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Omega-6 polyunsaturated fatty acids and their metabolites: a potential targeted therapy for pulmonary hypertension

Jiayao Wang[1,2†], Shunlian Hu[1,2†], Yahan Xu[1,2†] and Tao Wang[1,2*]

Abstract

Pulmonary hypertension (PH) is a progressive and life-threatening cardiopulmonary disease that is not uncommon. The modulation of the pulmonary artery (PA) involves various fatty acids, including omega-6 polyunsaturated fatty acids (ω-6 PUFAs) and ω-6 PUFAs-derived oxylipins. These lipid mediators are produced through cyclooxygenase (COX), lipoxygenase (LOX), cytochrome P450 (CYP450), and non-enzymatic pathways. They play a crucial role in the occurrence and development of PH by regulating the function and phenotype of pulmonary artery endothelial cells (PAECs), pulmonary artery smooth muscle cells (PASMCs), pulmonary fibroblasts, alveolar macrophages, and inflammatory cells. The alterations in ω-6 PUFAs and oxylipins are pivotal in causing vasoconstriction, pulmonary remodeling, and ultimately leading to right heart failure in PH. Despite the limited understanding of the PH pathophysiology, there is potential for novel interventions through dietary and pharmacological approaches targeting ω-6 PUFAs and oxylipins. The aim of this review is to summarize the significant advances in clinical and basic research on omega-6 PUFAs and oxylipins in pulmonary vascular disease, particularly PH, and to propose a potential targeted therapeutic modality against omega-6 PUFAs.

Keywords Pulmonary hypertension, Polyunsaturated fatty acids, Oxylipins, Targeted therapy

Introduction

Pulmonary hypertension (PH) is a group of hemodynamic disorders characterized by pulmonary vascular remodeling, vasoconstriction, and thrombosis, ultimately leading to right heart failure and mortality [1]. PH can be classified into five clinical subgroups: pulmonary arterial hypertension (PAH), PH due to left heart disease, PH due to chronic hypoxic lung disease, chronic thromboembolic PH (CTEPH), and PH with unclear and/or multifactorial mechanisms [2]. Currently, approved medications for targeted treating PH mainly include prostacyclin analogs, prostacyclin receptor agonists, phosphodiesterase 5 inhibitors, endothelin-receptor antagonists, and cGMP activators [3]. Notably, the efficacy of prostacyclin analogs and prostacyclin receptor agonists is strongly

†Jiayao Wang, Shunlian HU and Yahan Xu contributed equally to this work.

*Correspondence:
Tao Wang
wt7636@126.com
[1]Department of Respiratory and Critical Care Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, People's Republic of China
[2]The Center for Biomedical Research, Key Laboratory of Respiratory Disease, Tongji Hospital, Tongji Medical College, National Health Committee (NHC), Huazhong University of Science and Technology, Wuhan, People's Republic of China

influenced by the levels of oxylipins derived from polyunsaturated fatty acids (PUFAs).

Oxylipins are a family of oxidized fatty acids that are produced from PUFAs through various pathways, including cyclooxygenase (COX), lipoxygenase (LOX), cytochrome P450 (CYP450), and non-enzymatic (NE) pathways [4, 5]. They serve as primary mediators of PUFAs' actions. PUFAs can be categorized into two families based on the position of the double bond on the methyl terminal (ω; n-) end [6]. The predominant PUFAs include ω-3 PUFAs like α-linolenic acid (ALA, C18:3n3), eicosapentaenoic acid (EPA, C20:5n3), docosapentaenoic acid (DPA, C22:5n3), and docosahexaenoic acid (DHA, C22:6n3), as well as ω-6 PUFAs such as linoleic acid (LA, C18:2n6), dihomo-γ-linolenic acid (DGLA, C20:3n6), arachidonic acid (AA, C20:4n6), and adrenic acid (AdA, C22:4n6) [7] (Fig. 1). The ω-6 PUFAs and their metabolites have gained considerable attention in pulmonary vascular disease, particularly in PAH.

This review aims to summarize the current research efforts focusing on the molecular and cellular targets of ω-6 PUFAs and ω-6 PUFAs-derived oxylipins in the pathogenesis and progression of PH, and to propose a potential targeted therapeutic modality against omega-6 PUFAs.

Pulmonary hypertension

The pathogenesis of PH is extremely complex, with multiple factors such as genetic mutations, immunoinflammation, and vasoactive substance imbalance. The pathogenesis of PH mainly includes the following aspects:

Genetic factors

Genetics is a crucial factor in the pathogenesis of pulmonary hypertension. Notably, mutations in several genes, particularly BMPR2, have been implicated in the development of pulmonary hypertension (PH) [8]. The hiking of these genes affects the normal function of pulmonary vascular smooth muscle cells, leading to vascular structural abnormalities and remodeling.

Imbalance of vasoactive substances

Pulmonary vasoconstriction and diastole are co-regulated by systolic and diastolic factors secreted by the pulmonary vascular endothelium, the former mainly

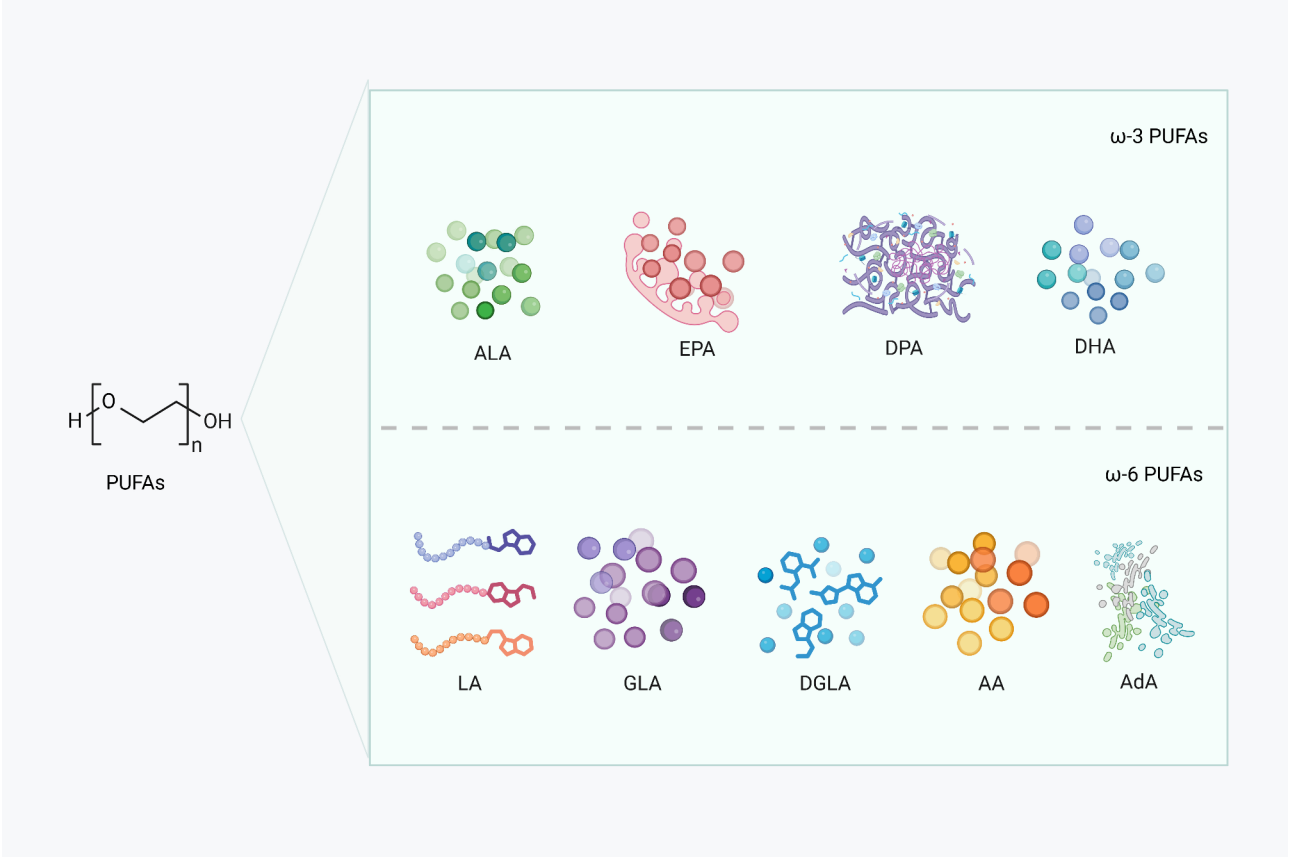

Fig. 1 The category of PUFAs. PUFAs: polyunsaturated fatty acids; ALA:α-linolenic acid; EPA: eicosapentaenoic acid; DPA: docosapentaenoic acid; DHA: docosahexaenoic acid; LA: linoleic acid; GLA: gamma-linolenic acid; DGLA: dihomo-γ-linolenic acid; AA: arachidonic acid; AdA: adrenic acid

endothelin-1 (ET-1), the latter mainly nitric oxide and prostacyclin.

Endothelin pathway The endothelin family mainly contains endothelin 1, 2, and 3. ET-1 is recognized as by far the most potent vasoconstrictor in the family and its receptors mainly include endothelin receptor A (ET RA) and endothelin receptor B (ET RB). The number of distribution of ET RA and ET RB varies in different tissues. The two receptors have different biological effects after binding to ET-1. ET-1 binds to ET RA to mediate the contraction and proliferation of VSMC, and binds to ET RB to mediate the diastole of VSMC.

NO pathway Nitric oxide (NO) is a principal mediator of endothelium-dependent vasodilation, generated through the enzymatic activity of endothelial nitric oxide synthase (eNOS) on L-arginine. This process results in the production of NO, which then diffuses to adjacent vascular smooth muscle cells (VSMCs) [9, 10]. There, it activates soluble guanylate cyclase, leading to the generation of cyclic guanosine monophosphate (cGMP) [11]. Cyclic guanosine monophosphate (cGMP) initiates the relaxation of vascular smooth muscle cells (VSMCs) by activating protein kinase G (PKG). This activation enhances the efflux of calcium ions (Ca2+) from the cells and diminishes the sensitivity of contractile proteins to Ca2+, leading to vasorelaxation. The enzyme phosphodiesterase-5 (PDE5) plays a critical role in terminating the vasodilatory effects of cGMP by breaking it down. A reduction in the activity of the NO-cGMP pathway, which is crucial for maintaining vascular tone, is a significant contributor to the increased pulmonary vasoconstriction characteristic of pulmonary hypertension (PH) [11].

Prostacyclin pathway Prostacyclin (PGI2) is generated from arachidonic acid by the action of vascular endothelial cell cyclooxygenase and prostacyclin synthase. Endothelium-derived PGI2 binds to the prostacyclin receptor (IP) in VSMC [12] and stimulates an increase in cyclic adenosine monophosphate (cAMP) through G-protein-coupled receptor signaling, activating protein kinase A (PKA), leading to a decrease in intracellular Ca2 + and enhanced vasodilation. PGI2 also attenuates VSMC constriction and PVR through inhibition of Rho-kinase. Moreover, PGI2 can target the nuclear peroxisome proliferator-activated receptor (PPAR) through endocytosis signaling, which regulates gene transcription, VSMC proliferation, and pulmonary vascular remodeling [13, 14].
When the above systolic and diastolic factors are imbalanced due to the expression of pulmonary vascular endothelial dysfunction, it may lead to pulmonary vascular smooth muscle contraction, thus causing pulmonary hypertension.

Mechanisms of inflammation and immune abnormalities

Abnormal immunoinflammation is an important part of the mechanism by which vascular remodeling occurs in PH, and a large number of studies have confirmed the massive infiltration of immune cells around the pulmonary vasculature and the deposition of complement, immunoglobulin, and inflammatory factors in patients with PH and animal models [15]. Additionally, there is a notable increase in the levels of various cytokines and the presence of specific autoantibodies in the peripheral blood of patients with PH. These findings indicate that altered immune cell function and the dysregulation of cytokine release significantly contribute to the pulmonary vascular remodeling observed in PH.

Abnormal energy metabolism

Recent studies have underscored metabolic irregularities, especially in glucose metabolism, within the pulmonary vascular wall cells in pulmonary hypertension (PH). Normally, these cells primarily generate energy through oxidative phosphorylation. The Warburg effect, characterized by a switch from aerobic phosphorylation to aerobic glycolysis in tumor cells—even when oxygen is abundant—is a distinct metabolic phenomenon. This shift is marked by an increased reliance on glycolysis for energy production, a feature often linked to cancer cell metabolism. Studies have also found that pulmonary vascular wall cells in PH display glucose metabolism anomalies similar to those in tumor cells, with increased glucose uptake and utilization observed in the lungs of PH patients and animal models, as evidenced by 18 F-FDG-PET imaging [16], and this aberrant metabolic switching promotes pulmonary artery smooth muscle cells (PASMC) proliferation and extracellular matrix production, which in turn drives pulmonary vascular remodeling [17, 18].

The above factors will combine to cause pulmonary vasoconstriction and pulmonary vascular remodeling.

Oxylipins and pulmonary hypertension

Evidence suggests a close link between oxylipins and various types of pulmonary hypertension (PH). Notably, oxylipins can have similar or opposing effects on specific pulmonary artery cells, underscoring the importance of maintaining their balance for pulmonary microenvironment stability (Fig. 2). For instance, elevated levels of oxylipins like PGE1, PGE2, and PGF2α are associated with the severity of PH from bronchopulmonary dysplasia [19]. In severe PH patients, lung tissue levels of 5-oxo-eicosatetraenoic acid, 5-HETE, 12-HETE, and 15-HETE are significantly elevated [20]. Among PH patients with a lower PGI2/TXB2 ratio, those with high levels of 12-HETE and 15-HETE have worse survival rates [21]. Additionally, urinary excretion of 11-dehydro-TXB2 is

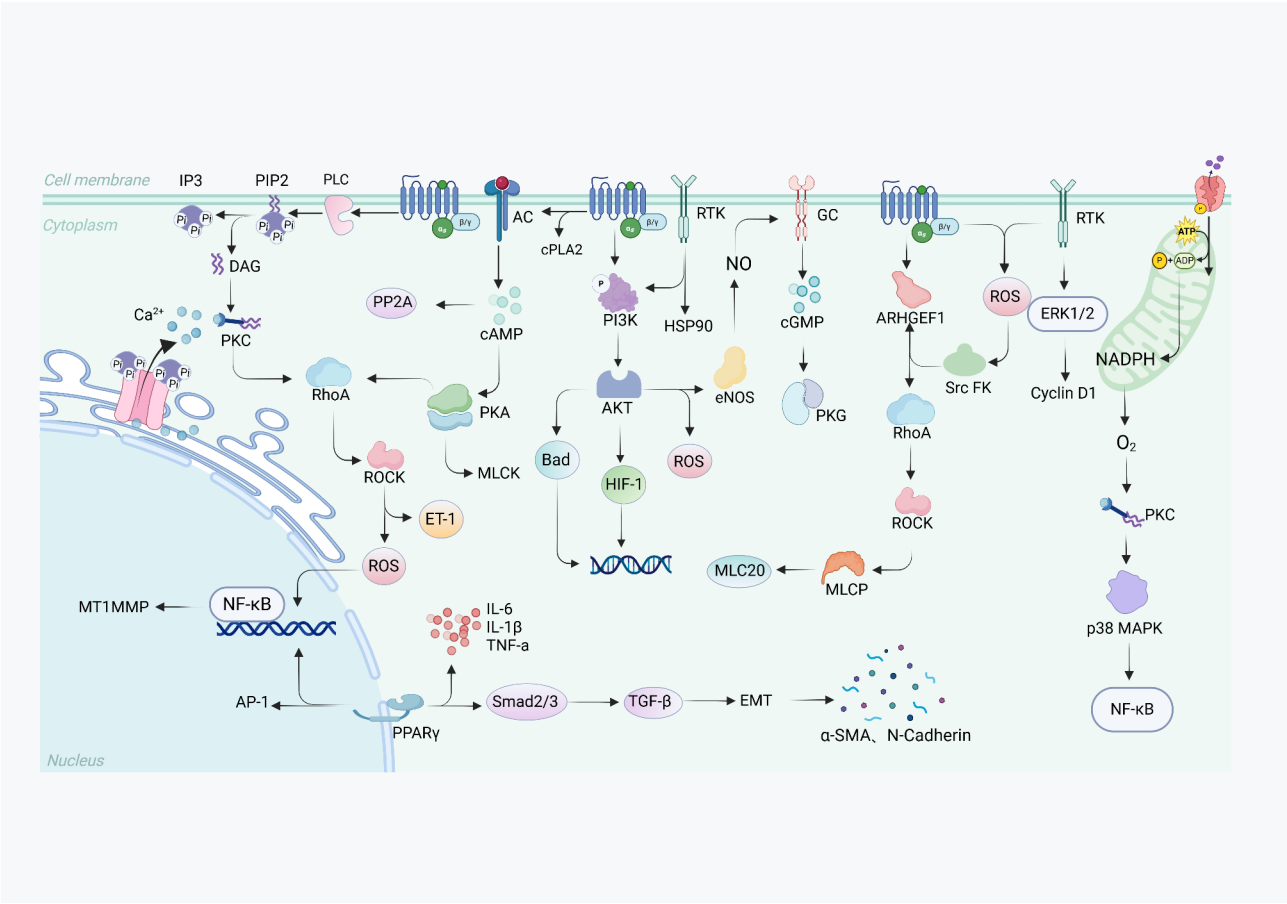

Fig. 2 The ω-6 PUFAs and their metabolites in pulmonary hypertension. AC: adenylate cyclase; AKT: protein kinase B; ARHGEF1: rho guanine nucleotide exchange factor 1; DAG: diacylglycerol; EMT: endothelial to mesenchymal transition; eNOS: endothelial nitric oxide synthase; GC: guanylate cyclase; IP3: inositol 1,4,5-trisphosphate; MAPK: mitogen-activated protein kinase; MT1MMP: matrix metalloproteinase-1; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; PIP2: phosphatidylinositol 4,5-bisphosphate; PI3K: phosphatidylinositol 3-kinase; PKA: protein kinase A; PKC: protein kinase C; PKG: protein kinase G; RhoA: ras homolog gene family member A; ROCK: Rho-associated coiled -coil-containing protein kinase; ROS: reactive oxygen speices; Src FK: src family kinase

elevated in PH patients, while 2,3-dinor-6-keto-prostaglandin F1α is decreased [22]. These findings indicate varying roles for oxylipins in PH, warranting further research to clarify their underlying mechanisms.

ω-6 polyunsaturated fatty acids and their metabolites Oxylipins

Linoleic acid (LA) and LA-derived Oxylipins

The bioactivities of LA and LA-derived oxylipins in PH are shown in Table 1.

Linoleic acid

Linoleic acid (LA) is a key polyunsaturated C18 fatty acid from dietary lipids, vital for cell membrane synthesis and cardiovascular health. It can increase cyclic adenosine monophosphate (cAMP) in pulmonary fibroblasts, indicating involvement in cell proliferation and extracellular matrix deposition [23]. Pulmonary hypertension (PH) involves abnormal responses in the pulmonary vascular endothelial layer, including proliferation, inflammation, and apoptosis of pulmonary artery endothelial cells (PAECs). Linoleic acid (LA) disrupts endothelial barrier function by enhancing albumin transfer between endothelial monolayers [24]. Additionally, LA exhibits proinflammatory properties by inducing DNA binding activity of nuclear factor-κB (NF-κB) and up-regulating the expression and production of interleukin-6 (IL-6) in PAECs [25, 26]. It may also influence pulmonary vessel contraction by reducing prostacyclin and increasing endothelial nitric oxide synthase (eNOS) activity [27, 28]. Furthermore, LA has been observed to decrease the expression and activation of PPARγ [29], which is known for its critical role in repairing DNA damage and reversing experimental pulmonary hypertension. Exposure to LA has been shown to increase intracellular calcium, nitric oxide, tetrahydropterin levels, and E-selectin expression in PAECs [30]. Collectively, these mechanisms suggest that LA may contribute to PA

Table 1 Biological activities of LA and LA-derived oxylipins in PH

Metabolite	Cell Type	Pathways	Biological process
Linoleic acid	Fibroblasts	Increases the level of cAMP	Cell proliferation and ECM deposition
	PAECs	Inducing DNA binding activity of NF-κB and upregulate IL-6 expression	Cell inflammatory
		Decrease PPARγ expression	Cell inflammatory
		Increases the transfer of albumin	The destruction of endothelial barrier function
		Decrease the produce of PGI2, PGE2 and PGF2α	The contraction of pulmonary blood vessels
		Increased intracellular calcium and peroxynitrite expression	Cell inflammatory
		Increasing caspase-3 activity and inducing Annexin V binding and DNA fragmentation	Apoptosis
13-HODE	VSMCs	Promoting calcium entry into cells	Vasoconstrictor
HPODE	PAECs	Reducing the proteoglycan metabolism of endothelial monolavers	The destruction of pulmonary artery endothelial barrier
9-HODE	Macrophages	Inhibiting the scavenging of ROS	Oxidative stress

inflammation, oxidative stress, cytotoxicity, and endothelial dysfunction.

Interestingly, LA can have varying and sometimes opposite effects on different blood vessels, and it is not yet fully understood whether these effects play a role in the development and progression of pulmonary hypertension.

LA Oxylipins from LOX pathway

13-HODE, derived from LA through the action of 15-LOX, functions as a vasoconstrictor in vascular smooth muscle cells by facilitating calcium entry. This process is believed to be mediated by 13-HODE's ability to increase cGMP levels in PASMCs, subsequently leading to a rise in intracellular calcium concentration ([Ca2+]i) through cGMP kinase-dependent L-type channel activation [31]. Furthermore, 13-HODE has been shown to attenuate the adhesion between thrombin-activated platelets and PAECs [32].

Hydroperoxy linoleic acid (HPODE) is an oxylipin that is produced from LA through the LOX pathway. HPODE has been found to reduce the metabolism of proteoglycans in endothelial monolayers and contribute to the disruption of pulmonary artery endothelial barrier function [33]. This suggests that HPODE may have a role in mediating endothelial dysfunction in the context of PH.

γ-Linolenic acid (GLA)

Diets rich in gamma-linolenic acid (GLA) have shown positive effects on pulmonary arterial hypertension (PAH) by increasing levels of PGE1 and 15-HETrE, which help reduce pulmonary inflammation and fibrosis [34]. Additionally, GLA protects the lung and heart from PAH and right ventricular failure [35]. These findings suggest that GLA may hold potential as a targeted treatment for PH.

Dihomo-γ-linolenic acid (DGLA) and DGLA-derived Oxylipins

DGLA Oxylipins from the COX pathway

Prostaglandin E1 (PGE1), synthesized from DGLA via the COX pathway, is a potent pulmonary vasodilator with therapeutic benefits for various pulmonary hypertension (PH) conditions. It notably reduces mean pulmonary artery pressure (PAP) and vascular resistance [36–40], thereby improving oxygenation and cardiopulmonary function in patients with severe PH [39, 41, 42]. PGE1 decreases vascular wall muscularization and the expression of von Willebrand factor (VWF) and PCNA in MCT-induced PH rats, leading to reduced PAP and right ventricular hypertrophy [43]. It also inhibits PASMC migration and proliferation through the CREB/PTEN signaling pathway, preventing pulmonary remodeling [44, 45]. However, it is worth noting that P J Pasricha et al. have suggested that PGE1 and PGE2 may stimulate rather than inhibit the proliferation of PASMCs [46].

Mesenchymal stem cells (MSCs) have emerged as a promising therapeutic option for PAH treatment [47]. PGE1 has been found to modulate MSC properties by regulating the hypoxia-inducible factor (HIF) pathway, thereby enhancing the therapeutic potential of MSCs in PAH [48].

DGLA Oxylipins from LOX pathway

While 15-hydroxy eicosatrienoic acid (15-HETrE) is widely acknowledged for its anti-inflammatory properties and its ability to mitigate lung inflammation and fibrosis caused by bleomycin [34], its precise role in the regulation of pulmonary hypertension (PH) is currently the subject of intense investigation.

Arachidonic acid (AA)-derived Oxylipins

COX pathway

Cyclooxygenase (COX) is pivotal for the conversion of arachidonic acid (AA) into prostaglandins (PGs) like PGI2, PGE2, PGD2, and PGF2α, as well as thromboxane.

Thromboxane A2 (TXA2), synthesized from AA via COX and thromboxane synthase 1 (TBXAS1), regulates pulmonary artery (PA) tension, promoting platelet aggregation, vasoconstriction, and cell mitosis. Increased TXA2 or the TXA2/PGI2 ratio in PAECs leads to PA constriction [49]. TXA2-induced pulmonary vasoconstriction is mediated through several mechanisms (Fig. 3). It inhibits Na^+/K^+-ATP activity [50, 51], inhibits voltage-gated potassium channel (K_v) currents [52, 53] and activates the PKCα–p38MAPK–Giα(alpha subunit of Gi)- cPLA2 pathway to leading to an increase in $[Ca^{2+}]i$ [54]. Additionally, it also activates the PKCζ-K(V)-L-type Ca2 + channel and modulates endothelial nitric oxide synthase (eNOS) through H2O2 and AKT pathways, all of which contribute to pulmonary vasoconstriction [55, 56]. Mechanistically, TXA2 promotes proliferation, contraction, and oxidative stress in PASMCs, leading to PA remodeling. For instance, the TXA2 mimetic U46619 activates the p38MAPK-NFκB-MT1MMP pathway in PASMCs, resulting in extracellular matrix degradation and cell proliferation [57, 58]. Moreover, TXA2 induces reactive oxygen species (ROS) production and src family kinase auto-phosphorylation, activating RhoA to promote cell contraction [59].

TXB2, the primary and stable metabolite of TXA2, is commonly used to assess the impact of TXA2. Its concentration in the bloodstream is notably elevated during PH [60]. The increased levels of 2,3-dinor-6-oxo-PGF1α and 2,3-dinor-TXB2 (major metabolites of thromboxane A2) in the urine of newborns with infective persistent PH suggest that TXB2 may serve as a mediator of this condition [61]. However, the precise role of TXB2, whether it acts as a cause or a consequence, remains unclear.

There are two types of PGs: classic PGs and cyclopentenone PGs (cyPGs). The latter category includes PGJ2, PGA1, PGA2, and metabolites of PGJ2 such as Δ12-PGJ2 and 15-deoxy-Delta (12,14)-prostaglandin J2 (15d-PGJ2) [62]. The roles of classical PGs and cyclopentenone PGs

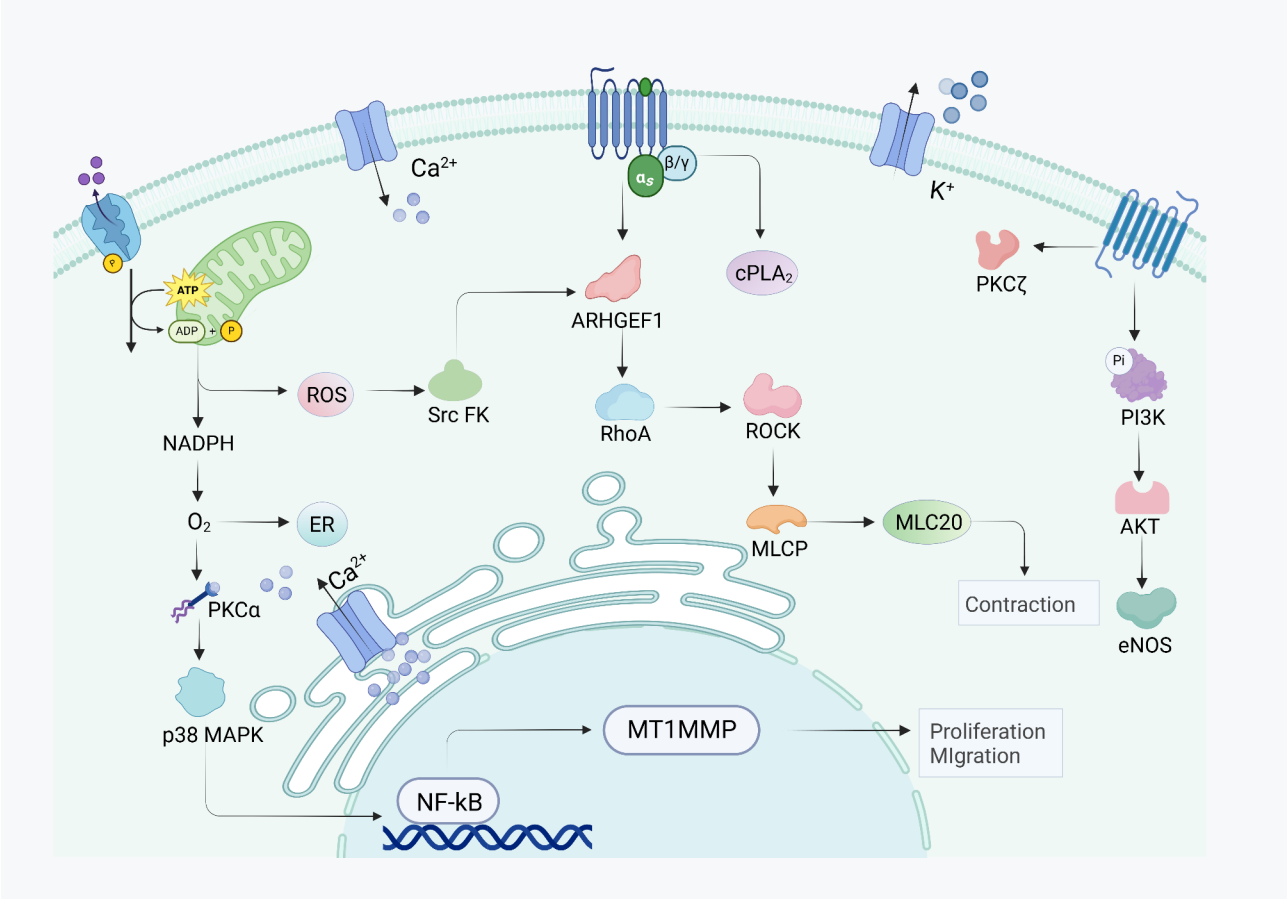

Fig. 3 TXA2 in pulmonary hypertension. ARHGEF1: rho guanine nucleotide exchange factor 1; MT1MMP: matrix metalloproteinase-1; PKC: protein kinase C; Src FK: src family kinase

(cyPGs) in the pulmonary vasculature are shown in Table 2.

PGH2, a crucial intermediate substance in the COX metabolic pathway where AA plays a pivotal role, is another significant mediator of pulmonary vasoconstriction [63, 64].

PGE2, a lipid signaling molecule known for its involvement in pain and inflammation, is a primary product of COX in human PASMCs. This molecule has been shown to bolster the barrier function of human pulmonary microvascular endothelial cells, which results in a decrease in vascular permeability [65]. This decrease in vascular permeability is a fundamental characteristic of inflammation. It is widely recognized that in acute hypoxic pulmonary arterial hypertension, PLA2 triggers the release of inflammatory mediators. Furthermore, there exists a positive correlation between PLA2 activity and PGE2 [66].

PLA2 is known to release inflammatory mediators in acute hypoxic pulmonary arterial hypertension, showing a positive correlation with PGE2 levels [66]. PGE2, mediated by cPLA2, is crucial for generating the cAMP signal that induces COX-2 expression [67, 68]. Additionally, it also mitigates lung dysfunction from endotoxemia by inhibiting inflammatory responses in neutrophils and lymphocytes, reducing TXB2, 6-keto-PGF1α, and LTB4 levels [69]. Interestingly, Conversely, endotoxins may increase PGI2 and PGE2 release, enhancing protein and neutrophil influx into alveoli, though the reasons for these discrepancies remain debated [70, 71]. In newborn lambs, low oxygen increases COX-1 activity, promoting PGI2 and PGE2 synthesis in pulmonary artery segments and PAECs [72]. Insufficient production of PGI2 and PGE2 may contribute to changes in vascular tension and vascular remodeling [73]. Additionally, inhibiting PI3K and p38 MAPK reduces PGE2 release by affecting COX activity [74]. There appears to be a positive feedback loop between COX-2 and PGE2, with COX-2 being a key source of prostanoids in inflammatory and proliferative diseases [75]. Furthermore, PGI2 has a clinical association with effective bronchodilation through EP4 receptor activation. PGE2 can dilate the human pulmonary vein by activating the EP4 receptor [76]. Notably, EP4 receptor expression is significantly reduced in the bronchi of group III pulmonary hypertension patients, suggesting that restoring its expression could benefit these patients [77]. In idiopathic pulmonary fibrosis (IPF), PGE2 shows antifibrotic effects by limiting fibroblast proliferation, migration, and collagen secretion [78–80]. However, further research is required to determine whether PGE2 affects the pathophysiology of PH by regulating pulmonary adventitial fibroblasts.

Prostaglandin F2α (PGF2α), a stable vasoactive compound produced by COX, is essential for regulating various physiological and pathological processes. It is involved in smooth muscle contraction,

Table 2 Classic PGs and cyclopentenone PGs (cyPGs) in pulmonary vascular

Metabolite	Cell Type	Biological mechanism	Biological process
PGE1	PASMCs	Activating the IP receptor and the phosphorylated CREB/PTEN/pAKT signaling pathway	Inhibiting migration and proliferation
	Mesenchymal stem cells	Increased the levels of HIF-1α	Reducing MSC apoptosis and increasing migration
PGE2	Neutrophils and lymphocytes	Reducing the level of TxB2, 6-keto-PGF1α, and LTB4	Anti-inflammatory
	Fibroblasts	Disrupting Ca2 + signaling	Anti-profibrotic
	Endothelial cells	Activating the EP4 receptor	Enhance the barrier function
	PASMCs	Generating the cAMP signal	Inhibiting proliferation and migration
PGF2α	PASMCs	Activating the TP receptors and FP receptors to raise [Ca2+]i	Vasoconstriction
	PASMCs	Activating the srcFK/Rho/MYPT-1 pathway	Cell contraction
	PASMCs	Upregulating the expression NADPH and gp91phox	Vasoconstriction
PGI2	PASMCs	Activating the IP receptor and up-regulating of FAS ligand	Promoting apoptosis
	PASMCs	Increasing the intracellular cAMP	Inhibiting proliferation and migration, inhibiting pulmonary vasoconstriction
PGD2	PASMCs	Activating the DP1/PKA/mTORC1 pathway	Cell hypertrophy and proliferation
	Fibroblasts	Activating the DP receptor/PKA/cAMP pathway	Inhibiting chemotaxis and migration
	Fibroblasts	Activating the DP receptor/cAMP pathway	Inhibiting TGF-β-induced collagen
8-epi-PGF2α	PASMCs	Activating the PKC/RhoA/ROCK pathway	Oxidative stress
	Endothelial cells	Oxidant-mediated alterations in monolayer barrier function	Monolayer barrier dysfunction
	Fibroblasts	Stimulating NOX4 expression and ROS generation	Proliferation and collagen synthesis
PGA2	PAECs	Activating the EP4 receptor and inhibiting the NF-κB pathway	Anti-inflammatory
	PAECs	Activating the EP4 receptor - Rap1/Rac1 GTPase	Barrier-protective
15d-PGJ2	PAECs	Activating the PPAR-γ and inhibiting NF-κB activation	Anti-inflammatory

vasoconstriction of blood vessels and bronchi, and inflammatory responses. In endotoxin-induced acute lung injury, PGF2α, along with thromboxane A2 (TXA2), can elevate pulmonary artery pressure (PAP), increase airway resistance, and decrease lung compliance [81]. The vasoconstrictive effects of PGF2α on pulmonary arteries are mediated through TP receptors [82–84] and involve calcium influx via a nonselective cation channel and an L-type calcium channel [85, 86]. In PASMCs, PGF2α activates srcFK-dependent Rho-kinase translocation and MYPT-1 phosphorylation, which contribute to calcium sensitization and contraction [87]. Additionally, PGF2α promotes the formation of superoxide and upregulates the expression of the NADPH oxidase subunit (gp91phox) in both PASMCs and PAECs [88].

PGI2, derived from arachidonic acid via COX-2 and PTGIS, has beneficial effects such as inhibiting platelet aggregation, vasodilation, and anti-inflammatory properties [89, 90]. In severe pulmonary hypertension (PH), decreased levels of PGI2 and related enzymes are linked to right ventricular fibrosis, pulmonary vasoconstriction, inflammation, proliferation of PASMCs and dysfunction of PAECs [90, 91]. The protective effects of PGI2 and its analogues in PH are well established. PGI2 induces PASMC apoptosis through the IP receptor and increases intracellular cAMP, facilitating vasodilation [92]. PGI2 also stimulates adenylate cyclase in PASMCs, resulting in increased intracellular cAMP levels and subsequent vasodilation [93]. Similarly, IP receptor agonists, which elevate intracellular cAMP levels, are used in the treatment of PH to inhibit pulmonary vasoconstriction, PASMC proliferation, and extracellular matrix synthesis [94]. Additionally, the NNMT-MNA pathway, associated with 6-keto-PGF1α, also provides protective effects in idiopathic pulmonary arterial hypertension (IPAH) [95].

PGD2 is derived from AA through the action of COX and two PGD2 synthases (PGDS): lipocalintype PGDS (L-PGDS) and hematopoietic PGDS (H-PGDS) [96]. Recent research by Jia et al. has shown that reduced expression of H-PGDS in infiltrating lung macrophages can lead to decreased PGD2 production, exacerbating hypoxia/SU5416-induced PH in mice [97]. Furthermore, PGD2 exerts vasodilatory effects through DP1 (D prostanoid receptor subtype 1) and mitigates hypoxia-induced pulmonary remodeling and PH via the PKA/mTORC1 pathway [98]. Elevated levels of PGD2 metabolite (PGD-M) in the urine of patients with primary PH suggest macrophage activation [99], which may drive inflammatory responses. Furthermore, PGD2 has been shown to inhibit the migration [100] and collagen secretion of lung fibroblasts by activating DP receptors [100]. It also inhibits the metalization of fibroblasts induced by TGF-β [101, 102]. However, PGD2 does not improve PAP and oxygenation in newborns with persistent pulmonary hypertension syndrome [103]. Overall, these findings emphasize the crucial role of PGD2 in PH pathophysiology.

Iso-prostaglandins, such as 8-isoprostane (also known as 8-epi-PGF2α) and 8-iso-PGF2α (also known as 8-iso-prostaglandin F2α), are prostaglandins that originate from the non-enzymatic peroxidation of esterified AA. This process occurs due to the presence of free radicals and reactive oxygen species (ROS). These iso-prostaglandins exert their effects by binding to the thromboxane receptor (TP).

Malonaldehyde (MDA), 4-hydroxynonenal (HNE), and 8-isoprostane are key indicators of lipid peroxidation linked to oxidative damage in cells. In conditions such as high-altitude pulmonary edema and endotoxin-induced pulmonary hypertension (PH), levels of 8-iso-PGF2α increase due to oxidative stress and inflammation [104, 105]. Studies in animal models have shown that increased 8-isoprostane levels contribute to PH and right ventricular hypertrophy, particularly in newborn rats exposed to hyperoxia. This effect involves the activation of the PKC/RhoA/ROCK pathway, leading to increased endothelin-1 production and oxidative stress in PASMCs [106, 107]. Additionally, 8-isoprostane stimulates the release of calcium signals and promotes the accumulation of superoxide anion in PASMCs, resulting in pulmonary vasoconstriction [108, 109]. Furthermore, 8-isoprostane has been found to disrupt the monolayer barrier function of vascular endothelial cells [110]. It also stimulates proliferation, collagen synthesis, expression of NADPH oxidase 4 (NOX4), and production of reactive oxygen species (ROS) in human lung fibroblasts [111]. These findings suggest that 8-isoprostane play an essential role in lung tissue inflammation and damage of hypoxia-related PH in humans. Another iso-prostaglandin, 8-iso-PGF2α, acts as a vasoconstrictor at high concentrations and a vasodilator at lower concentrations, highlighting its dual role [112].

CyPGs have been found to possess various beneficial properties, including the suppression of inflammatory responses, inhibition of proliferation and angiogenesis, and promotion of apoptosis. For instance, PGA2 enhances the barrier function of endothelial cells by inhibiting the inflammatory signal transduction induced by lipopolysaccharide (LPS) and inhibiting the expression of the NF-κB pathway and adhesion molecules ICAM-1 and VCAM1 in PAECs [113].

Similarly, 15d-PGJ2, act as the ligand of PPAR γ, exhibits anti-inflammatory, anti-proliferative, anti-fibrotic, cytoprotective, and catabolic effects in lung tissue, and plays a protective role in lung injury induced by endotoxin, bleomycin, and influenza virus [114–117]. Additionally, 15d-PGJ2 promotes the release of nitric oxide (NO) from PAECs in a manner independent of eNOS

expression [118]. However, further research is necessary to fully explore the unique therapeutic characteristics of cyPGs and to develop them as potent anti-inflammatory and anti-proliferative drugs.

In neonatal rats afflicted with persistent pulmonary hypertension (PH), the expression level of 6-keto-prostaglandin F1α (6-keto-PGF1α), a stable metabolite of prostacyclin, is elevated relative to the control group [119]. This upregulation may represent an adaptive mechanism aimed at countering the increased vascular resistance associated with PH.

LOX pathway

Lipoxygenase (LOX) plays a role in converting arachidonic acid (AA) into inflammatory lipid mediators, specifically hydroxyeicosatetraenoic acids (HETEs) and leukotrienes (LTs). These molecules are involved in oxidative stress, inflammation, and microvascular dysfunction in pulmonary arterial. One important enzyme, 5-lipoxygenase (5-LO), catalyzes the production of LTs, which have diverse pathological effects contributing to the development of pulmonary hypertension (PH). For instance, one major LTs called LTB4 has been identified as a regulator for various cell types observed in PAH, such as PASMCs, PAECs, and pulmonary fibroblasts. LTB4 induces proliferation in PASMCs and apoptosis in PAECs, activates fibroblasts in the pulmonary adventitia, and ultimately leads to vascular remodeling [120–122].

15-Hydroxyeicosatetraenoic acid (15-HETE), derived from arachidonic acid (AA) through the action of 15-lipoxygenase (15-LO), is implicated in pulmonary vascular remodeling and the development of pulmonary hypertension (PH) via a multitude of complex and interwoven mechanisms (Table 3). It promotes proliferation and phenotypic changes in PASMCs and PAECs, while also protecting PASMCs from apoptosis. Additionally, 15-HETE also enhances thrombosis and inflammation in pulmonary arteries. In PASMCs, it promotes the expression of sirtuin-1 (SIRT1) [123] and activates the PDGFRβ/15-LO-2/15-HETE signaling pathway, facilitating cell survival and proliferation [124]. Correspondingly, It inhibits hypoxia-induced apoptosis through positive feedback with hypoxia-inducible factor-1α (HIF-1α) and by activating ROCK, PI3K/AKT, and p38MAPK pathways [125–128]. Additionally, it upregulates inducible nitric oxide synthase (iNOS) and influences K + channel activity, reinforcing anti-apoptotic effects during hypoxia [129, 130]. Other than that, 15-HETE is associated with hypoxia-induced phenotypic changes in PASMCs, which involves activation of 15-LO/15-HETE-BMP4/

Table 3 15-HETE in pulmonary vascular.

	Biological mechanism	Biological process
15-HETE	promoting the transcription and translation of sirtuin-1	Promoting PASMC survival
	activating the platelet-derived growth factor-β receptor (PDGFRβ)/15-LO-2/15-HETE signaling pathway	Promoting PASMC proliferation and survival
	forming a positive feedback loop with hypoxia-inducible factor-1α (HIF-1α) and by activating the ROCK, PI_3K/AKT, and p38MAPK pathway	Inhibiting hypoxia-induced apoptosis of PASMCs
	up-regulating the expression of inducible nitric oxide synthase (iNOS) and suppressing the K^+ channel activation	Reinforcing the hypoxia-induced anti-apoptosis effect in PASMCs
	activating of 15-LO/15-HETE-BMP4/BMPRI and its downstream ERK and p38MAPK pathways	Hypoxia-induced phenotypic changes in PASMCs
	upregulating of the p38MAPK/EGR-1/FGF-2/TGF-β1 pathway in fibroblasts	Regulating pulmonary adventitial fibroblasts (PAFs) phenotypic changes and cell proliferation
	activating the 15-LO/15-HETE induced p38MAPK-dependent TGF-β1/Smad2/3 signal pathway	Adventitia fibrosis and phenotypic alterations of fibroblasts
	STAT3-mediated MMP-2 expression	Migration of pulmonary adventitia fibroblasts
	activating of the STAT3 signaling pathway	Proliferation of PAECs
	positive feedback loop involving placenta growth factor (PlGF), 15-LO, and 15-HETE	Proliferation and migration of PAECs
	Rho-kinase and p38 MAPK pathways	Migration of PAECs and the proliferation of p PASMCs
	upregulating the expression of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9)	Regulateing the proliferation、 migration、and cell cycle transition of PAECs, the migration of fibroblasts, thereby promoting angiogenesis
	positive interaction between 15-LO/15-HETE and NF-κB	Inducing apoptosis of cytotoxic T cell-dependent PAECs;promoting monocyte/macrophage infiltration
	5-LO/15-HETE signaling pathway	Platelet activation and thrombosis
	inhibiting whole-cell K currents mediated by the PKC signal 2 pathway, mediates ERK1/2 activation and caldesmon phosphorylation, induces PKC- δ and PKC- translocation, affects intracellular Ca^{2+} concentration, and influences the expression of Rho-associated serine/threonine kinase (ROCK)	Hypoxic pulmonary vasoconstriction

BMPRI and its downstream ERK and p38MAPK pathways [131]. Secondly, it has been observed that 15-HETE induces the upregulation of the p38MAPK/EGR-1/FGF-2/TGF-β1 pathway in fibroblasts, which contributes to the regulation of pulmonary adventitial fibroblasts (PAFs) phenotypic changes and cell proliferation [132]. Beyond this, the activation of the 15-LO/15-HETE induced p38MAPK-dependent TGF-β1/Smad2/3 signal pathway is crucial for adventitia fibrosis and phenotypic alterations of fibroblasts [133]0.15-HETE also stimulates migration of pulmonary adventitia fibroblasts through STAT3-mediated MMP-2 expression [134]. In PAECs, it promotes proliferation via STAT3 signaling and facilitates PAEC migration and PASMC proliferation under hypoxia [135]. A positive feedback loop involving placenta growth factor (PlGF), 15-LO, and 15-HETE induces the proliferation and migration of PAECs [136]. Also, during hypoxia, 15-HETE promotes the migration of PAECs and the proliferation of PASMCs via the Rho-kinase and p38 MAPK pathways [137, 138]. 15-HETE is involved in angiogenesis by regulating matrix metalloproteinases (MMP-2 and MMP-9), and it promotes inflammation through interactions with cytotoxic T cells and macrophages [139]. The involvement of 15-HETE in pulmonary artery inflammation includes inducing apoptosis of cytotoxic T cell-dependent PAECs [140] and promoting monocyte/macrophage infiltration through a positive interaction between 15-LO/15-HETE and NF-κB [141]. It contributes to thrombosis and vasoconstriction in PH, with in vitro studies showing that it can induce relaxation in pulmonary rings [142, 143]. Illustratively, 15-HETE inhibits whole-cell K currents mediated by the PKC signal 2 pathway [144], mediates ERK1/2 activation and caldesmon phosphorylation [145], induces PKC- δ and PKC- translocation [144], affects intracellular Ca^{2+} concentration [146], and influences the expression of Rho-associated serine/threonine kinase (ROCK) [147], ultimately leading to hypoxic pulmonary vasoconstriction. Overall, 15-HETE impacts multiple pathways leading to pulmonary artery vasoconstriction. Despite extensive research, clinical trials investigating these mechanisms remain limited, likely due to the complexity of studying 15-HETE in vitro.

15-prostaglandin dehydrogenase (15-PGDH) is an enzyme that degrades prostaglandins, converting 15(S)-HETE to 15-keto-6Z, 8Z, 11Z, 13E-eicosatetraenoic acid (15-KETE) [148]. This process activates the ERK1/2 pathway, promoting proliferation and migration of PAECs and increasing protease-activated receptor 2 (PAR-2) expression, which aids PASMCs proliferation [149, 150]. Additionally, the enzyme 5-hydroxyeicosatetraenoic acid dehydrogenase (5-HEDH) converts 15-HETE into 15-oxo-eicosatetraenoic acid (15-oxo-ETE), protecting PASMCs from apoptosis through the AKT signaling pathway [151].

12-hydroxy-eicosapentaenoic acid (12-HETE) is a metabolite of AA that is catalyzed by 12-lipoxygenase (12-LO). It has been observed that 12-HETE increases the concentration of calcium ($[Ca^{2+}]i$) in PASMCs, which typically contributes to vascular hypercontractility [31]. 12-HETE promotes the migration and angiogenesis of hypoxic PAECs and inhibits apoptosis in PAECs, partly through the activation of the PI3K/AKT signaling pathway [152]. Furthermore, it induces the phosphorylation of ERK1/ERK2, leading to an increase in hypoxia-induced proliferation of PASMCs [153]. These findings suggest a potential association between12-LOX and hypoxia-induced PH [31].

Although it remains unclear whether 5-HETE is involved in the occurrence and development of PH, early studies have shown that intrapulmonary infusion of 5-HETE can cause pulmonary vasoconstriction and pulmonary edema [154]. 5-HETE, along with 12-HETE and 15-HETE, has been shown to decrease the expression of Kv2.1 channels in both PASMCs and PA cultured under normoxic conditions [155]. Voelkel et al. found that inhibiting 5-lipoxygenase-activating protein (FLAP) and reducing 5-lipoxygenase (5-LO) levels can effectively reduce pulmonary vascular tension and ameliorate PH in hypoxic rats [156]. Additionally, 5-LO inhibitors have demonstrated the ability to inhibit the proliferation response of cultured PAECs in vitro [157].

CYP450 pathway

Cytochrome P450 (CYP450) enzymes metabolize arachidonic acid (AA) into various metabolites, including 16-, 17-, 18-, 19-, 20-HETE, and epoxyeicosatrienoic acids (EETs). The CYP2C and CYP2J gene subfamilies specifically produce EETs, such as 14,15-, 11,12-, 8,9-, and 5,6-EET, which have vascular protective effects through anti-inflammatory, anti-apoptotic, proliferative, and antioxidant actions. For instance, 8,9-EET, 11,12-EET, and 14,15-EET promote proliferation and protect PAECs from apoptosis via the JNK/c-Jun pathway, aiding PAEC growth and angiogenesis during pulmonary hypertension (PH) [158]. Conversely, soluble epoxide hydrolase (sEH) metabolizes EETs into less active dihydroxyeicosatrienoic acids (DHETs) and is linked to pulmonary vascular remodeling [159]. Inhibition of sEH can reduce proliferation of PASMCs and inflammation, mitigate pulmonary artery remodeling, and ameliorate monocrotaline (MCT)-induced PH in rats [160, 161]. The expression and activity of CYP enzymes influence bioactive product production. For instance, CYP2C29 expression in hypoxic mice increases over time [162], and activation of CYP2C9 can produce a substantial amount of superoxide dismutase [163], which stimulates the proliferation

Table 4 CYP2J2 in pulmonary hypertension

	Biological mechanism	Biological process
CYP2J2	activating PPARγ	exhibiting anti-inflammatory effects
	activating the PI3K/AKT pathway	exhibiting anti-apoptotic effects
	inhibiting TNF-α, PI_3K/AKT, and ERK pathways	apoptosis of PAECs
	inhibiting TGF-β	stimulating the migration of PASMCs
	increasing the expression and activity of nitric oxide synthase and inhibiting Smads signaling pathway	ameliorating MCT-induced PH and pulmonary inflammation

of primary PAECs in vitro and elicit pulmonary microangiogenesis. Likewise, Deletion of CYP2C44 worsens PH in female mice, and CYP2J deficiency only partially alleviates hypoxic PH [164]. The role of CYP2J2 in pulmonary hypertension is detailed in Table 4. Overexpression of CYP2J2 in lung ischemia-reperfusion injury with PH demonstrates anti-inflammatory effects via PPARγ activation and anti-apoptotic effects through the PI3K/AKT pathway [165]. In line with this, CYP2J2 overexpression inhibits apoptosis of PAECs and stimulates PASMC migration by downregulating TGF-β [166]. Additionally, CYP2J2 overexpression can ameliorate MCT-induced PH and pulmonary inflammation by increasing nitric oxide synthase activity and inhibiting Smads signaling [167].

5,6-EET has a dual role in regulating pulmonary artery tension. Under normoxic conditions, it relaxes pulmonary arteries [168], but under hypoxia, it causes pulmonary vasoconstriction [169], by depolarizing PASMCs, partly mediated by COX-1 and COX-2 [170]. In porcine pulmonary arteries, 5,6-EET induces dilation through the release of endothelium-derived nitric oxide, COX metabolites, and the activation of calcium-dependent potassium channels [171]. The response varies by vessel diameter: in larger extra-lobar pulmonary artery rings (> 2 mm), it relaxes blood vessels in a concentration- and COX-dependent manner, while in smaller intra-lobar rings (1–2 mm), it increases vascular tension via Rho-kinase activation [172, 173]. Overall, 5,6-EET can raise pulmonary vascular resistance, particularly when it requires an endothelial and COX-dependent TX/PGH2 receptor agonist [172, 174].

As previously mentioned, the derivative of 8,9-EET known as 8,9-EET analog(214) demonstrates a partial protective effect on PASMCs against apoptosis by activating the ROCK pathway. In contrast, 8,9-EET primarily exerts its influence on PAECs [175].

11,12-Epoxyeicosatrienoic acid (11,12-EET) induces partial vasorelaxation in the systemic circulation, yet it concurrently enhances right ventricular systolic pressure (RVSP) and hypoxic pulmonary vasoconstriction [176, 177]. Several explanations have been proposed for these contrasting effects. Firstly, 11,12-EET stimulates the combination of α and β (1) subunits of mitochondrial large-conductance Ca^{2+}-activated potassium (BK) channels in the lungs, while also assisting constrictor prostanoids such as PGH2 and TXA2 [176, 177]. Furthermore, the recruitment of transient receptor potential C6 channel to caveolae caused by 12-EET enhances the contractile response of hypoxic pulmonary artery [178].

1,12-EET increases pulmonary artery pressure (PAP) in a concentration-dependent manner and enhances hypoxia-induced pulmonary artery contraction via Rho-dependent and TRP C6-V5 pathways [179]. Similarly, exogenous 14,15-EET significantly raises right ventricular systolic pressure (RVSP) in mice exposed to hypoxia [180]. Furthermore, both 11,12-EET and 14,15-EET demonstrate anti-inflammatory effects in PAECs by mitigating inflammatory responses induced by oxidized low-density lipoprotein (ox-LDL). This is achieved by inhibiting LOX-1 receptor expression and suppressing the activation of mitogen-activated protein kinase (MAPK) and nuclear factor kappa-B (NF-κB) pathways [181].

20-hydroxyeicosatetraenoic acid (20-HETE) is a product of ω-hydroxylation of AA catalyzed by cytochrome P4504A (CYP4A). It serves as an endothelium-dependent pulmonary artery dilator and is essential for pulmonary vascular remodeling. In sheep, 20-HETE inhibits Na+-K+-ATPase activity in pulmonary arteries, leading to relaxation [182]. It also promotes acute pulmonary vasoconstriction through the Rho kinase pathway and induces NFAT3 translocation [183]. In PAECs, 20-HETE activates eNOS, enhancing the release of NO, which participates in pulmonary vascular relaxation [184]. This activation involves serine 1179 and AKT phosphorylation [185], PI_3K/AKT activation [186], and increased intracellular Ca2 + levels [187]. 20-HETE also protects PAECs from hypoxia-induced oxidative stress and apoptosis via PI3K/AKT and HIF-1α signaling pathways [188, 189].

Notably, 20-HETE also affects PASMCs. It induces the expression of BCL-2, which helps maintain mitochondrial membrane stability and reduces the activation of caspase-9 and caspase-3, thereby protecting PASMCs from apoptosis [190]. Independently of this, 20-HETE can induce PASMCs hyperproliferation and ROS production [191]. Furthermore, 20-HETE stimulates ROS production in PAECs, potentially promoting vascular repair [192]. Apart from that, 20-HETE inhibits the

expression of miR-143 and miR-133a, thereby inhibiting the synthetic/secretory phenotype of vascular smooth muscle cells [193]. Interestingly, 20-HETE can also play the opposite role by activating the MAPK1-ELK pathway [194].

In vascular endothelial cells, the 15-lipoxygenase (15-LO) metabolites of arachidonic acid (AA) play important roles. Specifically, 15-hydroxy-11,12-epoxyeicosatrienoic acid (15-H-11,12-HEETA) and 11,12,15-trihydroxy-eicosatrienoic acid (11,12,15-THETA) act as endothelium-derived hyperpolarizing factors. These metabolites induce vasodilation by activating K channels of smooth muscle [195].

Conclusion

In summary, this review emphasizes the significant role of ω-6 PUFAs and their metabolites in pulmonary hypertension (PH) initiation and progression. While the mechanisms remain unclear, evidence points to their therapeutic potential. Targeting the enzymes involved in the metabolism of these unstable oxidized lipids could lead to effective clinical strategies. A better understanding of these metabolic pathways may pave the way for novel drug development to treat PH more effectively.

Points for clinical practice

Currently, approved medications for targeted treating PH mainly include prostacyclin analogs, prostacyclin receptor agonists, phosphodiesterase 5 inhibitors, endothelin-receptor antagonists, and cGMP activators.

Questions for future research

The specific mechanisms of omege 6-PUFAs and their metabolites in pulmonary hypertension remain unclear, and more studies are needed in the future to explore their mechanisms of action and their application in different types of PH.

Currently omege 6-PUFAs and their metabolites are only used in animal models and cellular experiments of pulmonary hypertension, and still no relevant clinical studies have been conducted, and their efficacy in PH patients is ominous. However, due to their theoretical support, omege 6-PUFAs and their metabolites have a great potential for targeted therapy against high pressure in PH, and more studies are still needed to confirm this possibility.

The metabolites of omega-6-PUFAs are unstable in nature, and there are fewer products available for exogenous additives. Future studies need to develop stable dosage forms for the treatment of PH based on their properties, and combine metabolomics and multi-targeted intervention strategies to develop more effective individualized therapeutic regimens.

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J.W and S.H wrote the main manuscript text and plotted the tables, and Y. X prepared Fig. 3. T.W prepared the study. All authors reviewed the manuscript.

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References

1. Humbert M, Guignabert C, Bonnet S, Dorfmüller P, Klinger JR, Nicolls MR, Olschewski AJ, Pullamsetti SS, Schermuly RT, Stenmark KR, Rabinovitch M. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. 2019.
2. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. 2019.
3. Mandras SA, Mehta HS, Vaidya A. Pulmonary Hypertension: A Brief Guide for Clinicians. 2020; pp. 1978–1988.
4. Gabbs M, Leng S, Devassy JG, Monirujjaman M, Aukema HM. Advances in Our Understanding of Oxylipins Derived from Dietary PUFAs. 2015; pp. 513–540.
5. Larsson N, Lundström SL, Pinto R, Rankin G, Karimpour M, Blomberg A, Sandström T, Pourazar J, Trygg J, Behndig AF, Wheelock CE, Nording ML. Lipid mediator profiles differ between lung compartments in asthmatic and healthy humans. Eur Respir J 2014: 43(2): 453–63.
6. Bazinet RP, Layé S. Polyunsaturated fatty acids and their metabolites in brain function and disease. Nat Rev Neurosci 2014: 15(12): 771–85.
7. Du Y, Taylor CG, Aukema HM, Zahradka P. Role of Oxylipins generated from dietary PUFAs in the modulation of endothelial cell function. Prostaglandins Leukot Essent Fat Acids. 2020;160:102160.
8. Thenappan T, Ormiston ML, Ryan JJ, Archer SL. Pulmonary arterial hypertension: pathogenesis and clinical management. BMJ. 2018;360:j5492.
9. Budhiraja R, Tuder RM, Hassoun PM. Endothelial dysfunction in pulmonary hypertension. Circulation. 2004;109(2):159–65.
10. Klinger JR, Kadowitz PJ. The nitric oxide pathway in pulmonary vascular disease. Am J Cardiol. 2017;120(8s):S71–9.
11. Reinero M, Beghetti M, Tozzi P, Segesser LKV, Samaja M, Milano G. Nitric Oxide-cGMP pathway modulation in an experimental model of hypoxic pulmonary hypertension. J Cardiovasc Pharmacol Ther. 2021;26(6):665–76.
12. Whittle BJ, Silverstein AM, Mottola DM, Clapp LH. Binding and activity of the Prostacyclin receptor (IP) agonists, treprostinil and Iloprost, at human prostanoid receptors: treprostinil is a potent DP1 and EP2 agonist. Biochem Pharmacol. 2012;84(1):68–75.

13. Majed BH, Khalil RA. Molecular mechanisms regulating the vascular Prostacyclin pathways and their adaptation during pregnancy and in the newborn. Pharmacol Rev. 2012;64(3):540–82.
14. Hoshikawa Y, Voelkel NF, Gesell TL, Moore MD, Morris KG, Alger LA, Narumiya S, Geraci MW. Prostacyclin receptor-dependent modulation of pulmonary vascular remodeling. Am J Respir Crit Care Med. 2001;164(2):314–8.
15. Golembeski SM, West J, Tada Y, Fagan KA. Interleukin-6 causes mild pulmonary hypertension and augments hypoxia-induced pulmonary hypertension in mice. Chest. 2005;128(6 Suppl):s572–3.
16. Zhao L, Ashek A, Wang L, Fang W, Dabral S, Dubois O, Cupitt J, Pullamsetti SS, Cotroneo E, Jones H, Tomasi G, Nguyen QD, Aboagye EO, El-Bahrawy MA, Barnes G, Howard LS, Gibbs JS, Gsell W, He JG, Wilkins MR. Heterogeneity in lung (18)FDG uptake in pulmonary arterial hypertension: potential of dynamic (18)FDG positron emission tomography with kinetic analysis as a bridging biomarker for pulmonary vascular remodeling targeted treatments. Circulation. 2013;128(11):1214–24.
17. Li M, Riddle S, Zhang H, D'Alessandro A, Flockton A, Serkova NJ, Hansen KC, Moldovan R, McKeon BA, Frid M, Kumar S, Li H, Liu H, Caánovas A, Medrano JF, Thomas MG, Iloska D, Plecitá-Hlavatá L, Ježek P, Pullamsetti S, Fini MA, El Kasmi KC, Zhang Q, Stenmark KR. Metabolic reprogramming regulates the proliferative and inflammatory phenotype of adventitial fibroblasts in pulmonary hypertension through the transcriptional corepressor C-Terminal binding Protein-1. Circulation. 2016;134(15):1105–21.
18. Tuder RM, Davis LA, Graham BB. Targeting energetic metabolism: a new frontier in the pathogenesis and treatment of pulmonary hypertension. Am J Respir Crit Care Med. 2012;185(3):260–6.
19. La Frano MR, Fahrmann JF, Grapov D, Pedersen TL, Newman JW, Fiehn O, Underwood MA, Mestan K, Steinhorn RH, Wedgwood S. Umbilical cord blood metabolomics reveal distinct signatures of dyslipidemia prior to bronchopulmonary dysplasia and pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol. 2018;315(5):L870–81.
20. Bowers R, Cool C, Murphy RC, Tuder RM, Hopken MW, Flores SC, Voelkel NF. Oxidative stress in severe pulmonary hypertension. pp. 764–9.
21. Al-Naamani N, Sagliani KD, Dolnikowski GG, Warburton RR, Toksoz D, Kayyali U, Hill NS, Fanburg BL, Roberts KE, Preston IR. Plasma 12- and 15-hydroxyeicosanoids are predictors of survival in pulmonary arterial hypertension. 2016; pp. 224–33.
22. Christman BW, McPherson CD, Newman JH, King GA, Bernard GR, Groves BM, Loyd JE. An imbalance between the excretion of thromboxane and Prostacyclin metabolites in pulmonary hypertension. 1992; pp. 70–5.
23. Polgar P, Taylor L, Downing D. Unsaturated fatty acid effect on Cyclic AMP levels in human embryo lung fibroblasts. Prostaglandins. 1979;18(1):43–52.
24. Ramasamy S, Boissonneault GA, Lipke DW, Hennig B. Proteoglycans and endothelial barrier function: effect of Linoleic acid exposure to Porcine pulmonary artery endothelial cells. Atherosclerosis. 1993;103(2):279–90.
25. Hennig B, Toborek M, Joshi-Barve S, Barger SW, Barve S, Mattson MP, McClain CJ. Linoleic acid activates nuclear transcription factor-kappa B (NF-kappa B) and induces NF-kappa B-dependent transcription in cultured endothelial cells. Am J Clin Nutr. 1996;63(3):322–8.
26. Hennig B, Meerarani P, Ramadass P, Watkins BA, Toborek M. Fatty acid-mediated activation of vascular endothelial cells. Metabolism. 2000;49(8):1006–13.
27. Kaduce TL, Spector AA, Bar RS. Linoleic acid metabolism and prostaglandin production by cultured bovine pulmonary artery endothelial cells. Arteriosclerosis. 1982;2(5):380–9.
28. Meerarani P, Smart EJ, Toborek M, Boissonneault GA, Hennig B. Cholesterol attenuates Linoleic acid-induced endothelial cell activation. Metabolism. 2003;52(4):493–500.
29. Meerarani P, Reiterer G, Toborek M, Hennig B. Zinc modulates PPAR-gamma signaling and activation of Porcine endothelial cells. J Nutr. 2003;133(10):3058–64.
30. Saraswathi V, Wu G, Toborek M, Hennig B. Linoleic acid-induced endothelial activation: role of calcium and peroxynitrite signaling. J Lipid Res. 2004;45(5):794–804.
31. Stoll LL, Morland MR, Spector AA. 13-HODE increases intracellular calcium in vascular smooth muscle cells. Am J Physiol. 1994;266(4 Pt 1):C990–996.
32. Tloti MA, Moon DG, Weston LK, Kaplan JE. Effect of 13-hydroxyoctadeca-9,11-dienoic acid (13-HODE) on thrombin induced platelet adherence to endothelial cells in vitro. Thromb Res. 1991;62(4):305–17.
33. Ramasamy S, Lipke DW, Boissonneault GA, Guo H, Hennig B. Oxidized lipid-mediated alterations in proteoglycan metabolism in cultured pulmonary endothelial cells. Atherosclerosis. 1996;120(1–2):199–208.
34. Ziboh VA, Yun M, Hyde DM, Giri SN. gamma-Linolenic acid-containing diet attenuates bleomycin-induced lung fibrosis in hamsters. 1997; pp. 759–67.
35. Umar S, Nadadur RD, Li J, Maltese F, Partownavid P, van der Laarse A, Eghbali M. Intralipid prevents and rescues fatal pulmonary arterial hypertension and right ventricular failure in rats. Hypertension 2011: 58(3): 512–8.
36. Prielipp RC, McLean R, Rosenthal MH, Pearl RG. Hemodynamic profiles of prostaglandin E1, isoproterenol, Prostacyclin, and Nifedipine in experimental Porcine pulmonary hypertension. Crit Care Med. 1991;19(1):60–7.
37. Kunimoto F, Arai K, Isa Y, Koyano T, Kadoi Y, Saito S, Goto F. A comparative study of the vasodilator effects of prostaglandin E1 in patients with pulmonary hypertension after mitral valve replacement and with adult respiratory distress syndrome. Anesth Analg. 1997;85(3):507–13.
38. Radovancevic B, Vrtovec B, Thomas CD, Croitoru M, Myers TJ, Radovancevic R, Khan T, Massin EK, Frazier OH. Nitric oxide versus prostaglandin E1 for reduction of pulmonary hypertension in heart transplant candidates. J Heart Lung Transpl 2005: 24(6): 690–5.
39. Gupta N, Kamlin CO, Cheung M, Stewart M, Patel N. Prostaglandin E1 use during neonatal transfer: potential beneficial role in persistent pulmonary hypertension of the newborn. Arch Dis Child Fetal Neonatal Ed. 2013;98(2):F186–188.
40. Zhang CY, Ma ZS, Ma LL, Wang LX. Effect of prostaglandin E1 inhalation on pulmonary hypertension following corrective surgery for congenital heart disease. Exp Clin Cardiol. 2013;18(1):13–6.
41. Gee MH, Tahamont MV, Flynn JT, Cox JW, Pullen RH, Andreadis NA. Prostaglandin E1 prevents increased lung microvascular permeability during intravascular complement activation in sheep. Circ Res. 1987;61(3):420–8.
42. Lawrence KM, Berger K, Herkert L, Franciscovich C, O'Dea CLH, Waqar LN, Partridge E, Hanna BD, Peranteau WH, Avitabile CM, Hopper RK, Rintoul NE, Hedrick HL. Use of prostaglandin E1 to treat pulmonary hypertension in congenital diaphragmatic hernia. J Pediatr Surg. 2019;54(1):55–9.
43. Gupta V, Gupta N, Shaik IH, Mehvar R, Nozik-Grayck E, McMurtry IF, Oka M, Komatsu M, Ahsan F. Inhaled PLGA particles of prostaglandin E(1) ameliorate symptoms and progression of pulmonary hypertension at a reduced dosing frequency. Mol Pharm. 2013;10(5):1655–67.
44. Lai YJ, Hsu HH, Chang GJ, Lin SH, Chen WJ, Huang CC, Pang JS. Author correction: prostaglandin E1 attenuates pulmonary artery remodeling by activating phosphorylation of CREB and the PTEN signaling pathway. Sci Rep. 2018;8(1):11383.
45. Lai Y-J, Hsu H-H, Chang G-J, Lin S-H, Chen W-J, Huang C-C, Pang J-HS. Prostaglandin E1 attenuates pulmonary artery remodeling by activating phosphorylation of CREB and the PTEN signaling pathway. Sci Rep. 2017;7(1):9974.
46. Pasricha PJ, Hassoun PM, Teufel E, Landman MJ, Fanburg BL. Prostaglandins E1 and E2 stimulate the proliferation of pulmonary artery smooth muscle cells. Prostaglandins. 1992;43(1):5–19.
47. Cruz F, Rocco P. The potential of mesenchymal stem cell therapy for chronic lung disease. Expert Rev Respir Med. 2020;14(1):31–9.
48. Jiang D, Tuo L, Bai X, Bing W, Qu Q, Zhao X, Song G, Bi Y, Sun W. Prostaglandin E1 reduces apoptosis and improves the homing of mesenchymal stem cells in pulmonary arterial hypertension by regulating hypoxia-inducible factor 1 alpha. Stem Cell Res Ther. 2022;13(1):316.
49. Nakayama K, Ueta K, Tanaka Y, Tanabe Y, Ishii K. Stretch-induced contraction of rabbit isolated pulmonary artery and the involvement of endothelium-derived thromboxane A2. Br J Pharmacol. 1997;122(2):199–208.
50. Dey K, Rahaman SM, Chakraborti T, Chakraborti S. Role of phospholemman and the 70 kda inhibitor protein in regulating Na+/K + ATPase activity in pulmonary artery smooth muscle cells under U46619 stimulation. FEBS Lett. 2013;587(21):3535–40.
51. Tamaoki J, Tagaya E, Nishimura K, Isono K, Nagai A. Role of Na(+)-K + ATPase in Cyclic GMP-mediated relaxation of canine pulmonary artery smooth muscle cells. Br J Pharmacol. 1997;122(1):112–6.
52. Cogolludo A, Frazziano G, Cobeno L, Moreno L, Lodi F, Villamor E, Tamargo J, Perez-Vizcaino F. Role of reactive oxygen species in Kv channel Inhibition and vasoconstriction induced by TP receptor activation in rat pulmonary arteries. Ann N Y Acad Sci. 2006;1091:41–51.
53. Cogolludo A, Moreno L, Bosca L, Tamargo J, Perez-Vizcaino F. Thromboxane A2-induced Inhibition of voltage-gated K + channels and pulmonary vasoconstriction: role of protein kinase Czeta. 2003; pp. 656–63.
54. Chakraborti S, Roy S, Mandal A, Dey K, Chowdhury A, Shaikh S, Chakraborti T. Role of PKCalpha-p(38)MAPK-G(i)alpha axis in NADPH oxidase derived O(2)(.-)-mediated activation of cPLA(2) under U46619 stimulation in pulmonary artery smooth muscle cells. Arch Biochem Biophys 2012: 523(2): 169–80.

55. Cogolludo A, Moreno L, Lodi F, Tamargo J, Perez-Vizcaino F. Postnatal maturational shift from PKCzeta and voltage-gated K + channels to RhoA/Rho kinase in pulmonary vasoconstriction. Cardiovasc Res. 2005;66(1):84–93.
56. Kim HJ, Yoo HY, Jang JH, Lin HY, Seo EY, Zhang YH, Kim SJ. Wall stretch and thromboxane A(2) activate NO synthase (eNOS) in pulmonary arterial smooth muscle cells via H(2)O(2) and Akt-dependent phosphorylation. Pflugers Arch. 2016;468(4):705–16.
57. Chowdhury A, Roy S, Chakraborti T, Dey K, Chakraborti S. Activation of proMMP-2 by U46619 occurs via involvement of p(38)MAPK-NFkappaB-MT1MMP signaling pathway in pulmonary artery smooth muscle cells. Mol Cell Biochem. 2014;385(1–2):53–68.
58. Chowdhury A, Sarkar J, Chakraborti T, Chakraborti S. Role of Spm-Cer-S1P signalling pathway in MMP-2 mediated U46619-induced proliferation of pulmonary artery smooth muscle cells: protective role of epigallocatechin-3-gallate. Cell Biochem Funct. 2015;33(7):463–77.
59. MacKay CE, Shaifta Y, Snetkov VV, Francois AA, Ward JPT, Knock GA. ROS-dependent activation of RhoA/Rho-kinase in pulmonary artery: role of Src-family kinases and ARHGEF1. Free Radic Biol Med. 2017;110:316–31.
60. Freitas CF, Faro R, Dragosavac D, Clozel M, De Nucci G, Antunes E. Role of endothelin-1 and thromboxane A2 in the pulmonary hypertension induced by heparin-protamine interaction in anesthetized dogs. 2004; pp. 106–12.
61. Schweer H, Seyberth HW, Kuhl PG, Meese CO. Unusual metabolism of Prostacyclin in infants with persistent septic pulmonary hypertension. Eicosanoids. 1990;3(4):237–42.
62. Lee BR, Paing MH, Sharma-Walia N. Cyclopentenone prostaglandins: biologically active lipid mediators targeting inflammation. Front Physiol. 2021;12:640374.
63. Bowers RE, Ellis EF, Brigham KL, Oates JA. Effects of prostaglandin Cyclic endoperoxides on the lung circulation of unanesthetized sheep. J Clin Invest. 1979;63(1):131–7.
64. Tod ML, Cassin S, McNamara DB, Kadowitz PJ. Effects of prostaglandin H2 on perinatal pulmonary circulation. Pediatr Res. 1986;20(6):565–9.
65. Konya V, Ullen A, Kampitsch N, Theiler A, Philipose S, Parzmair GP, Marsche G, Peskar BA, Schuligoi R, Sattler W, Heinemann A. Endothelial E-type prostanoid 4 receptors promote barrier function and inhibit neutrophil trafficking. J Allergy Clin Immunol 2013: 131(2): 532–e540531.
66. Li H, He J, Lee S, Quan C, Ding J. The study of the relationship between the activity of phospholipase A2 and acute hypoxic pulmonary arterial pressure. Ann Ist Super Sanita. 1997;33(2):273–7.
67. Bradbury DA, Newton R, Zhu YM, El-Haroun H, Corbett L, Knox AJ. Cyclooxygenase-2 induction by Bradykinin in human pulmonary artery smooth muscle cells is mediated by the Cyclic AMP response element through a novel autocrine loop involving endogenous prostaglandin E2, E-prostanoid 2 (EP2), and EP4 receptors. J Biol Chem. 2003;278(50):49954–64.
68. El-Haroun H, Bradbury D, Clayton A, Knox AJ. Interleukin-1beta, transforming growth factor-beta1, and Bradykinin attenuate Cyclic AMP production by human pulmonary artery smooth muscle cells in response to Prostacyclin analogues and prostaglandin E2 by cyclooxygenase-2 induction and downregulation of adenylyl cyclase isoforms 1, 2, and 4. Circ Res. 2004;94(3):353–61.
69. Brigham KL, Serafin W, Zadoff A, Blair I, Meyrick B, Oates JA. Prostaglandin E2 Attenuation of sheep lung responses to endotoxin. J Appl Physiol (1985). 1988;64(6):2568–74.
70. Meyrick B, Hoover R, Jones MR, Berry LC Jr., Brigham KL. In vitro effects of endotoxin on bovine and sheep lung microvascular and pulmonary artery endothelial cells. J Cell Physiol. 1989;138(1):165–74.
71. Meyrick B, Berry LC Jr., Christman BW. Response of cultured human pulmonary artery endothelial cells to endotoxin. Am J Physiol. 1995;268(2 Pt 1):L239–244.
72. North AJ, Brannon TS, Wells LB, Campbell WB, Shaul PW. Hypoxia stimulates Prostacyclin synthesis in newborn pulmonary artery endothelium by increasing cyclooxygenase-1 protein. Circ Res. 1994;75(1):33–40.
73. Badesch DB, Orton EC, Zapp LM, Westcott JY, Hester J, Voelkel NF, Stenmark KR. Decreased arterial wall prostaglandin production in neonatal calves with severe chronic pulmonary hypertension. Am J Respir Cell Mol Biol. 1989;1(6):489–98.
74. Bradbury DA, Corbett L, Knox AJ. PI 3-kinase and MAP kinase regulate Bradykinin induced prostaglandin E(2) release in human pulmonary artery by modulating COX-2 activity. FEBS Lett. 2004;560(1–3):30–4.
75. Wang B, Wu L, Chen J, Dong L, Chen C, Wen Z, Hu J, Fleming I, Wang DW. Metabolism pathways of arachidonic acids: mechanisms and potential therapeutic targets. Signal Transduct Target Ther. 2021;6(1):94.
76. Foudi N, Kotelevets L, Louedec L, Leseche G, Henin D, Chastre E, Norel X. Vasorelaxation induced by prostaglandin E2 in human pulmonary vein: role of the EP4 receptor subtype. Br J Pharmacol. 2008;154(8):1631–9.
77. Ozen G, Benyahia C, Mani S, Boukais K, Silverstein AM, Bayles R, Nelsen AC, Castier Y, Danel C, Mal H, Clapp LH, Longrois D, Norel X. Bronchodilation induced by PGE is impaired in Group III pulmonary hypertension. 2020; pp. 161–174.
78. Mukherjee S, Sheng W, Michkov A, Sriarm K, Sun R, Dvorkin-Gheva A, Insel PA, Janssen LJ. Prostaglandin E2 inhibits profibrotic function of human pulmonary fibroblasts by disrupting Ca(2+) signaling. Am J Physiol Lung Cell Mol Physiol. 2019;316(5):L810–21.
79. Bozyk PD, Moore BB. Prostaglandin E2 and the pathogenesis of pulmonary fibrosis. Am J Respir Cell Mol Biol 2011: 45(3): 445–52.
80. Kohyama T, Ertl RF, Valenti V, Spurzem J, Kawamoto M, Nakamura Y, Veys T, Allegra L, Romberger D, Rennard SI. Prostaglandin E(2) inhibits fibroblast chemotaxis. Am J Physiol Lung Cell Mol Physiol. 2001;281(5):L1257–63.
81. Coker SJ, Hughes B, Parratt JR, Rodger IW, Zeitlin IJ. The release of prostanoids during the acute pulmonary response to E. coli endotoxin in anaesthetized cats. Br J Pharmacol. 1983;78(3):561–70.
82. Matsushita T, Hislop AA, Boels PJ, Deutsch J, Haworth SG. Changes in ANP responsiveness of normal and hypertensive Porcine intrapulmonary arteries during maturation. Pediatr Res. 1999;46(4):411–8.
83. Snetkov VA, Knock GA, Baxter L, Thomas GD, Ward JP, Aaronson PI. Mechanisms of the prostaglandin F2alpha-induced rise in [Ca2+]i in rat intrapulmonary arteries. J Physiol. 2006;571(Pt 1):147–63.
84. Olson NC. Role of 5-hydroxytryptamine in endotoxin-induced respiratory failure of pigs. Am Rev Respir Dis. 1987;135(1):93–9.
85. Vankova M, Snetkov VA, Knock GA, Aaronson PI, Ward JP. Euhydric hypercapnia increases vasoreactivity of rat pulmonary arteries via HCO3- transport and depolarisation. Cardiovasc Res. 2005;65(2):505–12.
86. Snetkov VA, Thomas GD, Teague B, Leach RM, Shaifta Y, Knock GA, Aaronson PI, Ward JP. Low concentrations of sphingosylphosphorylcholine enhance pulmonary artery vasoreactivity: the role of protein kinase C delta and Ca2 + entry. Hypertension. 2008;51(2):239–45.
87. Knock GA, Shaifta Y, Snetkov VA, Vowles B, Drndarski S, Ward JP, Aaronson PI. Interaction between Src family kinases and rho-kinase in agonist-induced Ca2+-sensitization of rat pulmonary artery. Cardiovasc Res. 2008;77(3):570–9.
88. Muzaffar S, Shukla N, Lobo C, Angelini GD, Jeremy JY. Iloprost inhibits superoxide formation and gp91phox expression induced by the thromboxane A2 analogue U46619, 8-isoprostane F2alpha, prostaglandin F2alpha, cytokines and endotoxin in the pig pulmonary artery. Br J Pharmacol. 2004;141(3):488–96.
89. Olschewski H, Rose F, Schermuly R, Ghofrani HA, Enke B, Olschewski A, Seeger W. Prostacyclin and its analogues in the treatment of pulmonary hypertension. Pharmacol Ther. 2004;102(2):139–53.
90. O'Connell C, Amar D, Boucly A, Savale L, Jaïs X, Chaumais M-C, Montani D, Humbert M, Simonneau G, Sitbon O. Comparative safety and tolerability of Prostacyclins in pulmonary hypertension. 2016; pp. 287–94.
91. Tamosiuniene R, Manouvakhova O, Mesange P, Saito T, Qian J, Sanyal M, Lin Y-C, Nguyen LP, Luria A, Tu AB, Sante JM, Rabinovitch M, Fitzgerald DJ, Graham BB, Habtezion A, Voelkel NF, Aurelian L, Nicolls MR. Dominant role for regulatory T cells in protecting females against pulmonary hypertension. 2018; pp. 1689–702.
92. Akagi S, Nakamura K, Matsubara H, Kusano KF, Kataoka N, Oto T, Miyaji K, Miura A, Ogawa A, Yoshida M, Ueda-Ishibashi H, Yutani C, Ito H. Prostaglandin I2 induces apoptosis via upregulation of Fas ligand in pulmonary artery smooth muscle cells from patients with idiopathic pulmonary arterial hypertension. Int J Cardiol. 2013;165(3):499–505.
93. Kelly LK, Porta NF, Goodman DM, Carroll CL, Steinhorn RH. Inhaled Prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. J Pediatr. 2002;141(6):830–2.
94. Gatfield J, Menyhart K, Wanner D, Gnerre C, Monnier L, Morrison K, Hess P, Iglarz M, Clozel M, Nayler O. Selexipag Active Metabolite ACT-333679 Displays Strong Anticontractile and Antiremodeling Effects but Low -Arrestin Recruitment and Desensitization Potential. 2017; pp. 186–199.
95. Fedorowicz A, Mateuszuk Ł, Kopec G, Skórka T, Kutryb-Zając B, Zakrzewska A, Walczak M, Jakubowski A, Łomnicka M, Słomińska E, Chlopicki S. Activation of the nicotinamide N-methyltransferase (NNMT)-1-methylnicotinamide (MNA) pathway in pulmonary hypertension. 2016; p. 108.
96. Seo M-J, Oh D-K. Prostaglandin synthases: molecular characterization and involvement in prostaglandin biosynthesis. Prog Lipid Res. 2017;66:50–68.

97. Jia D, Bai P, Wan N, Liu J, Zhu Q, He Y, Chen G, Wang J, Chen H, Wang C, Lyu A, Lazarus M, Su Y, Urade Y, Yu Y, Zhang J, Shen Y. Niacin Attenuates Pulmonary Hypertension Through H-PGDS in Macrophages. 2020; pp. 1323–1336.
98. He Y, Zuo C, Jia D, Bai P, Kong D, Chen D, Liu G, Li J, Wang Y, Chen G, Yan S, Xiao B, Zhang J, Piao L, Li Y, Deng Y, Li B, Roux PP, Andreasson KI, Breyer RM, Su Y, Wang J, Lyu A, Shen Y, Yu Y. Loss of DP1 aggravates vascular remodeling in pulmonary arterial hypertension via mTORC1 signaling. 2020; pp. 1263–76.
99. Robbins IM, Barst RJ, Rubin LJ, Gaine SP, Price PV, Morrow JD, Christman BW. Increased levels of prostaglandin D(2) suggest macrophage activation in patients with primary pulmonary hypertension. Chest. 2001;120(5):1639–44.
100. Kohyama T, Liu XD, Wen FQ, Kim HJ, Takizawa H, Rennard SI. Prostaglandin D2 inhibits fibroblast migration. Eur Respir J. 2002;19(4):684–9.
101. Ayabe S, Kida T, Hori M, Ozaki H, Murata T. Prostaglandin D2 inhibits collagen secretion from lung fibroblasts by activating the DP receptor. J Pharmacol Sci 2013: 121(4): 312–7.
102. Lacy SH, Epa AP, Pollock SJ, Woeller CF, Thatcher TH, Phipps RP, Sime PJ. Activated human T lymphocytes inhibit TGFβ-induced fibroblast to myofibroblast differentiation via prostaglandins D and E. Am J Physiol Lung Cell Mol Physiol. 2018;314(4):L569–82.
103. Soifer SJ, Clyman RI, Heymann MA. Effects of prostaglandin D2 on pulmonary arterial pressure and oxygenation in newborn infants with persistent pulmonary hypertension. J Pediatr. 1988;112(5):774–7.
104. Mishra A, Ali Z, Vibhuti A, Kumar R, Alam P, Ram R, Thinlas T, Mohammad G, Pasha MA. CYBA and GSTP1 variants associate with oxidative stress under hypobaric hypoxia as observed in high-altitude pulmonary oedema. Clin Sci (Lond). 2012;122(6):299–309.
105. Lipcsey M, Soderberg E, Basu S, Larsson A, Sjolin J, Astrom M, Eriksson MB. F2-isoprostane, inflammation, cardiac function and oxygenation in the endotoxaemic pig. Prostaglandins Leukot Essent Fat Acids. 2008;78(3):209–17.
106. Jankov RP, Luo X, Cabacungan J, Belcastro R, Frndova H, Lye SJ, Tanswell AK. Endothelin-1 and O2-mediated pulmonary hypertension in neonatal rats: a role for products of lipid peroxidation. 2000; pp. 289–98.
107. Yi SL, Kantores C, Belcastro R, Cabacungan J, Tanswell AK, Jankov RP. 8-Isoprostane-induced endothelin-1 production by infant rat pulmonary artery smooth muscle cells is mediated by Rho-kinase. pp. 942–9.
108. Gong Y, Yi M, Fediuk J, Lizotte PP, Dakshinamurti S. Hypoxic neonatal pulmonary arterial myocytes are sensitized to ROS-generated 8-isoprostane. Free Radic Biol Med. 2010;48(7):882–94.
109. Belik J, Jankov RP, Pan J, Yi M, Chaudhry I, Tanswell AK. Chronic O2 exposure in the newborn rat results in decreased pulmonary arterial nitric oxide release and altered smooth muscle response to isoprostane. 2004; pp. 725–30.
110. Hart CM, Karman RJ, Blackburn TL, Gupta MP, Garcia JG, Mohler ER. Role of 8-epi PGF2alpha, 8-isoprostane, in H2O2-induced derangements of pulmonary artery endothelial cell barrier function. 1998.
111. Vecchio D, Acquaviva A, Arezzini B, Tenor H, Martorana PA, Gardi C. Down-regulation of NOX4 expression by Roflumilast N-oxide reduces markers of fibrosis in lung fibroblasts. Mediators Inflamm. 2013;2013:745984.
112. Belik J, Jankov RP, Pan J, Yi M, Pace-Asciak CR, Tanswell AK. Effect of 8-iso-prostaglandin F2alpha on the newborn rat pulmonary arterial muscle and endothelium. 2003; pp. 1979–85.
113. Ohmura T, Tian Y, Sarich N, Ke Y, Meliton A, Shah AS, Andreasson K, Birukov KG, Birukova AA. Regulation of lung endothelial permeability and inflammatory responses by prostaglandin A2: role of EP4 receptor. Mol Biol Cell 2017: 28(12): 1622–35.
114. Liu D, Geng Z, Zhu W, Wang H, Chen Y, Liang J. 15-deoxy-Delta(1)(2),(1)(4)-prostaglandin J(2) ameliorates endotoxin-induced acute lung injury in rats. Chin Med J (Engl). 2014;127(5):815–20.
115. Genovese T, Cuzzocrea S, Di Paola R, Mazzon E, Mastruzzo C, Catalano P, Sortino M, Crimi N, Caputi AP, Thiemermann C, Vancheri C. Effect of Rosiglitazone and 15-deoxy-Delta12,14-prostaglandin J2 on bleomycin-induced lung injury. Eur Respir J. 2005;25(2):225–34.
116. Ando M, Murakami Y, Kojima F, Endo H, Kitasato H, Hashimoto A, Kobayashi H, Majima M, Inoue M, Kondo H, Kawai S, Hayashi I. Retrovirally introduced prostaglandin D2 synthase suppresses lung injury induced by bleomycin. Am J Respir Cell Mol Biol 2003: 28(5): 582–91.
117. Cloutier A, Marois I, Cloutier D, Verreault C, Cantin AM, Richter MV. The prostanoid 15-deoxy-Delta12,14-prostaglandin-j2 reduces lung inflammation and protects mice against lethal influenza infection. J Infect Dis. 2012;205(4):621–30.
118. Calnek DS, Mazzella L, Roser S, Roman J, Hart CM. Peroxisome proliferator-activated receptor gamma ligands increase release of nitric oxide from endothelial cells. Arterioscler Thromb Vasc Biol. 2003;23(1):52–7.
119. Ijsselstijn H, Zijlstra FJ, Van Dijk JP, De Jongste JC, Tibboel D. Lung eicosanoids in perinatal rats with congenital diaphragmatic hernia. Mediators Inflamm. 1997;6(1):39–45.
120. Tian W, Jiang X, Sung YK, Qian J, Yuan K, Nicolls MR. Leukotrienes in pulmonary arterial hypertension. 2014; pp. 387–393.
121. Tabata T, Ono S, Song C, Noda M, Suzuki S, Tanita T, Fujimura S. [Role of leukotriene B4 in monocrotaline-induced pulmonary hypertension]. 1997; pp. 160–6.
122. Tian W, Jiang X, Tamosiuniene R, Sung YK, Qian J, Dhillon G, Gera L, Farkas L, Rabinovitch M, Zamanian RT, Inayathullah M, Fridlib M, Rajadas J, Peters-Golden M, Voelkel NF, Nicolls MR. Blocking macrophage leukotriene b4 prevents endothelial injury and reverses pulmonary hypertension. p. 200ra117.
123. Li F, You Y, Zhu H. 15-HETE protects pulmonary artery smooth muscle cells against apoptosis via SIRT1 regulation during hypoxia. 2018; pp. 325–30.
124. Zhang L, Ma J, Shen T, Wang S, Ma C, Liu Y, Ran Y, Wang L, Liu L, Zhu D. Platelet-derived growth factor (PDGF) induces pulmonary vascular remodeling through 15-LO/15-HETE pathway under hypoxic condition. 2012; pp. 1931–9.
125. Yao L, Nie X, Shi S, Song S, Hao X, Li S, Zhu D. Reciprocal regulation of HIF-1α and 15-LO/15-HETE promotes anti-apoptosis process in pulmonary artery smooth muscle cells during hypoxia. 2012.
126. Ma J, Liang S, Wang Z, Zhang L, Jiang J, Zheng J, Yu L, Zheng X, Wang R, Zhu D. ROCK pathway participates in the processes that 15-hydroxyeicosatetraenoic acid (15-HETE) mediated the pulmonary vascular remodeling induced by hypoxia in rat. 2010; pp. 82–94.
127. Wang S, Wang Y, Jiang J, Wang R, Li L, Qiu Z, Wu H, Zhu D. 15-HETE protects rat pulmonary arterial smooth muscle cells from apoptosis via the PI3K/Akt pathway. Prostaglandins Other Lipid Mediat. 2010;91(1–2):51–60.
128. Yu X, Li T, Liu X, Yu H, Hao Z, Chen Y, Zhang C, Liu Y, Li Q, Mao M, Zhu D. Modulation of pulmonary vascular remodeling in hypoxia: role of 15-LOX-2/15-HETE-MAPKs pathway. Cell Physiol Biochem. 2015;35(6):2079–97.
129. Nie X, Song S, Zhang L, Qiu Z, Shi S, Liu Y, Yao L, Zhu D. 15-Hydroxyeicosatetraenoic acid (15-HETE) protects pulmonary artery smooth muscle cells from apoptosis via inducible nitric oxide synthase (iNOS) pathway. 2012; pp. 50–59.
130. Li Y, Li Q, Wang Z, Liang D, Liang S, Tang X, Guo L, Zhang R, Zhu D. 15-HETE suppresses K(+) channel activity and inhibits apoptosis in pulmonary artery smooth muscle cells. Apoptosis. 2009;14(1):42–51.
131. Yu X, Wei L, Lu P, Shen T, Liu X, Li T, Zhang B, Yu H, Zhu D. 15-Lipoxygenase promotes chronic hypoxia-induced phenotype changes of PASMCs via positive feedback-loop of BMP4. 2015; pp. 1489–502.
132. Zhang L, Chen Y, Li G, Chen M, Huang W, Liu Y, Li Y. TGF-β1/FGF-2 signaling mediates the 15-HETE-induced differentiation of adventitial fibroblasts into myofibroblasts. Lipids Health Dis. 2016;15:2.
133. Zhang L, Li Y, Chen M, Su X, Yi D, Lu P, Zhu D. 15-LO/15-HETE mediated vascular adventitia fibrosis via p38 MAPK-dependent TGF-β. 2014; pp. 245–57.
134. Zhang L, Li Y, Liu Y, Wang X, Chen M, Xing Y, Zhu D. STAT3-mediated MMP-2 expression is required for 15-HETE-induced vascular adventitial fibroblast migration. J Steroid Biochem Mol Biol. 2015;149:106–17.
135. Zhang M, Xin W, Ma C, Zhang H, Mao M, Liu Y, Zheng X, Zhang L, Yu X, Li H, Zhu D. Exosomal 15-LO2 mediates hypoxia-induced pulmonary artery hypertension in vivo and in vitro. Cell Death Dis 2018: 9(10): 1022.
136. Ma C, Wang Y, Shen T, Zhang C, Ma J, Zhang L, Liu F, Zhu D. Placenta growth factor mediates angiogenesis in hypoxic pulmonary hypertension. 2013; pp. 159–68.
137. Ma C, Li Y, Ma J, Liu Y, Li Q, Niu S, Shen Z, Zhang L, Pan Z, Zhu D. Key role of 15-lipoxygenase/15-hydroxyeicosatetraenoic acid in pulmonary vascular remodeling and vascular angiogenesis associated with hypoxic pulmonary hypertension. 2011; pp. 679–88.
138. Li Q, Mao M, Qiu Y, Liu G, Sheng T, Yu X, Wang S, Zhu D. Key role of ROS in the process of 15-Lipoxygenase/15-Hydroxyeicosatetraenoiccid-Induced pulmonary vascular remodeling in hypoxia pulmonary hypertension. 2016; p. e0149164.
139. Liu Y, Zhang H, Yan L, Du W, Zhang M, Chen H, Zhang L, Li G, Li J, Dong Y, Zhu D. MMP-2 and MMP-9 contribute to the angiogenic effect produced by hypoxia/15-HETE in pulmonary endothelial cells. 2018; pp. 36–50.
140. Ruffenach G, O'Connor E, Vaillancourt M, Hong J, Cao N, Sarji S, Moazeni S, Papesh J, Grijalva V, Cunningham CM, Shu L, Chattopadhyay A, Tiwari S, Mercier O, Perros F, Umar S, Yang X, Gomes AV, Fogelman AM, Reddy ST, Eghbali M. Oral 15-Hydroxyeicosatetraenoic acid induces pulmonary hypertension in mice by triggering T cell-Dependent endothelial cell apoptosis. 2020; pp. 985–96.

141. Li J, Rao J, Liu Y, Cao Y, Zhang Y, Zhang Q, Zhu D. 15-Lipoxygenase promotes chronic hypoxia-induced pulmonary artery inflammation via positive interaction with nuclear factor-κB. 2013; pp. 971–9.
142. Matsuda H, Miyatake K, Dahlén SE. Pharmacodynamics of 15(S)-hydroperoxyeicosatetraenoic (15-HPETE) and 15(S)-hydroxyeicosatetraenoic acid (15-HETE) in isolated arteries from guinea pig, rabbit, rat and human. J Pharmacol Exp Ther. 1995;273(3):1182–9.
143. Van Diest MJ, Herman AG, Verbeuren TJ. Influence of hypercholesterolaemia on the reactivity of isolated rabbit arteries to 15-lipoxygenase metabolites of arachidonic acid: comparison with platelet-derived agents and vasodilators. Prostaglandins Leukot Essent Fat Acids. 1996;54(2):135–45.
144. Li X, Ma C, Zhu D, Meng L, Guo L, Wang Y, Zhang L, Li Z, Li E. Increased expression and altered subcellular distribution of PKC-δ and PKC-ε in pulmonary arteries exposed to hypoxia and 15-HETE. Prostaglandins Other Lipid Mediat. 2010;93(3–4):84–92.
145. Lu C, Liu Y, Tang X, Ye H, Zhu D. Role of 15-hydroxyeicosatetraenoic acid in phosphorylation of ERK1/2 and Caldesmon in pulmonary arterial smooth muscle cells. Can J Physiol Pharmacol. 2006;84(10):1061–9.
146. Zheng X, Li Q, Tang X, Liang S, Chen L, Zhang S, Wang Z, Guo L, Zhang R, Zhu D. Source of the elevation Ca2 + evoked by 15-HETE in pulmonary arterial myocytes. Eur J Pharmacol. 2008;601(1–3):16–22.
147. Wang Y, Liang D, Wang S, Qiu Z, Chu X, Chen S, Li L, Nie X, Zhang R, Wang Z, Zhu D. Role of the G-protein and tyrosine kinase–Rho/ROK pathways in 15-hydroxyeicosatetraenoic acid induced pulmonary vasoconstriction in hypoxic rats. J Biochem. 2010;147(5):751–64.
148. Bergholte JM, Soberman RJ, Hayes R, Murphy RC, Okita RT. Oxidation of 15-hydroxyeicosatetraenoic acid and other hydroxy fatty acids by lung prostaglandin dehydrogenase. Arch Biochem Biophys 1987: 257(2): 444–50.
149. Ma C, Liu Y, Wang Y, Zhang C, Yao H, Ma J, Zhang L, Zhang D, Shen T, Zhu D. Hypoxia activates 15-PGDH and its metabolite 15-KETE to promote pulmonary artery endothelial cells proliferation via ERK1/2 signalling. 2014; pp. 3352–63.
150. Wei L, Yu X, Shi H, Zhang B, Lian M, Li J, Shen T, Xing Y, Zhu D. 15-PGDH/15-KETE plays a role in hypoxia-induced pulmonary vascular remodeling through ERK1/2-dependent PAR-2 pathway. 2014; pp. 1476–88.
151. Sugumaran PK, Wang S, Song S, Nie X, Zhang L, Feng Y, Ma W, Zhu D. 15-oxo-Eicosatetraenoic acid prevents serum deprivation-induced apoptosis of pulmonary arterial smooth muscle cells by activating pro-survival pathway. 2014; pp. 89–98.
152. Zhang C, Ma C, Yao H, Zhang L, Yu X, Liu Y, Shen T, Zhang L, Zhang F, Chen X, Zhu D. 12-Lipoxygenase and 12-hydroxyeicosatetraenoic acid regulate hypoxic angiogenesis and survival of pulmonary artery endothelial cells via PI3K/Akt pathway. 2018; pp. L606–16.
153. Preston IR, Hill NS, Warburton RR, Fanburg BL. Role of 12-lipoxygenase in hypoxia-induced rat pulmonary artery smooth muscle cell proliferation. 2006; pp. L367–74.
154. Burhop KE, Selig WM, Malik AB. Monohydroxyeicosatetraenoic acids (5-HETE and 15-HETE) induce pulmonary vasoconstriction and edema. 1988; pp. 687–698.
155. Guo L, Qiu Z, Zhang L, Chen S, Zhu D. Hypoxia suppresses Kv 2.1 channel expression through endogenous 15-hydroxyeicosatetraenoic acid in rat pulmonary artery. J Physiol Sci. 2010;60(5):373–81.
156. Voelkel NF, Tuder RM, Wade K, Höper M, Lepley RA, Goulet JL, Koller BH, Fitzpatrick F. Inhibition of 5-lipoxygenase-activating protein (FLAP) reduces pulmonary vascular reactivity and pulmonary hypertension in hypoxic rats. 1996; pp. 2491–8.
157. Walker JL, Loscalzo J, Zhang Y-Y. 5-Lipoxygenase and human pulmonary artery endothelial cell proliferation. 2002; pp. H585–93.
158. Ma J, Zhang L, Han W, Shen T, Ma C, Liu Y, Nie X, Liu M, Ran Y, Zhu D. Activation of JNK/c-Jun is required for the proliferation, survival, and angiogenesis induced by EET in pulmonary artery endothelial cells. 2012; pp. 1093–105.
159. Keserü B, Barbosa-Sicard E, Schermuly RT, Tanaka H, Hammock BD, Weissmann N, Fisslthaler B, Fleming I. Hypoxia-induced pulmonary hypertension: comparison of soluble epoxide hydrolase deletion vs. Inhibition. 2010; pp. 232–40.
160. Revermann M, Barbosa-Sicard E, Dony E, Schermuly RT, Morisseau C, Geisslinger G, Fleming I, Hammock BD, Brandes RP. Inhibition of the soluble epoxide hydrolase attenuates monocrotaline-induced pulmonary hypertension in rats. 2009; pp. 322–31.
161. Wepler M, Beloiartsev A, Buswell MD, Panigrahy D, Malhotra R, Buys ES, Radermacher P, Ichinose F, Bloch DB, Zapol WM. Soluble epoxide hydrolase deficiency or Inhibition enhances murine hypoxic pulmonary vasoconstriction after lipopolysaccharide challenge. 2016; pp. L1213–21.
162. Pokreisz P, Fleming I, Kiss L, Barbosa-Sicard E, Fisslthaler B, Falck JR, Hammock BD, Kim I-H, Szelid Z, Vermeersch P, Gillijns H, Pellens M, Grimminger F, van Zonneveld A-J, Collen D, Busse R, Janssens S. Cytochrome P450 epoxygenase gene function in hypoxic pulmonary vasoconstriction and pulmonary vascular remodeling. 2006; pp. 762–70.
163. Kandhi S, Alruwaili N, Wolin MS, Sun D, Huang A. Reciprocal actions of constrictor prostanoids and superoxide in chronic hypoxia-induced pulmonary hypertension: roles of EETs. 2019; p. 2045894019895947.
164. Beloiartsev A, Da Glória Rodrigues-Machado M, Zhou GL, Tan TC, Zazzeron L, Tainsh RE, Leyton P, Jones RC, Scherrer-Crosbie M, Zapol WM. Pulmonary hypertension after prolonged hypoxic exposure in mice with a congenital deficiency of Cyp2j. 2015; pp. 563–70.
165. Joshi SR, Lakhkar A, Dhagia V, Zias AL, Soldatos V, Oshima K, Jiang H, Gotlinger K, Capdevila JH, Schwartzman ML, McMurtry IF, Gupte SA. Cyp2c44 gene disruption exacerbated pulmonary hypertension and heart failure in female but not male mice. 2016; pp. 360–8.
166. Feng W, Xu X, Zhao G, Li G, Liu T, Zhao J, Dong R, Wang DW, Tu L. EETs and CYP2J2 inhibit TNF-α-induced apoptosis in pulmonary artery endothelial cells and TGF-β1-induced migration in pulmonary artery smooth muscle cells. 2013; pp. 685–93.
167. Zheng C, Wang L, Li R, Ma B, Tu L, Xu X, Dackor RT, Zeldin DC, Wang DW. Gene delivery of cytochrome p450 epoxygenase ameliorates monocrotaline-induced pulmonary artery hypertension in rats. 2010; pp. 740–9.
168. Tan JZ, Kaley G, Gurtner GH. Nitric oxide and prostaglandins mediate vasodilation to 5,6-EET in rabbit lung. 1997; pp. 561–566.
169. Strielkov I, Krause NC, Knoepp F, Alebrahimdehkordi N, Pak O, Garcia C, Ghofrani HA, Schermuly RT, Seeger W, Grimminger F, Sommer N, Weissmann N. Cytochrome P450 epoxygenase-derived 5,6-epoxyeicosatrienoic acid relaxes pulmonary arteries in normoxia but promotes sustained pulmonary vasoconstriction in hypoxia. Acta Physiol (Oxf). 2020;230(1):e13521.
170. Moreland KT, Procknow JD, Sprague RS, Iverson JL, Lonigro AJ, Stephenson AH. Cyclooxygenase (COX)-1 and COX-2 participate in 5,6-epoxyeicosatrienoic acid-induced contraction of rabbit intralobar pulmonary arteries. 2007; pp. 446–54.
171. Fuloria M, Smith TK, Aschner JL. Role of 5,6-epoxyeicosatrienoic acid in the regulation of newborn piglet pulmonary vascular tone. 2002; pp. L383–9.
172. Stephenson AH, Sprague RS, Losapio JL, Lonigro AJ. Differential effects of 5,6-EET on segmental pulmonary vasoactivity in the rabbit. 2003; pp. H2153–61.
173. Losapio JL, Sprague RS, Lonigro AJ, Stephenson AH. 5,6-EET-induced contraction of intralobar pulmonary arteries depends on the activation of Rho-kinase. 2005; pp. 1391–6.
174. Zhu D, Bousamra M, Zeldin DC, Falck JR, Townsley M, Harder DR, Roman RJ, Jacobs ER. Epoxyeicosatrienoic acids constrict isolated pressurized rabbit pulmonary arteries. 2000; pp. L335–43.
175. Ma J, Zhang L, Li S, Liu S, Ma C, Li W, Falck JR, Manthati VL, Reddy DS, Medhora M, Jacobs ER, Zhu D. 8,9-Epoxyeicosatrienoic acid analog protects pulmonary artery smooth muscle cells from apoptosis via ROCK pathway. pp. 2340–53.
176. Loot AE, Moneke I, Keserü B, Oelze M, Syzonenko T, Daiber A, Fleming I. 11,12-EET stimulates the association of BK channel α and β(1) subunits in mitochondria to induce pulmonary vasoconstriction. 2012; p. e46065.
177. Kandhi S, Zhang B, Froogh G, Qin J, Alruwaili N, Le Y, Yang Y-M, Hwang SH, Hammock BD, Wolin MS, Huang A, Sun D. EETs promote hypoxic pulmonary vasoconstriction via constrictor prostanoids. 2017; pp. L350–9.
178. Loot AE, Fleming I. Cytochrome P450-derived epoxyeicosatrienoic acids and pulmonary hypertension: central role of transient receptor potential C6 channels. 2011; pp. 140–7.
179. Keserü B, Barbosa-Sicard E, Popp R, Fisslthaler B, Dietrich A, Gudermann T, Hammock BD, Falck JR, Weissmann N, Busse R, Fleming I. Epoxyeicosatrienoic acids and the soluble epoxide hydrolase are determinants of pulmonary artery pressure and the acute hypoxic pulmonary vasoconstrictor response. 2008; pp. 4306–15.
180. Kandhi S, Froogh G, Qin J, Luo M, Wolin MS, Huang A, Sun D. EETs Elicit Direct Increases in Pulmonary Arterial Pressure in Mice. 2016; pp. 598–604.
181. Jiang JX, Zhang SJ, Liu YN, Lin XX, Sun YH, Shen HJ, Yan XF, Xie QM. EETs alleviate ox-LDL-induced inflammation by inhibiting LOX-1 receptor expression in rat pulmonary arterial endothelial cells. Eur J Pharmacol. 2014;727:43–51.
182. Singh TU, Choudhury S, Parida S, Maruti BS, Mishra SK. Arachidonic acid inhibits Na^+-K^+-ATPase via cytochrome P-450, Lipoxygenase and protein kinase C-dependent pathways in sheep pulmonary artery. 2012; pp. 84–90.

183. Yaghi A, Sims SM. Constrictor-induced translocation of NFAT3 in human and rat pulmonary artery smooth muscle. Am J Physiol Lung Cell Mol Physiol 2005: 289(6): L1061–74.
184. Jacobs ER, Zhu D, Gruenloh S, Lopez B, Medhora M. VEGF-induced relaxation of pulmonary arteries is mediated by endothelial cytochrome P-450 hydroxylase. Am J Physiol Lung Cell Mol Physiol. 2006;291(3):L369–77.
185. Chen Y, Medhora M, Falck JR, Pritchard KA, Jacobs ER. Mechanisms of activation of eNOS by 20-HETE and VEGF in bovine pulmonary artery endothelial cells. Am J Physiol Lung Cell Mol Physiol. 2006;291(3):L378–85.
186. Bodiga S, Gruenloh SK, Gao Y, Manthati VL, Dubasi N, Falck JR, Medhora M, Jacobs ER. 20-HETE-induced nitric oxide production in pulmonary artery endothelial cells is mediated by NADPH oxidase, H2O2, and PI3-kinase/Akt. Am J Physiol Lung Cell Mol Physiol. 2010;298(4):L564–74.
187. Yu M, McAndrew RP, Al-Saghir R, Maier KG, Medhora M, Roman RJ, Jacobs ER. Nitric oxide contributes to 20-HETE-induced relaxation of pulmonary arteries. J Appl Physiol (Bethesda Md: 1985). 2002;93(4):1391–9.
188. Sugumaran P, Narayanan V, Zhu D, Medhora M, Jacobs ER, Chandramohan Y, Selvaraj V, Dhanasekaran A. Prophylactic supplementation of 20-HETE ameliorates hypoxia/reoxygenation injury in pulmonary vascular endothelial cells by inhibiting apoptosis. 2020; p. 151461.
189. Dhanasekaran A, Bodiga S, Gruenloh S, Gao Y, Dunn L, Falck JR, Buonaccorsi JN, Medhora M, Jacobs ER. 20-HETE increases survival and decreases apoptosis in pulmonary arteries and pulmonary artery endothelial cells. Am J Physiol Heart Circ Physiol. 2009;296(3):H777–86.
190. Wang Z, Tang X, Li Y, Leu C, Guo L, Zheng X, Zhu D. 20-Hydroxyeicosatetraenoic acid inhibits the apoptotic responses in pulmonary artery smooth muscle cells. Eur J Pharmacol 2008: 588(1).
191. Wang J, Lian G, Luo L, Wang T, Xu C, Wang H, Xie L. Role of 20-hydroxyeicosatetraenoic acid in pulmonary hypertension and proliferation of pulmonary arterial smooth muscle cells. 2020; p. 101948.
192. Medhora M, Chen Y, Gruenloh S, Harland D, Bodiga S, Zielonka J, Gebremedhin D, Gao Y, Falck JR, Anjaiah S, Jacobs ER. 20-HETE increases superoxide production and activates NAPDH oxidase in pulmonary artery endothelial cells. Am J Physiol Lung Cell Mol Physiol 2008: 294(5): L902–11.
193. Lakhkar A, Dhagia V, Joshi SR, Gotlinger K, Patel D, Sun D, Wolin MS, Schwartzman ML, Gupte SA. 20-HETE-induced mitochondrial superoxide production and inflammatory phenotype in vascular smooth muscle is prevented by glucose-6-phosphate dehydrogenase Inhibition. Am J Physiol Heart Circ Physiol. 2016;310(9):H1107–17.
194. Lakhkar A, Dhagia V, Joshi SR, Gotlinger K, Patel D, Sun D, Wolin MS, Schwartzman ML, Gupte SA. 20-HETE-induced mitochondrial superoxide production and inflammatory phenotype in vascular smooth muscle is prevented by glucose-6-phosphate dehydrogenase Inhibition. 2016; pp. H1107–17.
195. Chawengsub Y, Gauthier KM, Campbell WB. Role of arachidonic acid Lipoxygenase metabolites in the regulation of vascular tone. 2009; pp. H495–507.

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