H₂S functions as a signaling molecule only at physiological, relatively low concentrations. At higher concentrations, H₂S becomes toxic by inhibiting cytochrome c oxidase (complex IV) of the mitochondrial respiratory chain, impairing cellular respiration (Jiang et al., 2024; Nishimura et al., 2024). To

prevent this toxicity, H₂S bioavailability is tightly regulated through its safe storage as bound sulfane sulfur and/or efficient catabolism (Ichinose and Hindle, 2024). In mammals, H₂S is primarily oxidized in mitochondria via the sulfide oxidation pathway, with thiosulfate and sulfate as the final products (Iciek and Biliska-Wilkosz, 2022; Paul, 2022). Three enzymes are involved in H₂S catabolism: sulfide quinone oxidoreductase (SQR), persulfide dioxygenase (ETHE1), and rhodanese (thiosulfate sulfurtransferase, TST) (Hildebrandt and Grieshaber, 2008). The oxidation pathway begins with SQR, which catalyzes the formation of SQR persulfide (SQR-SSH) at one of its two Cys-SH residues (Jackson et al., 2012). SQR is a flavoprotein bound to the inner mitochondrial membrane. As it oxidizes, a noncovalently bound FAD is reduced, and electrons are transferred to coenzyme Q, contributing to the electron transport chain and ATP production. For this reason, H₂S is considered the first inorganic substrate for oxidative phosphorylation, similar to succinate (Goubert et al., 2007). SQR has a high catalytic rate, ensuring efficient H₂S catabolism. The sulfur atom from SQR-SSH is transferred to GSH, forming glutathione persulfide (GSSH), which can then be oxidized to sulfite (SO₃²⁻) by ETHE1 or transferred to sulfite by TST to form thiosulfate. Sulfite is further oxidized to sulfate by sulfite oxidase (SO), or it can directly accept sulfur from SQR-SSH, producing thiosulfate. Some studies suggest that endogenous reducing compounds, such as DHLA, may also accept sulfur from SQR-SSH (Kabil and Banerjee, 2014). Additionally, GSSH can donate sulfur to proteins, forming protein persulfides. H₂S can also be oxidized by hemoproteins, where thiosulfate and inorganic polysulfides bind to heme iron. Initially, H₂S binds to Fe³⁺ in methemoglobin (MetHb), and additional H₂S molecules combine to form persulfide or polysulfide chains (Vitvitsky et al., 2015). These can be oxidized in the presence of oxygen to thiosulfate, which is then released. This oxidation process is particularly important in erythrocytes, which lack mitochondria. Other proteins, such as catalase, superoxide dismutase (SOD), and SOD2, can also oxidize H₂S to polysulfides, using oxygen or hydrogen peroxide as electron acceptors (Olson et al., 2017; Olson et al., 2018).

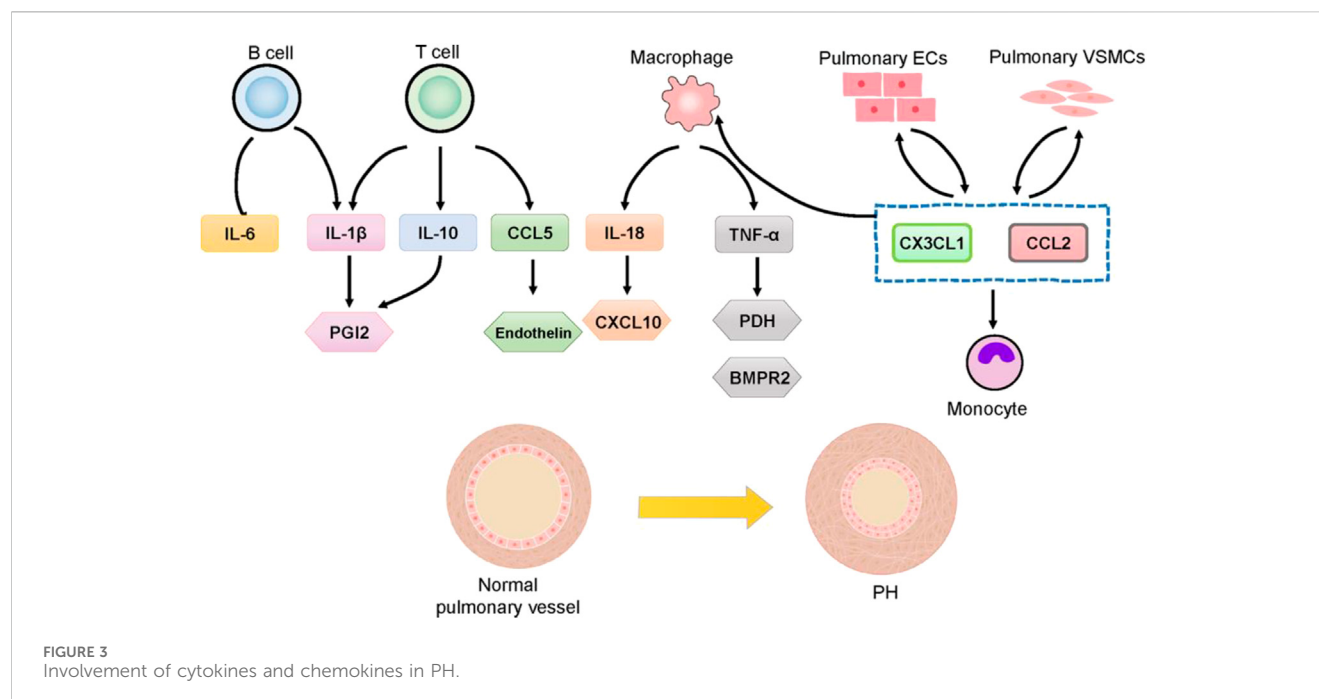
The signaling pathways modulated by H₂S

More and more studies have demonstrated that H₂S exerts regulatory effects by regulating diverse signaling pathways (Tao et al., 2024; Zhu et al., 2024), including modulation of epigenetic modifications, protein expression, activity, and localization, as well as influencing the redox microenvironment and interacting with other gasotransmitters such as NO and CO. H₂S was also found to impact cellular signaling pathways, such as phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), mitogen-activated protein kinase (MAPK), and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) (Tao et al., 2024). H₂S influences gene transcription through epigenetic regulation, particularly by modulating DNA methylation, a process involving the addition of methyl groups to DNA that often silences gene expression without altering the nucleotide sequence (Tao et al., 2024). In mammalian cells, DNA methylation predominantly occurs at the C5 position of CpG dinucleotides, facilitated by DNA methyltransferases (DNMTs) (Yang et al., 2025). H₂S suppresses Dnmt3a transcription via S-sulfhydration of the interferon regulatory factor 1 (IRF1), reducing methylation of the mitochondrial transcription factor A (TFAM) promoter in the vascular system (Li and Yang, 2015). This regulation helps maintain mitochondrial DNA (mtDNA) copy number and supports transcription of mtDNA-encoded genes (Li and Yang, 2015). Histones are proteins that package DNA into stable structural units, and their modification plays a crucial role in regulating gene expression and cellular functions. As epigenetic marks, histone modifications, such as acetylation, methylation, phosphorylation, and ubiquitination, can be inherited and are essential for recruiting or activating downstream effectors (Liu and Si, 2024). H₂S can enhance the expression and activity of histone deacetylase (HDAC), specifically silent mating type information regulator 2 homolog 1 (SIRT1). This effect is attributed to the S-sulfhydration of SIRT1 by H₂S, which increases its zinc binding, thereby promoting its stability and deacetylation activity (Calabrese and Scuto, 2020). Activation of SIRT1 by H₂S protects against diabetic nephropathy (Ahmed et al., 2019), mitigates insulin resistance (IR)-induced apoptosis in cardiomyocytes (Liu et al., 2017), and reduces atherosclerotic plaque formation (Du et al., 2019). Noncoding RNAs, which do not code for proteins, play essential regulatory roles in cellular processes. These RNAs are primarily classified into microRNAs (miRNAs), intronic RNAs, long noncoding RNAs (lncRNAs), circular RNAs, and extracellular RNAs (Sun et al., 2016; Zhang and Sun, 2020b; Zhang and Sun, 2020a; 2021). Several noncoding RNAs have been implicated in the protective effects of H₂S. For example, upregulation of miR-221 has been shown to attenuate ischemia-induced heart failure (Su et al., 2015; Verjans et al., 2018; Li M. et al., 2020). However, downregulation of miR-21 by the H₂S donor DATS promotes neovascularogenesis and may prevent cardiovascular diseases (Chiang et al., 2013). Transcription factors (TFs) are proteins that bind to specific DNA sequences to regulate gene transcription. Nuclear factor E2-related factor 2 (Nrf2) is a key TF involved in controlling the expression of numerous antioxidant genes. H₂S activates Nrf2 by S-sulfhydrating Kelch-like ECH-associated protein 1 (Keap1), which releases Nrf2 from repression, thereby mitigating oxidative stress (Hourihan et al.,

2013). Additionally, sulfhydration of Keap1, an E3 ubiquitin ligase substrate adaptor, inhibits its ability to degrade Nrf2, leading to the restoration of antioxidant gene expression. Specific S-sulfhydration sites on Keap1, such as Cys-151 in cellular aging and Cys-151 and Cys-273 in atherosclerosis associated with diabetes, are critical for this antioxidant defense mechanism (Xie et al., 2016). Ubiquitin is first activated by the ubiquitin-activating enzyme (E1), then transferred to the ubiquitin-conjugating enzyme (E2), and finally attached to the substrate by the ubiquitin ligase (E3) with the assistance of substrate adaptors. The ubiquitin-tagged proteins are subsequently recognized and degraded by the proteasome. H₂S has been shown to reduce the levels of muscle RING finger 1 (MuRF1) and atrogin-1, two muscle-specific E3 ligases, thus mitigating immobilization-induced skeletal muscle atrophy (Lu et al., 2020; Yang et al., 2024). Additionally, H₂S enhances S-sulfhydration at Cys-44 in MuRF1, which helps prevent cardiac muscle degradation in diabetic cardiomyopathy (DCM) (Sun et al., 2020; Peng et al., 2022). The activation of the PI3K/Akt signaling pathway mediates many protective effects of H₂S, including the regulation of autophagy, apoptosis, and inflammation. For instance, H₂S prevents osteoblast apoptosis to alleviate osteoporosis progression (Yan et al., 2017) and reduces reactive oxygen species (ROS) production and inflammation, protecting against ventilator-induced lung injury (Spasov et al., 2017) by activating the PI3K/Akt signaling pathway. In addition to its role in anti-inflammatory and anti-apoptotic processes, H₂S activates PI3K/Akt signaling in the treatment of neurological diseases (Xu et al., 2018; Li et al., 2021). In addition, H₂S inhibits MAPK signaling, providing therapeutic benefits in inflammatory and fibrotic conditions. This action protects alveolar epithelial cells against inflammation, injury, and apoptosis via the repression of prolyl hydroxylase 2/HIF-1 α /MAPK signaling, suggesting its potential in treating COPD and pulmonary fibrosis (Guan et al., 2020). H₂S also modulates the mTOR signaling pathway, a key regulator of cellular and organismal metabolism in response to environmental changes (Hou et al., 2017). In high-fat diet (HFD)-induced obesity, H₂S reverses abnormal activation of mTOR and IKK/NF- κ B pathways, alleviating hypothalamic inflammation (Zhao et al., 2022). Furthermore, H₂S suppresses the JAK/STAT signaling pathway to reduce inflammation and apoptosis, as observed in diabetes-induced myocardial fibrosis (Liu et al., 2018). The downregulation of JAK/STAT and NF- κ B signaling by H₂S also helps recover the protective effects of preconditioning against ischemia-reperfusion injury in aging hearts by reducing ROS levels (Li et al., 2016). In summary, H₂S plays a crucial role as a gasotransmitter in regulating multiple signaling pathways, contributing to cellular homeostasis and protection against pathological conditions.

Immune regulatory mechanism of PH

Pulmonary vascular remodeling in PAH is often marked by perivascular inflammatory infiltration, involving T Cells, B Cells, macrophages, dendritic cells (DCs), mast cells, and neutrophils (Figure 3). This suggests that immune cells play a significant role in pulmonary vascular remodeling (Galiè et al., 2009; Amaya-Uribe et al., 2019). T Cells, particularly helper T Cells (Th cells) and regulatory T Cells (Tregs), are critical components of the adaptive



immune response and are pivotal in the pathogenesis of PH (Rabinovitch et al., 2014; Wang R. R. et al., 2022). Th cells promote a pro-inflammatory response, while Tregs maintain self-tolerance and prevent autoimmunity. The balance and homeostasis of T Cells and their cytokines are essential to prevent the loss of self-tolerance, influencing inflammation and PAH progression (Gaowa and Zhou, 2014). Macrophages, key players in the innate immune system, present antigens to T Cells, thereby activating the adaptive immune system (Zhao et al., 2024). Pulmonary inflammation mediated by macrophages is crucial in pulmonary vascular remodeling (El Chami and Hassoun, 2012). In PAH models and patients with left heart disease-related PH, macrophages are elevated, along with increased lung IL-6 levels (Kherbeck et al., 2013). In a chronic thromboembolic PH mouse model, F4/80 positive monocytes/macrophages accumulate in high-flow arteries (Breitling et al., 2017). Increased monocyte recruitment chemokines and peripheral blood monocytes are observed in PH, with monocytes potentially differentiating into perivascular macrophages upon migrating to the pulmonary vasculature (Florentin et al., 2018). This process is facilitated by the activation of chemokine ligand 2 (CCL2) and C-X3-C motif chemokine ligand 1 (CX3CL1) (Florentin et al., 2018). B Cells can differentiate into plasma cells, which produce autoantibodies, and they play a crucial role in immune responses by collaborating with antigen-presenting DCs and lymphoid organs through antigen presentation, cytokine production, and the facilitation of T effector cell differentiation (Kherbeck et al., 2013). B Cells have been shown to play a functional role in PH, with B Cell depletion therapy demonstrating potential in reducing right ventricular systolic pressure and vascular remodeling in experimental PH (Breitling et al., 2017). This therapy has also shown promise as an effective and safe adjuvant treatment for systemic sclerosis-PAH and systemic lupus erythematosus-PAH (Hennigan et al., 2008; Zamanian et al., 2021). The accumulation

of perivascular immune cells and intravascular infiltration, coupled with elevated cytokine levels, leads to increased vascular inflammation and dysfunction, playing critical regulatory roles in PAH and correlating with disease severity (Groth et al., 2014). Circulating cytokine levels are important markers for the diagnosis and treatment of PAH, and targeting specific cytokine responses and pathways is considered a promising therapeutic strategy (Groth et al., 2014). Certain cytokines and chemokines have been associated with poor clinical outcomes in PAH patients and may serve as biomarkers for disease progression. For instance, IL-1 β and TNF- α are linked to the accumulation of extracellular matrix proteins, such as fibronectin, which are prevalent in PAH lesions. In contrast, IL-6 is associated with the proliferation of VSMCs (Fujita et al., 2002; Zhong et al., 2021). A deeper understanding of the roles of immune cells, cytokines, and chemokines in PH and their impact on abnormal angiogenesis and pulmonary artery remodeling is necessary. Although the immune/inflammatory components of PH require further clarification, recent studies in animal models have shown that anti-inflammatory therapies can reduce or even reverse PH effects. Current therapeutic drugs for PH primarily target vasodilation but also exhibit immunomodulatory properties (Cohen-Kaminsky et al., 2014). However, no approved treatments specifically target the inflammatory processes associated with pulmonary vascular diseases.

Tacrolimus, a calcineurin inhibitor with immunoregulatory and anti-inflammatory properties, has been shown to reverse disease progression in PAH rat models induced by MCT and hypoxia, restore pulmonary artery endothelial cell function, and activate BMPR2 receptor signaling by displacing FKBP12 from the BMPRI co-receptor (Spiekerkoetter et al., 2013). B Cell depletion therapy using rituximab, an anti-CD20 monoclonal antibody, has reduced rheumatoid factor, IL-12, and IL-17 levels in patients. Statins, known for their anti-inflammatory and

immunomodulatory functions, have improved right ventricular remodeling in patients with idiopathic PH, hereditary PH, and connective tissue disease-associated PH (Kao, 2005). Elevated circulating inflammatory markers are observed in patients with chronic embolic PH and PAH, with some patients showing clinical improvement following treatment with corticosteroids or immunosuppressants (Sanchez et al., 2006). The evidence suggests that suppressing immunity and inflammation may be a potential strategy for PH treatment. However, while immunosuppressants effectively inhibit immune cell function and reduce inflammation, no immunosuppressants have been approved for PH treatment, and the therapeutic effects of most immunomodulators are still under clinical investigation.

Role and mechanisms of H₂S in HPH

HPH is a critical process that can develop in various cardiac and pulmonary diseases following acute or chronic hypoxia. It is characterized by elevated PAP and increased vascular resistance, resulting from a combination of hypoxic vasoconstriction and vascular remodeling. The pathophysiology of HPH involves progressive pulmonary vasoconstriction, vascular inflammation, oxidative stress, and structural remodeling of pulmonary vessels (Tian, 2008; Yan et al., 2008; Olson et al., 2010; Evans et al., 2011). In early 2003, Tang's group demonstrated the significance of H₂S in pulmonary circulation, showing reduced H₂S levels in lung tissues and plasma, along with inhibited expression and activity of cystathionine γ -lyase (CSE) in the pulmonary arteries and lung tissues of HPH rats (Chunyu et al., 2003). Notably, supplementation with a H₂S donor significantly reduced PAP and mitigated pulmonary vascular remodeling (Chunyu et al., 2003). Subsequent studies have further elucidated that endogenous H₂S inhibits the development of HPH, with downregulation of the H₂S pathway identified as a key mechanism in its progression (Chunyu et al., 2003). Therefore, insufficient H₂S production contributes to the pathogenesis of HPH (Chen and Wang, 2012; Liu et al., 2012; Yang et al., 2012; Chen et al., 2020; Roubenne and Marthan, 2021).

It is noted that the vasorelaxant mechanisms of H₂S are relevant for the management of PH (Munteanu et al., 2024). To date, H₂S exerts vasodilatory effects primarily by activating ATP-sensitive potassium (KATP) channels, causing membrane hyperpolarization and relaxation of VSMCs (Song et al., 2023). Additionally, H₂S inhibits L-type calcium channels, reducing calcium influx and promoting VSMC relaxation. Beyond ion channel modulation, H₂S stimulates sGC, increasing cyclic guanosine monophosphate (cGMP) levels, which activate protein kinase G (PKG) (Huerta de la Cruz et al., 2023). PKG then phosphorylates vasodilator-stimulated phosphoprotein (VASP), facilitating smooth muscle relaxation. H₂S also enhances NO signaling by increasing NO bioavailability through the inhibition of its degradation and activation of endothelial nitric oxide synthase (eNOS), further elevating cGMP levels and enhancing vasodilation (Cirino and Szabo, 2023). In addition, H₂S modulates endothelium-derived hyperpolarizing factor (EDHF) pathways, promoting VSMC relaxation through gap junctions. H₂S also activates transient receptor potential (TRP) channels, particularly TRPV4, in endothelial cells, which stimulates calcium entry and the

production of vasodilators like NO and prostacyclin, helping regulate vascular tone (Teoh et al., 2020; Liu X. Y. et al., 2022). These multifaceted mechanisms of H₂S-induced vasodilation highlight its potential for treating vascular diseases such as PH (Lv et al., 2021). The complex interplay between ion channel modulation, cyclic nucleotide signaling, NO pathways, and protein sulfhydration makes H₂S a promising therapeutic target for managing PH-induced vascular tone dysfunction. H₂S modulates hypoxia-induced pulmonary vasoconstriction by mitigating ROS production and regulating calcium signaling (Madden et al., 2012). Interestingly, studies on the effects of H₂S on pulmonary vasodilation function and PH are limited. In spite of this, the ability of H₂S to counteract endothelial dysfunction and restore vascular homeostasis suggests a promising therapeutic role in managing pulmonary vascular disorders, including PH.

In a rat model of PH established by exposure to normobaric hypoxic conditions for 3 weeks, the H₂S-generating enzyme activity in lung tissue and pulmonary artery was significantly downregulated (Zhang et al., 2003; Geng et al., 2004). Propargylglycine (PPG), an inhibitor of endogenous H₂S production worsened PH in hypoxic rats by increasing endogenous production of NO and the expression of NOS in pulmonary arteries (Zhang et al., 2004). This finding indicates that a negative feedback interaction exists between the NO/NOS system and the H₂S/CSE system in the development of HPH (Zhang et al., 2004). Plasma CO levels and the expression of heme oxygenase (HO-1) were significantly elevated in HPH rats, whereas these upregulations were further aggravated by exogenously applied H₂S (Qingyou et al., 2004). By contrast, exogenous administration of PPG, an inhibitor of CSE, inhibited the plasma H₂S contents and worsened HPH by downregulating plasma CO levels and suppressing the expressions of HO-1 in pulmonary arteries (Qingyou et al., 2004), indicating that the crosstalk between H₂S and CO may participate in the development of HPH. These interconnected gasotransmitter pathways may mutually influence each other, thereby playing a significant regulatory role in the progression of HPH (Zhang et al., 2004).

Oxidative stress plays a role in the development of HPH by regulating the proliferation and migration of pulmonary VSMCs and ECs. Administration of NaHS reduced mean pulmonary artery pressure in HPH rats by reducing the levels of oxidized GSH and enhancing total antioxidant capacity in the lung (Wei et al., 2008). This finding suggests that H₂S acts as an antioxidant in HPH, partially through attenuating GSSG levels (Wei et al., 2008). Compared with normal rats, the apoptosis of arteriae pulmonalis in HPH rats was significantly lower, as evidenced by increased Bcl-2 protein and decreased Bax protein (Xu et al., 2011). Plasma H₂S levels and the CSE mRNA level in HPH rats were significantly lower than those in control rats (Xu et al., 2011). These results obtained suggested that the endogenous H₂S system may be closely linked to HPH, and suppression of the H₂S/CSE system may increase the Bcl-2/Bax ratio, inhibit apoptosis of pulmonary VSMCs, and ultimately contribute to HPH development (Xu et al., 2011). Prostacyclin (PGI₂), an effective but costly vasodilator, is commonly used in the treatment of PH. Endogenous PGI₂ formation primarily depends on cyclooxygenase-2 (COX-2) expression, which is reportedly downregulated in hypoxia-induced PAH. H₂S has been shown to upregulate COX-2 (Hu et al., 2008), but plasma H₂S levels are reduced during hypoxia-induced pulmonary vascular

remodeling (Tian, 2014). It is possible that H₂S may inhibit hypoxia-induced proliferation of pulmonary VSMCs and mitigate PH by upregulating the COX-2/PGI₂ signaling pathway. To explore this, Li et al. assessed the effects of H₂S on chemical hypoxia-induced proliferation of pulmonary VSMCs (Li et al., 2014). Exposure to cobalt chloride (CoCl₂) significantly suppressed the COX-2 expression and PGI₂ release in pulmonary VSMCs, which was reversed by supplementation of H₂S (Li et al., 2014). These findings suggest that modulating endogenous H₂S production or administering H₂S donors like NaHS could offer a novel therapeutic strategy for PAH by upregulation of the COX-2/PGI₂ axis (Li et al., 2014).

H₂S exerts anti-inflammatory, antioxidative, and other biological effects across various organs. The exaggerated proliferation and apoptosis resistance of pulmonary VSMCs are central to vascular remodeling in PH. It was found that H₂S significantly inhibited hypoxia-induced pulmonary VSMCs and reversed chronic hypoxia-induced PH by suppressing endoplasmic reticulum (ER) stress markers in both *in vivo* and *in vitro* models (Wu et al., 2019). Also, H₂S was reported to inhibit activating transcription factor 6 (ATF6) and mitigate the hypoxia-induced decline in mitochondrial calcium levels (Wu et al., 2019). Consequently, H₂S effectively inhibits hypoxia-induced proliferation, migration, and oxidative stress of pulmonary VSMCs. Attenuating ER stress with exogenous H₂S represents a promising therapeutic strategy for PH with high translational potential (Wu et al., 2019).

Mesenchymal stem cells (MSCs) derived from the placenta, bone marrow, adipose, and other tissues have emerged as a promising regenerative therapy for PH over the last decade (Pullamsetti et al., 2014). MSC delivery significantly inhibits pulmonary artery remodeling, slowing PAH progression (Malliaras and Marbán, 2011). However, low cell retention and engraftment after delivery pose significant challenges to the effectiveness of MSC-based therapy (Malliaras and Marbán, 2011). Increasing evidence suggests that programmed cell death (PCD), including ferroptosis, is closely linked to the low engraftment and survival rates of transplanted MSCs (Li X. et al., 2020). Ferroptosis, which can be induced in MSCs by erastin, has been shown to affect MSC viability and differentiation (Lan et al., 2022; Han et al., 2024). Inhibiting ferroptosis has been found to maintain MSC viability, enhance differentiation, and improve the efficacy of transplanted MSCs in various disease models (Liu J. et al., 2022). However, the direct impact of ferroptosis on MSC delivery in PAH remains underexplored. *In vivo*, CSE overexpression improved the survival of erastin-treated MSCs delivered to mice with HPH (Hu et al., 2023). *In vitro*, CSE overexpression enhanced H₂S production and inhibited ferroptosis-related markers in erastin-treated MSCs (Hu et al., 2023). Notably, upregulation of the CSE/H₂S pathway induced Keap1 S-sulfhydration, which contributed to the inhibition of ferroptosis (Hu et al., 2023). Thereafter, upregulation of the CSE/H₂S pathway in CMSCs inhibits ferroptosis and enhances their suppressive effect on vascular remodeling in mice with HPH (Hu et al., 2023). The protective effect of the CSE/H₂S pathway against ferroptosis in CMSCs is mediated via S-sulfhydration of Keap1 and subsequent activation of Nrf2 signaling. This study provides a novel therapeutic avenue for improving the efficacy of transplanted MSCs in PH (Hu et al., 2023). Additionally, the ability of CSE to inhibit

ferroptosis suggests that genetic approaches to manipulate CSE expression and H₂S production could further enhance the protective capacity of MSCs in PH (Hu et al., 2023).

Role of H₂S in MCT-induced PH

MCT, a toxic alkaloid, induces the proliferation of pulmonary VSMCs and inflammation of endothelial cells, leading to right heart dysfunction due to cardiac overload. The MCT-induced PH model is widely used as a classical animal model of PH. Evidence for the role of H₂S in MCT-induced PH is emerging. Previously, Basar et al. found that plasma H₂S levels were not changed in the MCT-induced PH of rats (Sirmagul et al., 2013). Importantly, they did not examine the direct role of H₂S in MCT-induced PH (Sirmagul et al., 2013). Later, Jin's group showed that the endogenous H₂S/CSE pathway was suppressed in MCT-induced PH rats, and exogenous H₂S reduced pulmonary artery pressure, reversed pulmonary vascular structural remodeling by suppressing phosphorylation of NF-κB p65 and IκBα MCT-treated rats (Feng et al., 2017). Hence, they showed the first evidence that the downregulated H₂S/CSE pathway was responsible for PH in MCT-induced rat by suppressing NF-κB-mediated endothelial inflammation (Feng et al., 2017). In line with this, Sevin's group demonstrated that H₂S levels were reduced, and L-cysteine-induced relaxations were impaired in the pulmonary arteries from MCT-induced PH rats (Turhan et al., 2022). The H₂S donor, Na₂S, prevented increased pulmonary artery pressure and hypertrophy by improving endothelial dysfunction (Turhan et al., 2022). Further studies have elucidated the mechanisms by which H₂S exerts its effects in MCT-induced PH rats (Zhang D. et al., 2019). H₂S was found to inhibit pulmonary arterial endothelial cell inflammation and prevent vascular remodeling, likely by suppressing the NF-κB signaling pathway and endothelial-mesenchymal transition (EndMT) (Zhang D. et al., 2019; Zhang H. et al., 2019). *In vivo* and *in vitro* findings revealed that H₂S directly deactivates the inhibitor of kappa B kinase subunit beta (IKKβ) by sulfhydrating its Cys179, thereby preventing NF-κB activation and reducing endothelial cell inflammation in PH (Zhang D. et al., 2019). Additionally, H₂S was shown to control MCT-induced PH by inhibiting mast cell aggregation and degranulation, as well as the release of interleukin-6 (IL-6) (Zhang D. et al., 2019). The inhibition of the NF-κB pathway and subsequent EndMT in pulmonary arteries further underscores the beneficial effects of H₂S in the development of MCT-induced PH (Zhang D. et al., 2019).

Interestingly, enhanced endogenous sulfur dioxide (SO₂) level in endothelial cells and increased enzymatic activity of aspartate aminotransferase (AAT), a major SO₂ synthesis enzyme, were observed in a rat model of MCH-induced PH (Zhang D. et al., 2018). The H₂S donor reversed the CSE knockdown-induced increase in endogenous SO₂ levels and AAT activity (Zhang D. et al., 2018). Mechanistically, H₂S sulfhydrated AAT1/2 proteins, restoring the reduced sulfhydration of AAT1/2 observed in CSE knockdown endothelial cells (Zhang D. et al., 2018). Furthermore, the AAT inhibitor L-aspartate-β-hydroxamate (HDX), which blocked the CSE knockdown-induced upregulation of the endogenous SO₂/AAT pathway, exacerbated the activation of the nuclear factor-κB pathway and increased levels of downstream

inflammatory factors, including ICAM-1, TNF- α , and IL-6 in endothelial cells (Zhang D. et al., 2018). *In vivo*, H₂S restored the MCT-induced deficiency in endogenous H₂S production and reversed the upregulation of the endogenous SO₂/AAT pathway via the sulfhydration of AAT1 and AAT2 (Zhang D. et al., 2018). In conclusion, this study demonstrated that H₂S inhibits endogenous SO₂ generation by inactivating AAT through the sulfhydration of AAT1/2 (Zhang D. et al., 2018). The increase in endogenous SO₂ may serve a compensatory role when the H₂S/CSE pathway is downregulated in MCT-induced PH, thereby providing protective effects against endothelial inflammatory responses (Zhang D. et al., 2018). In summary, H₂S shows significant potential in mitigating MCT-induced PH by attenuating the activation of the NF- κ B pathway, thereby diminishing inflammation in pulmonary arterial endothelial cells and alleviating vascular remodeling. Additionally, H₂S might protect endothelial cells and other critical immune cells from damage by inhibiting PCD pathways such as ferroptosis, which deserved further studies. H₂S, as an important immunoregulatory molecule, exhibits significant therapeutic potential in MCT-induced PH. In the future, strategies to regulate H₂S production or utilize H₂S donors could offer novel therapeutic approaches, particularly in targeting immunoregulation in MCT-induced PH.

Role of H₂S in high pulmonary blood flow-induced PH

PH is a prevalent complication of CHD patients, which is characterized by a left-to-right shunt and elevated pulmonary blood flow. A significant pathological consequence of PH is the structural remodeling of the pulmonary vasculature. The mechanisms underlying the structural changes in response to high pulmonary blood flow remain inadequately understood. Studies have shown that high pulmonary blood flow induces high shear stress on endothelial cells and VSMCs in pulmonary arteries, leading to maladaptive changes in vascular structure and function. In rat models, high pulmonary blood flow-induced PH was established through the creation of an abdominal aorta/inferior vena cava shunt. It was reported that following 4 weeks of shunting, the H₂S/CSE pathway in lung tissue was upregulated (Xiaohui et al., 2005; Li et al., 2006a). However, after 11 weeks, the pathway was downregulated, coinciding with a marked increase in pulmonary arterial systolic pressure (PASP) and the onset of pulmonary vascular remodeling (Xiaohui et al., 2005; Li et al., 2006a). Supplementation with an exogenous H₂S donor in shunt rats reduced vascular remodeling and successfully lowered PASP (Shi et al., 2003; Xiaohui et al., 2005; Li et al., 2006a). H₂S might exert its regulatory effects on PH induced by increased pulmonary blood flow through multiple mechanisms. H₂S inhibited the proliferation of pulmonary VSMCs via inhibiting the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway, thereby alleviating pulmonary vascular remodeling in PH rats induced by high pulmonary blood flow (Li et al., 2006a). Additionally, H₂S suppressed the inflammatory response in pulmonary arteries by downregulating the NF- κ B pathway in PH rats with increased pulmonary blood flow (Jin et al., 2008). Several studies revealed that H₂S promoted collagen degradation within pulmonary artery walls and reduced extracellular matrix (ECM)

accumulation, mitigating vascular remodeling and PH induced by high pulmonary blood flow (Li et al., 2008; Lv et al., 2021).

The contents of ICAM-1, IL-8 and MCP-1 contents in lung tissue were higher in shunt rats, this was prevented by H₂S (Jin et al., 2008). The anti-inflammatory role of H₂S in PH induced by high pulmonary blood flow was associated with upregulation of I κ B α expression and downregulation of NF- κ B p65 expression, thus inhibiting the expression of inflammatory related factors (Jin et al., 2008). Of note, H₂S also modulated the production of vasoactive peptides, including endothelin-1 (ET-1), atrial natriuretic peptide (ANP), calcitonin gene-related peptide (CGRP), and pro-adrenomedullin peptide (PAMP), thereby influencing pulmonary hemodynamics and vascular structure (Li et al., 2006b). Specifically, H₂S inhibited the production of endogenous vasoconstrictors such as ET-1, ANP, and CGRP, while promoting plasma PAMP levels, leading to vasodilation and relief of PH (Li et al., 2006b). Moreover, H₂S induced the apoptosis of pulmonary VSMCs by activating the Fas/caspase3 pathway and inhibiting the Bcl-2 pathway, thereby ameliorating high pulmonary blood flow-induced PH (Li et al., 2009). L-arginine is a semi-essential amino acid that serves as a precursor to NO, a critical signaling molecule involved in vascular homeostasis. In the context of PH, L-arginine plays a significant role due to its involvement in NO production through the action of NOS enzymes. NO is a potent vasodilator that helps regulate pulmonary vascular tone, inhibits smooth muscle cell proliferation, and reduces platelet aggregation. It has been revealed that L-arginine ameliorates PH and pulmonary vascular structural remodeling induced by high pulmonary blood flow (Yanfei et al., 2006). L-arginine-mediated attenuation of PH is attributed to the upregulation of the H₂S/CSE system (Yanfei et al., 2006). This finding suggests that the interaction between the H₂S and NO pathways is implicated in high pulmonary blood flow-induced pulmonary vascular remodeling and PH (Yanfei et al., 2006). To sum up, H₂S may show down the development of high pulmonary blood flow-induced PH by inhibiting the proliferation of pulmonary VSMCs, promoting collagen degradation, suppressing the inflammatory response, influencing pulmonary hemodynamics and vascular structure, activating the Fas/caspase3 pathway, inhibiting the Bcl-2 pathway, and interacting with NO. However, the effectiveness of H₂S supplementation in high pulmonary blood flow-induced PH remains a subject of ongoing research, as its benefits may vary depending on the underlying etiology of the condition and the stage of disease progression. More importantly, the role of H₂S in modulating immune cell functions within the context of high pulmonary blood flow-induced PH is an emerging area of research with significant therapeutic implications. As a gasotransmitter, H₂S is known to exert anti-inflammatory, antioxidant, and vasodilatory effects, which are particularly relevant in the pathogenesis of high pulmonary blood flow-induced PH, a condition characterized by vascular remodeling, immune cell infiltration, and elevated pulmonary pressures. Targeting the H₂S pathway in immune cells may offer a novel strategy to attenuate the inflammatory and remodeling processes in high pulmonary blood flow-induced PH, potentially improving clinical outcomes in patients with this challenging condition. Future research should focus on elucidating the specific immune cell populations affected by H₂S, the molecular pathways involved, and the potential for combination therapies that enhance H₂S signaling in conjunction with other treatments for high pulmonary blood flow-induced PH.

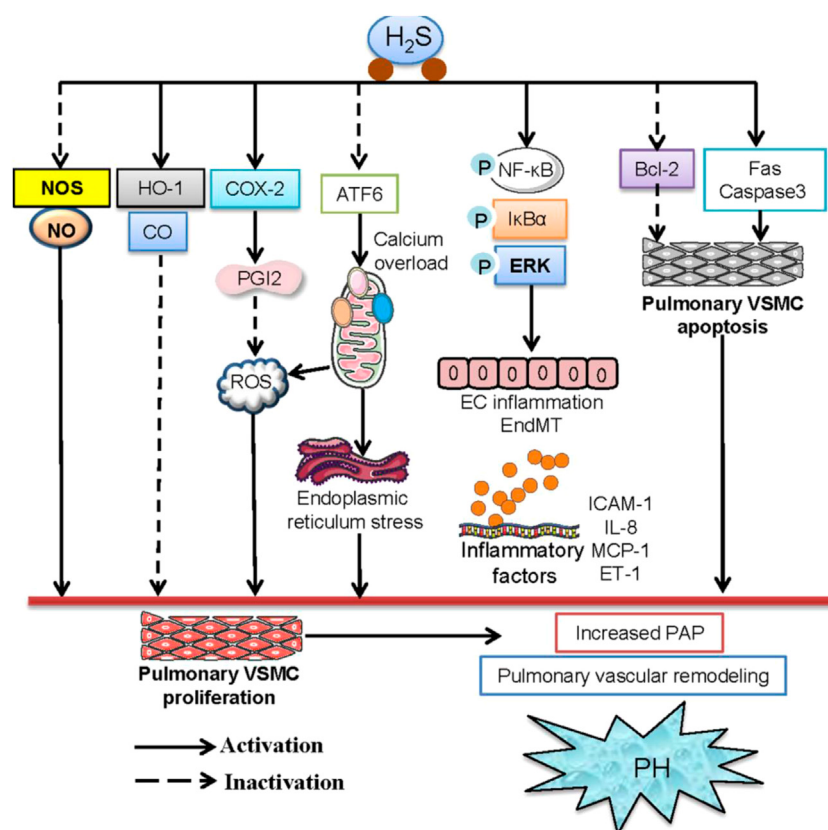


FIGURE 4

The signaling pathways involved in the protection of H₂S against PH. H₂S ameliorated PH by decreasing endogenous production of NO and the expression of NOS and elevating the HO-1/CO pathway in pulmonary arteries. H₂S may inhibit hypoxia-induced proliferation of pulmonary VSMCs and mitigate PH by upregulating the COX-2/PGI₂ signaling pathway. H₂S was reported to inhibit ATF6 and mitigate the hypoxia-induced decline in mitochondrial calcium levels. H₂S effectively inhibits hypoxia-induced proliferation, migration, oxidative stress, and ER stress of pulmonary VSMCs. H₂S reduced pulmonary artery pressure, reversed pulmonary vascular structural remodeling by suppressing phosphorylation of NF-κB p65 and IκBα, thus downregulating the levels of downstream inflammatory factors, including ICAM-1, TNF-α, and IL-6 in pulmonary endothelial cells. H₂S induced the apoptosis of pulmonary VSMCs by activating the Fas/caspase3 pathway and inhibiting the Bcl-2 pathway, thereby ameliorating high pulmonary blood flow-induced PH.

Role of H₂S in PH associated with COPD

PH is a common and serious complication of COPD. The relationship between PH and COPD is multifaceted, with PH contributing to the morbidity and mortality associated with COPD. In COPD, chronic inflammation, alveolar destruction, and hypoxia lead to structural and functional changes in the pulmonary vasculature. The destruction of alveolar walls reduces the number of capillaries in the lungs, increasing vascular resistance and PAP. The development of PH in COPD patients significantly worsens the prognosis. It is associated with increased exertional dyspnea, reduced exercise capacity, and decreased survival. PH can exacerbate right ventricular dysfunction due to the increased workload placed on the right heart to pump blood through the narrowed pulmonary arteries, eventually leading to right heart failure. Understanding the relationship between these conditions is crucial for optimizing the management and improving outcomes in patients with COPD. Further research is needed to better understand the mechanisms driving PH in COPD and to develop targeted therapies that can effectively address this challenging complication.

Serum H₂S levels were diminished in patients with COPD-related PH and H₂S levels were negatively correlated with PASP, indicating that H₂S may play an important role in the pathogenesis of COPD-related PH (Yuan et al., 2019; Liao et al., 2021). Chen et al. found that serum H₂S levels were significantly higher in patients with stable COPD compared to controls and patients with acute exacerbation of COPD (AECOPD) (Chen et al., 2005). Serum H₂S levels also varied significantly with the severity of airway obstruction in stable COPD, being lower in patients with stage III obstruction compared to those with stage I obstruction (Chen et al., 2005). Furthermore, AECOPD patients with PH exhibited lower serum H₂S levels than those with normal resting PASP (Chen et al., 2005). Serum H₂S levels in COPD patients were positively correlated with NO levels, FEV₁% predicted values, and the percentages of sputum lymphocytes and macrophages (Chen et al., 2005). Conversely, serum H₂S was negatively correlated with PASP and the percentage of sputum neutrophils (Chen et al., 2005). These results suggest that endogenous H₂S may play a role in the pathogenesis of PH associated with COPD and could serve as a noninvasive marker of disease activity and severity (Chen et al., 2005). Han and colleagues investigated the role of H₂S in COPD

TABLE 1 The therapeutic impact of H₂S on the improvement of PH.

H ₂ S regulators	Animal or cells	Effects	Mechanisms	References
NaHS	Hypoxic PH rats	Amelioration of PH and pulmonary vascular remodeling	Increased plasma H ₂ S level and upregulated CSE in lung tissue	Chunyu et al. (2003)
NaHS	Normobaric hypoxia-induced broilers	Amelioration of PH and right ventricular hypertrophy	Increased plasma concentrations of and H ₂ S	Yang et al. (2012)
NaHS	Hypoxic PH rats	Amelioration of PH and pulmonary vascular remodeling	Inhibition of elastin expression of extracellular matrix accumulation	Chen et al. (2020)
Cysteine	Hypoxic rat lung	Reduction in the increases in arterial pressure during hypoxia	Decreased hypoxic pulmonary vasoconstriction	Madden et al. (2012)
NaHS	Hypoxic PH rats	Amelioration of PH and pulmonary vascular remodeling	Increased CSE activity and CSE mRNA in lung tissue	Zhang et al. (2003)
PPG	Hypoxic PH rats	Aggravation of PH	Increased endogenous production of NO	Zhang et al. (2004)
NaHS	Hypoxic PH rats	Amelioration of PH and pulmonary vascular remodeling	Increased plasma CO level and the expressions of HO-1 in pulmonary arteries	Qingyou et al. (2004)
NaHS	Hypoxic PH rats	Amelioration of PH and pulmonary vascular remodeling	Attenuation of oxidized glutathione content	Wei et al. (2008)
NaHS	Hypoxia-induced pulmonary VSMCs	Attenuation of cell proliferation	Upregulation of the COX-2/PGI(2) axis	Li et al. (2014)
GY4137	Hypoxic PH rats	Decreased pulmonary vascular resistance, and pulmonary artery remodeling	Inactivation of activating transcription factor 6 activation, and decreased mitochondrial calcium	Wu et al. (2019)
GY4137	Hypoxia-induced pulmonary VSMCs	Attenuation of cell proliferation	Inactivation of activating transcription factor 6 activation, and decreased mitochondrial calcium	Wu et al. (2019)
NaHS	MCT-induced PH rats	Attenuation of PH and pulmonary vascular remodeling	Attenuation of endothelial inflammation and NF-κB inactivation	Feng et al. (2017)
NaHS	Hypoxia-induced pulmonary arterial endothelial cells	Attenuation of pulmonary inflammatory response	Attenuation of endothelial inflammation and NF-κB inactivation	Feng et al. (2017)
Na ₂ S	MCT-induced PH rats	Attenuation of PH and pulmonary vascular remodeling	Promotion of pulmonary relaxation	Turhan et al. (2022)
NaHS	MCT-induced PH rats	Attenuation of PH and pulmonary endothelial inflammation	Activation of IKKβ via sulphydrating IKKβ at Cys179 to inhibit NF-κB	Zhang D. et al. (2019)
NaHS	MCT-induced PH rats	Attenuation of PH and pulmonary endothelial inflammation	Inhibition of the NF-κB-Snail pathway and the subsequent EndMT in pulmonary arteries	Zhang H. et al. (2019)
NaHS	MCT-induced PH rats	Attenuation of PH and pulmonary vascular remodeling	Upregulation of sulfur dioxide (SO ₂)	Zhang D. et al. (2018)
NaHS	High pulmonary blood flow-induced PH rats	Attenuation of PVR and downregulation of PCNA expression	Inhibition of the ERK/MAPK, NO/NOS pathway and activation of the CO/HO pathway	Li et al. (2006a)
NaHS	High pulmonary blood flow-induced PH rats	Attenuation of PH and pulmonary endothelial inflammation	Inhibition of the NF-κB-Snail pathway	Jin et al. (2008)
NaHS	High pulmonary blood flow-induced PH rats	Attenuation of PH and pulmonary endothelial inflammation	Regulation of vasoactive peptide ET-1, ANP, CGRP and PAMP	Li et al. (2006b)
NaHS	High pulmonary blood flow-induced PH rats	Attenuation of PH and pulmonary vascular remodeling	Activation of the Fas/caspase3 pathway and inhibition of the Bcl-2 pathway	Li et al. (2009)
NaHS	Tobacco smoke (TS)-induced emphysema mice	Attenuation of mean linear intercepts, bronchial wall thickness	Upregulation of Nrf2, CGL, and CBS in pulmonary artery endothelial cells	Han et al. (2011)
SFN	SU5416 and 10% hypoxia (SuHx)-induced PH mice	Attenuation of pulmonary vascular remodeling, fibrosis, and inflammation	Activation of Nrf2 and inhibition of NLRP3 inflammasome	Kang et al. (2020)
SFN			Activation of Nrf2	Zhang et al. (2022)

(Continued on following page)

TABLE 1 (Continued) The therapeutic impact of H₂S on the improvement of PH.

H ₂ S regulators	Animal or cells	Effects	Mechanisms	References
	SU5416 and 10% hypoxia (SuHx)-induced PH mice	Attenuation of right ventricular dysfunction		
SFN	Chronic hypoxia-induced PH mice	Attenuation of right ventricular hypertrophy and pulmonary arteries remodeling	Inhibition of inflammation and oxidative stress	Pan et al. (2023)
Allicin	MCT-induced PH rats	Attenuation of right ventricular dysfunction	Decrease in medial wall thickness of pulmonary arteries	Bombicz et al. (2017)
Allicin	MCT-induced PH rats	Prevention of pulmonary vessel wall thickness	Inhibition of inflammation and fibrosis	Sánchez-Gloria et al. (2021)
Allicin	MCT-induced PH rats	Attenuation of right ventricular hypertrophy and pulmonary arteries remodeling	Improvement of coronary endothelial function and vasoreactivity	Sun and Ku (2006)

pathogenesis using a mouse model of tobacco smoke (TS)-induced emphysema (Han et al., 2011). TS exposure significantly decreased the protein expression of CSE, CBS, nuclear erythroid-related factor 2 (Nrf2), phosphorylated-Akt (P (ser473)-Akt), and the glutathione/oxidized GSH ratio in the lung, effects that were largely reversed by H₂S (Han et al., 2011). NaHS treatment mitigated TS-induced increases in mean linear intercepts, bronchial wall thickness, and total cell counts in bronchoalveolar lavage fluid, including neutrophils, monocytes, and tumor necrosis factor α (Han et al., 2011). Furthermore, NaHS attenuated the rise in right ventricular systolic pressure, pulmonary vascular wall thickness, and the ratio of RV/LV+S in TS-exposed mice (Han et al., 2011). Notably, Akt knockdown abrogated the protective effects of NaHS against TS-induced apoptosis and the downregulation of Nrf2, CGL, and CBS in pulmonary artery endothelial cells (Han et al., 2011). These findings demonstrate that NaHS confers protection against TS-induced oxidative stress, airway inflammation, and remodeling, thereby attenuating the progression of emphysema and PH in COPD mice (Han et al., 2011). The usage of H₂S donors may hold therapeutic potential for the prevention and treatment of COPD caused by TS exposure (Han et al., 2011; Chen and Wang, 2012). These results indicated that H₂S might have clinical significance in the treatment of COPD-related PH by exerting anti-inflammatory and anti-oxidative effects.

Therapeutic potential of organosulfur compounds in PH

In addition to *A. sativum* derivatives, other natural sulphur compounds show promise for the management of PH (Mirhadi et al., 2024). Organosulfur compounds (OSCs) are subdivided into allylic sulfur compounds, indoles, isothiocyanates and sulforaphane (SFN) which are known for their therapeutic characteristics such as anti-inflammatory, antioxidative and antimicrobial properties (Kim et al., 2018; Putnik et al., 2019). The sulfur atom in OSCs underpins their unique properties, making them effective in treating oxidative stress-mediated diseases. OSCs are known to activate the Nrf2 signaling pathway, a critical therapeutic target for

combating oxidative stress (Egbujor and Petrosino, 2022). Additionally, OSCs have demonstrated anti-inflammatory effects in both *in vitro* studies and clinical settings (Sahu, 2002). Glucosinolates (GSTs), precursors of isothiocyanates, are abundant in plants of the *Brassica* (Cruciferous) genus. When chewed or damaged by insects, GSTs undergo hydrolysis by the enzyme myrosinase, producing isothiocyanates, thiocyanates, and other bioactive compounds. In the *Allium* genus, organosulfur compounds (OSCs) are classified into two types: (1) volatile, oil-soluble sulfur compounds, such as diallyl sulfides, responsible for their characteristic pungent aroma and flavor, and (2) less odorous, water-soluble compounds like S-allylmercaptocysteine (SAMC) and S-allylcysteine (SAC), found in aqueous *A. sativum* extracts. The pharmacological activity of *A. sativum*-derived OSCs is primarily due to allicin, which forms in high concentrations when *A. sativum* is crushed or cut (Iciek et al., 2009; Lawson and Hunsaker, 2018). Sulforaphane (SFN), a 4-methylsulfinylbutyl isothiocyanate, is a biologically active phytonutrient primarily derived from the *Brassica* family, especially broccoli (Mirhadi et al., 2024). Its isothiocyanate group ensures a bioavailability of approximately 80%, with broccoli sprouts containing nearly ten times the SFN concentration of mature broccoli (Jaiswal et al., 2011). SFN exhibits diverse biological properties, including antioxidant, antimicrobial, anti-inflammatory, immunomodulatory, chemopreventive, cardioprotective, and neuroprotective effects (Angeloni et al., 2015; Qi et al., 2016; Romeo and Iori, 2018). In a study by Kang et al. (2020), PH and right ventricular dysfunction were induced in hypoxic male mice using semaxanib (SU5416), a VEGFR inhibitor (Wang Y. et al., 2022). Treatment with SFN improved right ventricular structure and function as assessed by transthoracic echocardiography. SFN upregulated Nrf2 expression and its downstream gene NQO1, reduced the inflammatory mediator NLRP3, and mitigated Su5416 and hypoxia (SuHx)-induced RV remodeling (Wang Y. et al., 2022). It also attenuated pulmonary vascular remodeling, fibrosis, and inflammation (Kang et al., 2020). SFN treatment reversed elevated right ventricular systolic pressure (RVSP) and improved right ventricular diastolic/systolic function in SuHx-induced PAH mice (Zhang et al., 2022). In hypoxic PAH models, SFN enhanced apoptosis in pulmonary artery smooth

muscle cells (PASMCs) while reducing apoptosis in pulmonary microvascular endothelial cells (Zhang et al., 2022). It lowered right ventricular hypertrophy and pulmonary artery remodeling, reduced IL-6 and TNF- α levels in the lungs and serum, and inhibited NF- κ B activation in PASMCs (Zhang et al., 2022). Additionally, SFN boosted antioxidant defenses by increasing total GSH levels, SOD activity, SOD2 expression, and the GSH/GSSG ratio. This was accompanied by a reduction in ROS production, as well as serum malondialdehyde (MDA) content (Qin and Qiao, 2022; Pan et al., 2023). These effects collectively highlight the potential of SFN to mitigate oxidative stress, inflammation, and structural remodeling in PH. Therefore, the protective effects of sulfur-containing compounds such as sulforaphane are well recognized. These compounds offer a foundation for future research and development of H₂S-based anti-PH drugs.

Conclusions and future directions

As a recognized vasodilator, H₂S has prompted investigations into its effects on PH and related diseases such as CHD and COPD. H₂S inhibits pulmonary VSMC proliferation, modulates vascular cell apoptosis, prevents collagen remodeling, and induces pulmonary vasodilation via KATP channel activation (Figure 4) (Tang et al., 2006; Yang et al., 2008), mitigating vascular endothelial cell inflammation, and regulating immune cell functions. Furthermore, H₂S interacts with CO and NO signaling pathways to maintain pulmonary vascular function and normal circulation (Roubenne and Marthan, 2021). However, under certain pathological conditions, the endogenous H₂S is downregulated, contributing to the onset and development of PH. Although the precise cellular mechanisms underlying these dysregulations remain unclear, reduced H₂S bioavailability is pivotal in promoting endothelial dysfunction, exacerbated inflammation, oxidative stress, and altered smooth muscle cell proliferation within the pulmonary artery walls. Future clinical investigations may consider H₂S and its related metabolic factors (such as L-cysteine, homocysteine, CSE, CBS, and 3-MST as relevant biomarkers for assessing the prognosis and risk of developing PH from CHD and COPD.

Evidence suggests that H₂S offers protective effects in PH, positioning it as a potential target for new treatment strategies involving H₂S-releasing molecules (Table 1). These therapeutic benefits have been primarily demonstrated in studies utilizing H₂S donors, with NaHS and Na₂S being the most widely used due to their cost-effectiveness, water solubility, and ability to rapidly release H₂S under physiological conditions. Sulfide salts, for instance, rapidly release H₂S, enabling quick and efficient distribution. In healthy individuals, intravascular administration of Na₂S has been shown to elevate blood concentrations of H₂S and thiosulfates, as well as exhaled H₂S levels, within minutes of injection (Toombs et al., 2010). However, the rapid release of H₂S from sulfide salts can lead to high concentrations that may negatively impact mitochondrial function, particularly in susceptible individuals, such as PH patients. Consequently, the

slow-releasing H₂S donors, such as GYY4137 and dithiolthione compounds, offer an attractive alternative, providing controlled release and sustained H₂S bioavailability that more closely mimics endogenous production rates, thereby reducing the risk of bolus effects (Giustarini et al., 2010; Rose et al., 2015). The natural H₂S donors, such as *A. sativum* extracts, have been shown to significantly lower blood pressure in hypertensive patients in multiple clinical trials (Ried, 2016). More evidence supporting the therapeutic potential of H₂S in treating PH is highly required, and the concerning immunomodulatory mechanisms by which H₂S influences the pulmonary vascular systems need to be fully elucidated.

In summary, H₂S-releasing molecules have shown considerable potential in attenuating vascular and cardiac alterations associated with PH. The development of both synthetic and natural H₂S-releasing molecules offers a promising avenue for new therapeutic strategies for PH, warranting further preclinical investigations before clinical implementation.

Author contributions

X-XZ: Writing – original draft, Conceptualization, Data curation, Formal Analysis, Investigation, Validation, Visualization. C-YZ: Conceptualization, Formal Analysis, Investigation, Validation, Visualization, Writing – review and editing. Q-BL: Investigation, Software, Validation, Visualization, Writing – review and editing. A-YZ: Data curation, Investigation, Software, Writing – review and editing. X-YM: Software, Validation, Writing – review and editing. J-BS: Investigation, Visualization, Writing – review and editing. GC: Software, Validation, Writing – review and editing. A-JX: Investigation, Visualization, Writing – review and editing. H-JS: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review and editing. X-WN: Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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