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The role of lactate metabolism and lactylation in pulmonary arterial hypertension

Tong-yu Peng[1], Jun-mi Lu[2], Xia-lei Zheng[1], Cheng Zeng[1] and Yu-hu He[1*]

Abstract

Pulmonary arterial hypertension (PAH) is a complex and progressive disease characterized by elevated pulmonary artery pressure and vascular remodeling. Recent studies have underscored the pivotal role of metabolic dysregulation and epigenetic modifications in the pathogenesis of PAH. Lactate, a byproduct of glycolysis, is now recognized as a key molecule that links cellular metabolism with activity regulation. Recent findings indicate that, in addition to altered glycolytic activity and dysregulated. Lactate homeostasis and lactylation—a novel epigenetic modification—also play a significant role in the development of PAH. This review synthesizes current knowledge regarding the relationship between altered glycolytic activity and PAH, with a particular focus on the cumulative effects of lactate in pulmonary vascular cells. Furthermore, lactylation, an emerging epigenetic modification, is discussed in the context of PAH. By elucidating the complex interplay between lactate metabolism and lactylation in PAH, this review aims to provide insights into potential therapeutic targets. Understanding these metabolic pathways may lead to innovative strategies for managing PAH and improving patient outcomes. Future research should focus on the underlying mechanisms through which lactylation influences the pathophysiology of PAH, thereby aiding in the development of targeted interventions.

Keywords Pulmonary arterial hypertension, Glycolysis, Lactate, Lactylation, Protein translational modifications

Background

Pulmonary hypertension (PH) encompasses a group of multifactorial disorders characterized by a mean pulmonary arterial pressure exceeding 20 mmHg at rest, as measured by right heart catheterization [1, 2]. Currently, PH is classified into five categories based on its underlying pathophysiological mechanisms and clinical features. This paper specifically focuses on pulmonary arterial hypertension (PAH), the most extensively studied subtype of PH. Current estimates indicate that PH affects approximately 1% of the global population, with prevalence increasing to 10% among individuals aged 65 and older [3]. PAH is a life-threatening condition characterized by elevated pulmonary arterial pressure due to increased pulmonary vascular resistance, which can lead to right heart failure and mortality [1, 4, 5]. PAH represents a significant global health challenge, affecting individuals across all age groups. Since the National Institutes of Health established PAH registries in the early 1980s, significant advancements have been made in the diagnosis and treatment of PAH. Currently, PAH treatment primarily focuses on addressing the dysfunction of pulmonary arterial endothelial cells (PAECs) and alleviating vascular constriction [6]. It is noteworthy that sotatercept, a fusion protein recently approved by the

*Correspondence:
Yu-hu He
heyuhu1986@126.com
[1] Department of Cardiology, The Second Xiangya Hospital, Central South University, Changsha 410011, Hunan, China
[2] Department of Pathology, The Second Xiangya Hospital, Central South University, Changsha 410011, Hunan, China

U.S. Food and Drug Administration, targets activins and growth differentiation factors involved in the development of PAH. Its primary mechanisms include the inhibition of pathological TGF-β signaling, suppression of cell proliferation, promotion of apoptosis, and attenuation of inflammatory responses, thereby reversing vascular remodeling [7]. Lactate is a crucial molecule in regulating cellular metabolism and activity. Research indicates that lactate serves not only as a metabolic intermediate but also as a signaling molecule, playing an active role in the development of various cardiovascular diseases. Lactylation, an emerging epigenetic modification, has garnered increasing attention in recent years. A growing body of evidence suggests that abnormal cellular metabolism and epigenetic dysregulation contribute to the progression of PAH, with lactate-induced post-translational histone modifications playing a critical role in these changes [8–10].

This paper primarily reviews the key mechanisms underlying PAH and its associated processes of lactylation. It summarizes the latest advancements in glycolysis, lactate metabolism, and lactylation phenomena in cardiovascular diseases such as PAH, providing new insights for understanding the disease and guiding future research directions and potential therapeutic targets.

PAH

Classification

PH was historically classified into two categories: (1) Primary pulmonary hypertension, and (2) Secondary pulmonary hypertension. However, since the second World Symposium on PH in 1998, PH has been officially classified into five categories based on pathophysiology and clinical characteristics: (1) PAH, (2) PH associated with left heart disease, (3) PH associated with lung diseases and/or hypoxia, (4) PH due to pulmonary artery obstructions, and (5) PH with unclear and/or multifactorial mechanism (Fig. 1) [1]. Among these, PAH is the most recognized and extensively researched subtype, serving as the primary focus of this review. PAH can be further classified into congenital and acquired types based on their underlying causes. Congenital PAH includes idiopathic, heritable PAH, and PAH associated with congenital heart disease (CHD). Acquired PAH encompasses PAH induced by drugs or toxins, PAH related to connective tissue disease or portal hypertension, and PAH associated with schistosomiasis or HIV infection [1–3].

Epidemiology

Epidemiology of congenital PAH

Relevant studies indicate that the prevalence of PAH in recent years is approximately 25 cases per million people, while the incidence rate is about 5 cases per million people (Fig. 2) [11, 12]. Humbert et al. identified idiopathic pulmonary arterial hypertension (IPAH) as the most common subtype. Among the 674 patients with PAH included in their study, 264 cases were classified as IPAH, accounting for around 40% of all cases, with heritable PAH representing only 4% [13]. CHD accounts for nearly one-third of all major congenital anomalies. It is one of the most prevalent congenital anomalies, affecting approximately 8 out of every 1,000 live births globally, though incidence varies by region and time [14]. With advancements in medical diagnostics techniques and treatment levels, survival rates for CHD patients have improved. Currently, CHD prevalence among adults is estimated at 0.5 per 1000, with 4–6% of these patients likely developing PAH [15, 16]. Based on these data, the global incidence of PAH caused by CHD is estimated to be 25 cases per million people, a figure corroborated by findings from Maron et al. [11, 17–27].

Epidemiology of acquired PAH

Several drugs and toxins have been identified as risk factors for PAH and are now included in the current classification system. For instance, Benfluorex, which was approved in Europe in 1976 for lipid lowering and diabetes treatment, has been linked to PAH cases. Between 1999 and 2011, the French PAH network recorded 85 PAH cases associated with Benfluorex exposure [28]. Similarly, Montani et al. reported that more than 13 out of 2900 patients treated with Dasatinib for chronic myeloid leukemia developed PAH, with an estimated incidence of at least 0.45% for Dasatinib-induced PAH [29]. Humbert et al. noted that connective tissue disease, portal hypertension, and HIV-related PAH accounted for 15.3%, 10.4%, and 6.2% of all PAH cases, respectively [13]. In many regions, including Europe and North America, systemic sclerosis is the most common cause of connective tissue disease-related PAH, while systemic lupus erythematosus is more prevalent in Southeast Asia. This regional variation may reflect differences in disease patterns worldwide [30–32]. Epidemiological studies indicate that over 200 million people globally are infected with schistosomiasis, a parasitic disease. A Brazilian study reported that the incidence of PAH among patients with hepatosplenic schistosomiasis was 4.6% [33, 34]. Although HIV infection is not a common cause of PAH, studies from Switzerland and France have reported a PAH incidence ranging from 0 to 5% among HIV-positive individuals. Given the substantial number of people living with HIV worldwide, HIV could emerge as a significant infectious cause of PAH [35].

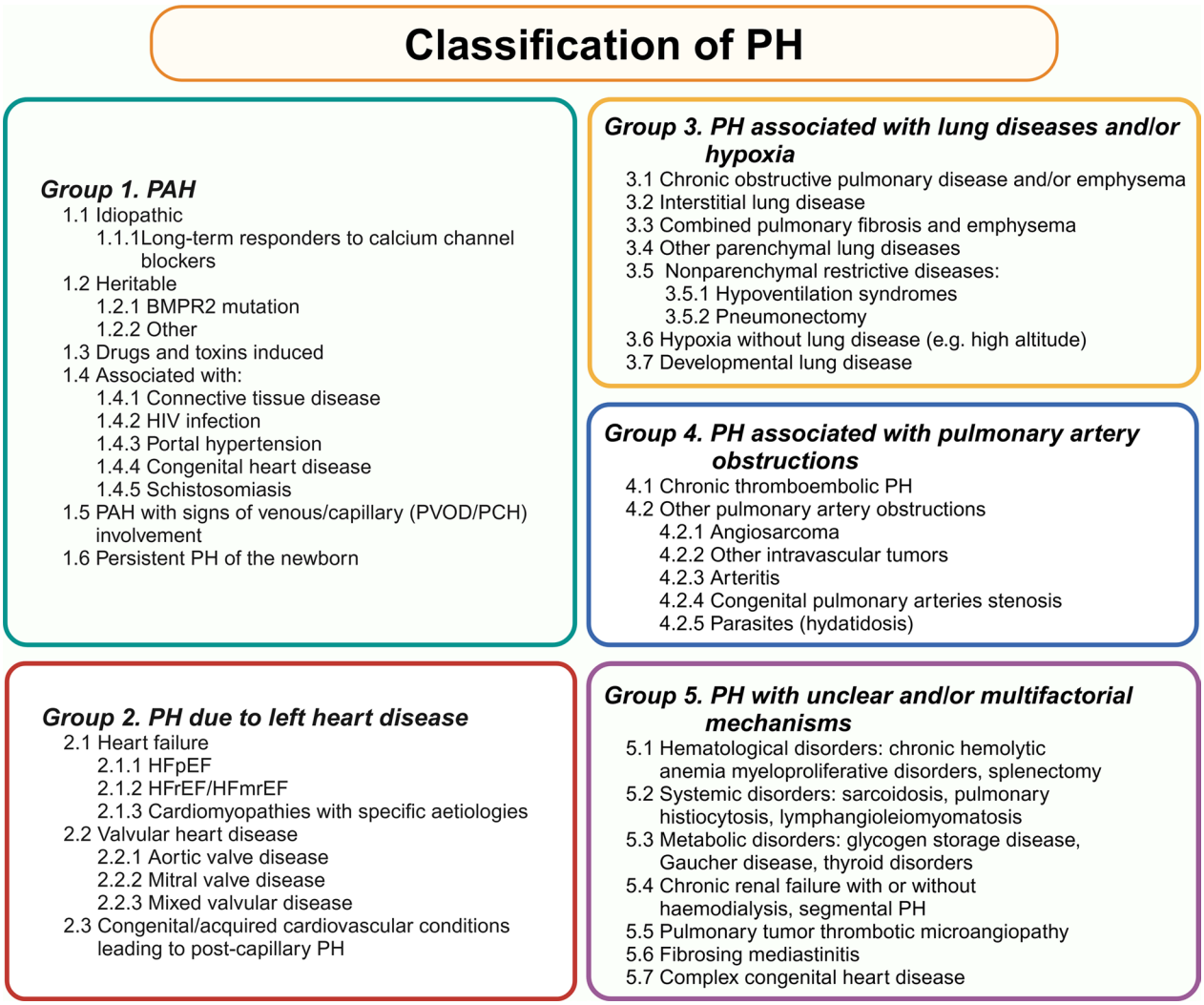

Fig. 1 We summarized the classification of PH. (HIV, Human Immunodeficiency Virus; PVOD, Pulmonary Veno-Occlusive Disease; PCH, Pulmonary capillary haemangiomatosis; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart Failure with Reduced Ejection Fraction; HFmrEF, heart failure with mid-range Ejection Fraction). Created using BioRender.com

Mechanism of PAH

PH is a disease encompassing various pathological pathways, and detailing the specific mechanisms of each subtype falls beyond the scope of this review (Table 1) [1, 17]. Among these, PAH (WHO Group 1) is the most recognized and extensively researched subtype, making it the primary focus of this review. Pulmonary vascular remodeling is a common characteristic of all types of PH, manifesting as structural and functional changes in the distal vascular system of the pulmonary circulation, primarily affecting the pulmonary arterioles in PAH [36]. PAH is a rare and severe disease characterized by complex pathology involving multiple molecular processes. Factors contributing to this include metabolic dysfunction [4, 37], epigenetic modifications [38], gene mutations [39, 40], DNA damage [41–43], inflammation and

(See figure on next page.)

Fig. 2 Epidemiological overview of PH, including both congenital and acquired forms. Congenital PAH primarily includes idiopathic and heritable subtypes, with CHD being a significant cause. Acquired PAH is associated with conditions such as connective tissue disease, portal hypertension, and HIV infection, as well as drug-induced cases. The figure also highlights PAH cases linked to specific drugs (e.g., Benfluorex and Dasatinib) and diseases (e.g., schistosomiasis and HIV infection). Additionally, the epidemiological characteristics of PH associated with left heart disease, lung disease, pulmonary artery obstructions, and multifactorial mechanisms are summarized [17–27]. Created using BioRender.com

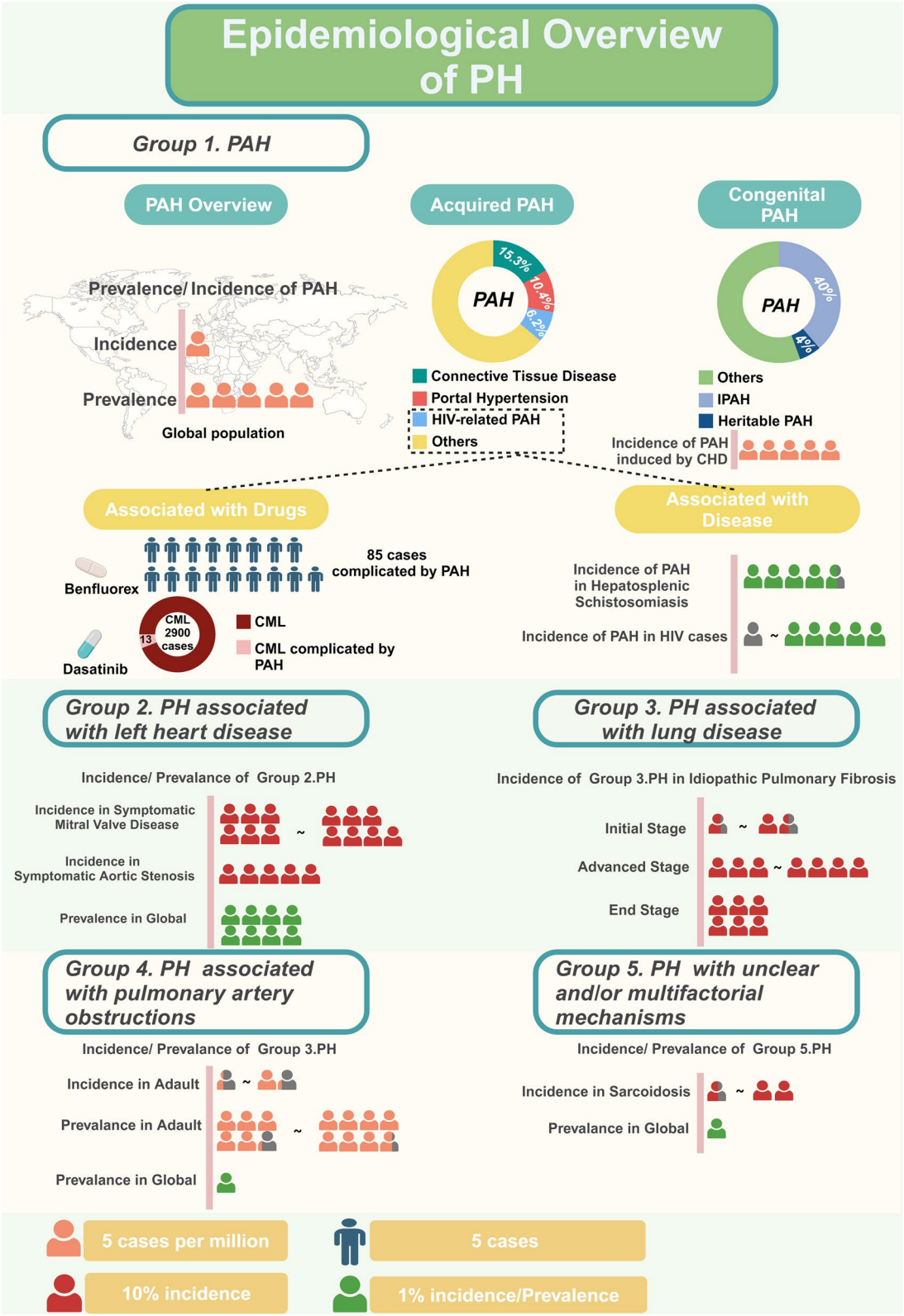

Fig. 2 (See legend on previous page.)

Table 1 The overview of pathophysiology and pathway in PH

WHO	Mechanisms	Pathophysiology	Targets/pathway	References
1	Vascular remodeling of pulmonary arteries	Pulmonary vasculopathy: Medial hyperplasia, Intimal proliferation, Plexiform lesions RV failure	Endothelin pathway NO-sGC-cGMP pathway Prostacyclin pathway	[50] [58, 61] [53]
2	PH associated with left-sided heart disease	Variable degree of pulmonary congestion, vasoconstriction, vascular remodeling	SAC/MAPKS pathway Rho-kinase pathway NO-sGC-cGMP pathway Endothelin pathway	[49, 62] [51] [57] [54, 55]
3	PH associated with lung disease	Remodeling of airways, lung parenchyma, and vessels	PGI2 pathway	[48, 59]
4	PH associated with pulmonary artery obstructions	Distal/ Proximal PA fibrotic obstruction Micro-vasculopathy	Fibrinolysis pathway[a]	[52, 60]
5	PH with unclear and/or multifactorial mechanisms	Spontaneous EEC formation[b]	Platelet activation and the activation of coagulation pathway[c]	[47, 56]

PA pulmonary artery, *EEC* erythropoietin-independent erythroid colony; [a]Chronic thrombo-embolic pulmonary hypertension; [b]group 5 myeloproliferative disorders; [c]group 5 chronic hemolytic anemia

oxidative stress [9, 44] and endothelial dysfunction [45, 46]. These factors collectively contribute to the remodeling and luminal narrowing of pulmonary arterioles, resulting in right ventricular hypertrophy and failure, ultimately leading to patient mortality.

Molecular dysfunction

Abnormal signaling and metabolic dysregulation in pulmonary vascular cells may contribute to the development of PAH, alongside several currently investigated pathways, including the nitric oxide pathway, prostacyclin pathway, endothelin-1 pathway, transforming growth factor pathway, renin–angiotensin–aldosterone system pathway, RhoA/ROCK signaling pathway, platelet-derived growth factor pathway, peroxisome proliferator-activated receptors pathway, HIF1 pathway, protein kinase B pathway, mitochondrial phosphatase and tensin homolog-induced kinase 1 pathway, and the HIPPO and p53 signaling pathways [36, 63]. Recent studies have identified potential mechanisms that contribute to PAH, including abnormalities in mitochondrial metabolic dynamics, potassium channel disorders, calcium homeostasis irregularities, and hormonal imbalances.

Mitochondrial metabolic dynamics abnormalities Mitochondrial dysfunction in PAH involves a metabolic shift from glucose oxidation to uncoupled aerobic glycolysis, a phenomenon known as the Warburg effect (Fig. 3). Furthermore, recent studies indicate that the accumulation of mitochondrial heat shock protein 90 enhances aerobic glycolysis and mitochondrial stress responses in cultured pulmonary artery smooth muscle cells (PASMCs) derived from PAH patients and serves as a critical regulator of vascular remodeling [64]. Fatty acid oxidation-related genes are upregulated in PAH, and the inhibition or deletion of carnitine palmitoyltransferase 1 can reduce the severity of PAH in mice [65]. Under normal conditions, cell proliferation and apoptosis are regulated by mitochondrial dynamics, specifically through fission and fusion processes. Mitochondrial fission is associated with nuclear division, while mitochondrial fusion inhibits cell proliferation and promotes oxidative metabolism. However, this dynamic balance is disrupted in PAH, which typically exhibits upregulated fission and downregulated fusion [66]. Consequently, PASMCs in PAH demonstrate increased proliferative capacity. Experimental evidence indicates that inhibiting fission or promoting fusion leads to cell cycle arrest and apoptosis, resulting in the regression of experimental PAH [67, 68]. Meanwhile, the "metabolic theory" proposed by Paulin et al. also places mitochondrial inhibition at the core of PAH pathogenesis. They highlighted that this theory could explain many features of the vascular phenotype observed in PAH [69].

Dysfunction of pulmonary arterial cells In the development of PAH, the roles of PAECs, PASMCs, and pulmonary fibroblasts are significant [18]. From a pathological perspective, the apoptosis-resistant phenotype of PAECs and the increased proliferation of PASMCs drive PAH progression [46]. Endothelial cells (ECs) play a crucial role in maintaining vascular homeostasis, with studies indicating that endothelial injury often occurs early in PAH [70–72]. ECs are key players in the initiation and progression of PAH, with many characteristics of the disease resulting from EC dysfunction, including vasoconstriction, vascular wall proliferation and remodeling, recruitment of inflammatory factors, hypercoagulability, thrombosis, oxidative stress, and endothelial-to-mesenchymal transition [73–

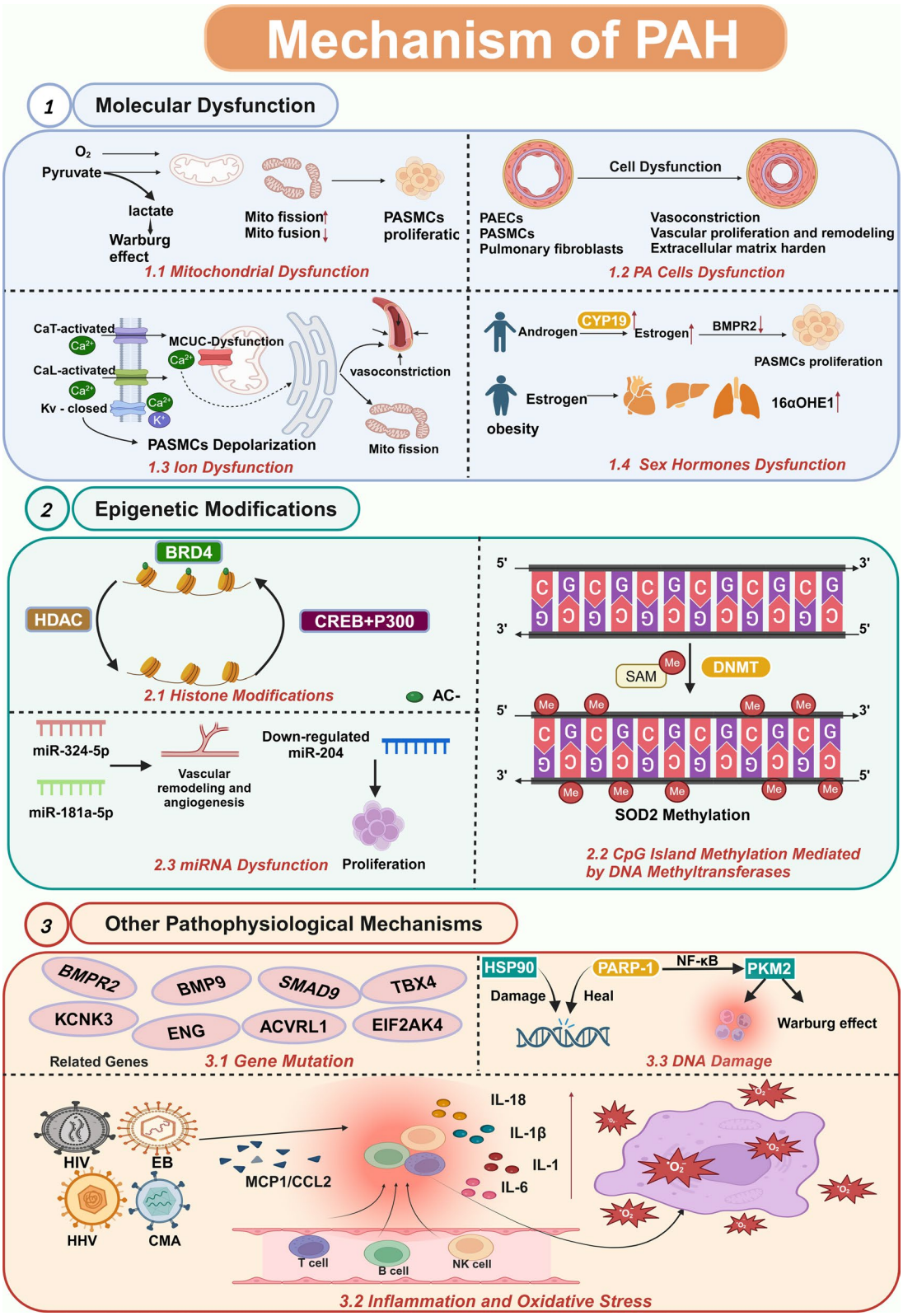

Fig. 3 The mechanism of PAH. The main characteristics of PAH include pulmonary vascular contraction and the proliferation and remodeling of PASMCs, resulting in structural and functional changes. Factors contributing to PAH include metabolic dysfunction, epigenetic modifications, gene mutations, DNA damage, inflammation, and oxidative stress. (Mito, mitochondrial; BMPR2, bone morphogenetic protein receptor type 2; 16αOHE1, 16α-hydroxyestrone; DNMT, DNA methylation; Me, methylation). Created using BioRender.com

75]. Research indicates that after EC dysfunction, interactions with other cells, such as vascular smooth muscle cells, lead to vascular injury [76]. Current treatment strategies for PAH continue to focus on endothelial cell-related pathways: (1) enhancing the nitric oxide-cyclic guanosine monophosphate pathway, (2) enhancing prostacyclin receptor activity, and (3) inhibiting the endothelin pathway [6]. In rapidly proliferating cells, glutamine plays a crucial role. Increased breakdown of glutamine in pulmonary fibroblasts activates mTOR and promotes the hydroxylation of proline in collagen, resulting in a stiffer extracellular matrix. Enhanced glutamine catabolism also promotes endothelial dysfunction, and the use of glutaminase inhibitors can suppress the proliferation of PAECs in vivo, alleviating monocrotaline-induced PAH [77, 78]. The characteristics of PASMCs in PAH resemble those of cancer cells, characterized by increased inflammatory factor production and excessive proliferation, which leads to vascular remodeling. Targeting PASMC proliferation with drugs such as Celastramycin can reduce excessive proliferation and inflammation, thereby improving PAH in animal models [79]. Studies indicate that in hypoxic environments, the progression of PAH is accelerated in endothelial-specific AMPK knockout mice, with enhanced PASMC proliferation; this phenomenon is prevented by metformin, an AMPK activator [80–82].

Ion metabolism abnormalities Ion metabolism abnormalities associated with PAH have primarily focused on potassium channel disorders. However, in addition to voltage-gated potassium channels, the pathogenesis of PAH may also involve various transient receptor potential channels, calcium-sensing proteins, and calcium-activated chloride channels [83–86]. Researchers have identified that heterozygous functional loss mutations in the *KCNK3* gene (member 3 of the potassium channel subfamily K) are responsible for hereditary PAH, as *KCNK3* encodes an outwardly rectifying potassium (K+) channel [87, 88]. Studies indicate that potassium channel dysregulation plays a significant role in both the immediate and long-term regulation of pulmonary vascular function in PAH [89]. Antigny et al. also noted that pharmacological activation of *KCNK3* can alleviate monocrotaline-induced PAH, thereby supporting this viewpoint [88]. Mitochondrial oxygen sensors mediate the regulation of pulmonary oxygen uptake, while oxygen-sensitive Kv channels are regulated by these sensors [90]. Research shows that Kv channel expression decreases in PAH, and gene therapy targeting Kv channels can restore pulmonary vascular contraction and improve PAH [91]. Moreover, Michelakis et al. discovered that chronic hypoxia-induced PAH is associated with the suppression of Kv channel expression and function in PASMCs, leading to a shift in the cellular redox balance toward a more reduced state. Notably, the metabolic modulator dichloroacetate has been shown to prevent and reverse PAH by restoring Kv channel expression and function [92]. Interestingly, closure of Kv channels has been found to cause depolarization of PASMCs [93], which activating voltage-dependent calcium channels and L-type calcium channels, which increases cytosolic calcium concentration [94–96]. The increase in intracellular calcium ion concentration leads to vascular contraction [97], while elevated potassium ion levels contribute to apoptosis resistance [98]. Researchers have found that calcium channel inhibitors, such as nifedipine, are effective in treating certain PAH patients who exhibit acute vasodilatory responses [99]. Additionally, aside from L-type calcium channels, T-type calcium channels have also been implicated in excessive proliferation and apoptosis resistance of PASMCs in patients with idiopathic PAH [100]. The mitochondrial calcium uniporter complex (MCUC) is an ion channel that facilitates the entry of calcium into the mitochondrial matrix [101]. Dysfunction of MCUC increases calcium ion concentration in the endoplasmic reticulum, promoting vasoconstriction and mitochondrial fission while simultaneously reducing calcium concentration within the mitochondria and inhibiting calcium-dependent metabolic enzymes, thereby suppressing oxidative metabolism [102]. Research has demonstrated that restoring MCUC expression can reduce mitochondrial fission and alleviate experimental PAH induced by monocrotaline [84]. The function of MCUC appears to connect ion metabolism abnormalities with mitochondrial metabolic dysfunction observed in PAH.

Abnormalities in sex hormone metabolism An epidemiological study indicates that 70% to 80% of patients with PAH are women [4]. In the body, androgens are converted to estrogens through the action of aromatase, which is more active in the pulmonary vasculature of patients with PAH. Accumulating evidence suggests that abnormalities in sex hormone metabolism exist in both animal models and patients with PAH [103]. Existing research indicates that estrogens may primarily induce a proliferative phenotype in PASMCs by downregulating the expression of bone morphogenetic protein receptor type II, rendering women more susceptible to PAH [104]. Notably, abnormalities in estrogen metabolism due to obesity can induce PAH by increasing the production of 16α-hydroxyestrone in visceral adipose tissue, which leads to oxidative stress and subsequently mediates the onset of PAH [105].

Epigenetic modification mechanisms

In recent years, researchers have identified several potential mechanisms, including genetic and inflammatory

factors, that may contribute to endothelial cell damage and promote endothelial dysfunction in PAH. However, the role of epigenetic regulation in endothelial cell function has only recently begun to be explored in detail [9]. Epigenetics refers to changes in gene expression that occur independently of alterations in the DNA sequence. An increasing body of evidence suggests that the activation of endothelial cells is regulated by epigenetic mechanisms. The three primary known epigenetic mechanisms are: (1) histone modification; (2) CpG island methylation mediated by DNA methyltransferases; and (3) dysregulation of microRNAs (miRNAs) [106]. Defects in these pathways may result in increased expression of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), nuclear factor-kappa B (NF-κB), type I interferons, and interferon regulatory factors. Studies indicate that the elevated expression of these inflammatory factors may facilitate the development of PAH [107].

Histone modifications Histone modifications, particularly those regulated by histone deacetylases (HDACs), have received significant attention in recent years due to their essential role in cell proliferation and survival. Histone modifications alter chromatin structure without altering the underlying genetic sequence, thereby influencing nuclear processes associated with development, tissue differentiation, cell responsiveness, and biological phenotypes [38]. In studies examining lung tissues from patients with IPAH and rat models of chronic hypoxia-induced PAH, Zhao et al. identified increased expression of HDACs in remodeled pulmonary vasculature. Furthermore, the use of HDAC inhibitors, such as valproic acid and trichostatin A, alleviated PAH in rats, suggesting that elevated HDAC activity may play a role in the vascular pathology of PAH [108]. In another study, Kim et al. found that the transcriptional activity of MEF2, a key factor in endothelial cells, was markedly impaired in pulmonary arterial endothelial cells from PAH patients. This impairment was caused by the excessive accumulation of two class IIa HDACs in the nucleus, further indicating the involvement of histone modifications in PAH development [109]. Additionally, Xu et al. discovered that acetylation of histones H3 and H4 was significantly elevated in a rat model of persistent pulmonary hypertension of the newborn (PPHN). Their study demonstrated that nitric oxide (NO), produced by endothelial nitric oxide synthase (eNOS), played a crucial role in the pathophysiology of PPHN. Compared with controls, the PPHN rats exhibited increased histone acetylation in the promoter region of the eNOS gene in pulmonary vascular endothelial cells, suggesting that elevated eNOS expression in PPHN is associated with histone modifications [110]. Grobs et al. identified ATP citrate lyase as a key enzyme in histone acetylation, playing a crucial role in PAH primarily by regulating the proliferation and survival of vascular smooth muscle cells [111]. Pullamsetti et al. demonstrated that the epigenetic coactivator P300, in complex with CBP, interacts with multiple transcription factors and functions as a transcriptional coactivator to influence PAH by regulating histone acetylation. Their study found that inhibiting the P300/CBP complex reduces distal pulmonary vascular remodeling, improves hemodynamics, and reverses established PAH models [112]. Moreover, studies have identified BRD4, an epigenetic reader protein that recognizes and binds to acetylated histones, as a crucial contributor to the pathogenesis of PAH [113]. Consistently, a multicenter preclinical study by Van der Feen et al. confirmed the therapeutic potential of the BRD4-related inhibitor RVX208 in rodent models of PAH. Based on these findings, they advocate for clinical trials investigating the use of the epigenetic modulator RVX208 in PAH patients [114]. However, the precise mechanisms linking histone modifications to PAH pathogenesis remain unclear and require further investigation.

CpG island methylation mediated by DNA methyltransferases DNA methylation is a covalent modification that involves transferring a methyl group to the 5th carbon of cytosine within CpG dinucleotide sequences, resulting in the formation of 5-methylcytosine [45]. Early research underscored the significance of DNA methylation in endothelial cell function and the specific expression of eNOS, mediated by the VEGF signaling pathway [115]. As previously mentioned, eNOS plays a key role in PAH pathogenesis. Notably, Chan et al. demonstrated that DNA methylation is crucial for the transcriptional regulation and endothelial cell-specific expression of the eNOS gene [116]. Particularly noteworthy is the research conducted by Archer et al., which first proposed that methylation of superoxide dismutase 2 (SOD2) constitutes a novel epigenetic mechanism in PAH. They reported that downregulation of SOD2 methylation impairs hydrogen peroxide-mediated redox signaling, activates hypoxia-inducible factor 1 (HIF-1), and promotes a proliferative and anti-apoptotic state. Increased expression of SOD2 has been shown to restore mitochondrial function, inhibit the proliferation of PASMCs, and partially reverse established PAH [117]. Additionally, Rexhaj et al. discovered that offspring of mice subjected to dietary restriction during pregnancy exhibited more severe PAH, which was associated with increased DNA methylation [118]. Moreover, studies have indicated that DNA methylation may either activate or suppress inflammatory pathways

associated with PAH [9, 119]. These findings support the notion that DNA methylation is closely associated with PAH development.

miRNAs dysregulation In PAH, miRNA dysregulation occurs in lung tissues and in cultured PAECs, PASMCs, and fibroblasts [10]. Although research on the role of RNA in PAH pathogenesis remains limited, non-coding RNAs have emerged as crucial regulators of post-transcriptional activity in endothelial cells. Although non-coding RNAs do not possess intrinsic epigenetic properties, their expression is frequently regulated by epigenetic modifications of their gene promoters [120]. Non-coding RNAs, including miRNAs and long non-coding RNAs, can regulate endothelial cell function by promoting the proliferation of smooth muscle cells and facilitating endothelial-mesenchymal transition [121]. Furthermore, the study by Sindi et al. highlighted the role of novel miRNAs, including miR-181a-5p and miR-324-5p, in regulating vascular remodeling and angiogenesis [122]. Courboulin et al. were the first to reveal that the downregulation of miR-204 leads to increased cell proliferation and reduced apoptosis, thereby promoting PAH progression and correlating with disease severity [123]. These findings indicate that miRNA dysregulation is closely linked to the pathogenesis of PAH.

Other pathophysiological mechanisms

In addition to metabolic dysfunction and epigenetic modifications, the roles of gene mutations, DNA damage, inflammation, and oxidative stress in the pathogenesis of PAH warrant significant attention. However, the specific mechanisms involved are complex and multifaceted; therefore, this section offers only a concise overview.

Gene mutations To date, several gene mutations have been linked to the development of PAH, including those in *BMPR2*, [124] *BMP9*, [40] *ACVRL1*, [125] *ENG*, [126] *SMAD9*, [127] *KCNK3*, [87] *EIF2AK4*, [128] *TBX4* [129].

Inflammation and oxidative stress Inflammation and oxidative stress are key factors in the pathological progression of PAH. Research indicates that PAH is associated with immune dysregulation and abnormalities in the function of B cells, natural killer lymphocytes, and regulatory T cells (Tregs) [130, 131]. The use of Tregs with high expression can prevent experimental PAH [132]. Numerous retrospective and prospective studies have indicated elevated levels of cytokines, including interleukin-1β, IL-1, IL-6, and IL-8, as well as chemokines such as CCL2/MCP-1 in patients with PAH. These levels are also correlated with inflammatory factors, including CD-20 and TNF-α [46, 133, 134]. Research has shown that leukotriene B4, secreted by macrophages in the lungs of PAH rats, induces apoptosis in PAECs and promotes PASMC proliferation [135]. Additionally, PAH is associated with latent viral infections, including HIV, HHV, Epstein-Barr virus, and cytomegalovirus, which are closely linked to inflammation [136]. Notably, patients with PAH frequently exhibit signs of chronic inflammation, characterized by elevated circulating cytokine levels and inflammatory infiltration around blood vessels [137, 138]. Chronic inflammation and maladaptive fibrosis play crucial roles in PAH, particularly among patients with connective tissue diseases, including systemic lupus erythematosus and scleroderma, as well as infections such as HIV and schistosomiasis [10]. Interestingly, fibroblasts isolated from the pulmonary arteries of patients with PAH and experimental models exhibit hyperproliferation, anti-apoptotic features, and a pro-inflammatory phenotype, characterized by increased levels of inflammatory molecules and myofibroblast markers [139, 140]. These changes associated with chronic inflammation are linked to epigenetic modifications, including increased HDAC activity and decreased miR-124 expression [141]. Collectively, these findings underscore the significant role of inflammation in the progression of PAH. Inflammation and oxidative stress are interconnected; inflammatory stimuli can induce oxidative stress, which may subsequently drive the development of PAH through various downstream pathways [142].

DNA damage The body can experience DNA damage in response to harmful agents, such as toxic substances, which may impair DNA integrity and function. Inflammation and oxidative stress associated with PAH can induce DNA damage [46]. Given that microsatellite instability and somatic mutations have been identified in the lungs of PAH patients, DNA damage and repair dysregulation are strongly implicated as triggers for PAH progression [42, 43]. This perspective is supported by research conducted by Meloche et al., which found that PARP-1, a key enzyme involved in DNA repair, is overexpressed in the distal pulmonary arteries and PASMCs of patients with PAH. Further animal experiments demonstrated that PARP-1 inhibitors can reduce right ventricular pressure and reverse the progression of PAH, thereby confirming the involvement of DNA damage in the disease process [143]. Similarly, Shimauchi et al. reported that during maladaptive right ventricular remodeling, the increased activity of PARP1 significantly promotes the expression and nuclear function of pyruvate kinase M2 (PKM2), leading to a series of aberrant metabolism-inflammation signaling loops. Notably, they proposed that mild activation of PARP1 may facilitate DNA repair and cell survival to some extent, whereas prolonged excessive activation

exerts detrimental effects. For instance, PARP1 can stimulate PKM2 expression via NF-κB, contributing to the Warburg effect and inflammation [144]. Moreover, Boucherat et al. reported that the accumulation of the mitochondrial chaperone heat shock protein 90 is a key feature of PAH in PASMCs and contributes to vascular remodeling through mechanisms such as DNA damage. They demonstrated that Gamitrinib, a inhibitor of mitochondrial chaperone heat shock protein 90, reduces mitochondrial DNA content and repair capacity, thereby suppressing PASMCs proliferation and resistance to apoptosis [64]. Collectively, these studies confirm the critical role of DNA damage in the pathogenesis of PAH.

Lactylation

Phenomenon of lactylation

Post-translational modifications of proteins play a crucial role in regulating their biological functions and managing dynamic interactions with other molecules [145]. Historically, lactate, a byproduct of glycolysis, was regarded primarily as a metabolic waste product contributing to muscle fatigue and tissue damage [146]. However, a groundbreaking study conducted by Dr. Yingming Zhao's team at the University of Chicago in 2019 revealed that lactate can influence gene expression through a mechanism known as histone lactylation. They identified 28 lactylation sites on core histones in both human and mouse cells. Their research demonstrated that hypoxia and bacterial infections induce glycolysis, resulting in lactate accumulation. Lactate functions as a precursor or directly modifies lysine residues on histones through lactylation. They found that the increased lactylation of histone 3 lysine 18 induces the expression of late wound healing-related genes associated with M1 macrophage polarization, and is linked to the upregulation of M2-like genes, facilitating the phenotypic shift toward anti-inflammatory M2 macrophages. Overall, they reported the role of endogenous lactylation modifications in regulating the homeostasis of M1 macrophages challenged by bacteria [147]. Similarly, Gaffney's research team also observed the phenomenon of lactylation [148]. Initially observed in human histones, lactylation not only provides a molecular basis for lactate-mediated gene expression but also enhances our understanding of the biological functions of lactate metabolism. Despite these exciting discoveries, the occurrence of lactylation on non-histone proteins and its downstream functional consequences remain poorly understood. Wan et al. employed mass spectrometry (MS/MS) to analyze lactylated peptides and utilized tandem mass spectrometry to reliably identify novel lactylated proteins and modification sites. This method broadened the detection of lactylation beyond histones to include other proteins within the human proteome [149, 150].

Mechanisms of lactylation

Mechanisms of histone lactylation

Lactate, a key glycolytic metabolite, is noteworthy for its production even under fully aerobic conditions in cancer cells—a phenomenon termed the Warburg effect. Sharma et al. found that mitochondrial defects and impaired ATP production accelerate lactate production through the Warburg effect, acidifying the tumor microenvironment and promoting cell growth and survival [151]. Pathological conditions, such as tumors, infections, and ischemia–reperfusion events, facilitate lactate entry into cells via monocarboxylate transporter (MCT). MCT1 primarily mediates lactate influx, whereas MCT4 is responsible for lactate efflux (Fig. 4). Additionally, the chaperone protein CD147 facilitates the expression and localization of MCTs at the cell surface. Lactate can also enter cells through GPR81, a G-protein-coupled receptor that regulates lactate transport. GPR81 regulates lactate transport across the cell membrane, inhibiting cAMP and protein kinase A-mediated signaling pathways [152, 153]. Under hypoxic conditions, in addition to the influx of exogenous lactate into cells, HIFs can upregulate glycolytic genes and suppress the citric acid cycle through targeted transcription and translation, thereby stimulating increased lactate production [154]. Intracellular lactate is converted into lactoyl-CoA by lactoyl-CoA synthetase. The lactoyl group from lactoyl-CoA is subsequently enzymatically transferred to lysine residues on proteins. This process involves three classes of enzymes termed "writers," "erasers," and "readers." Initially, "Writers" transfer the lactoyl group to lysine residues on histones or non-histone proteins. Lysine residues on histones, particularly those enriched in gene promoter regions, undergo modifications that alter protein structure and function, resulting in lactylation. This modification subsequently affects gene expression and downstream signaling pathways. Zhang et al. identified the acetyltransferase p300 as a "writer" of lactylation, responsible for transferring L-lactate to histones and inducing histone lactylation. Their study demonstrated that the overexpression of p300 significantly increased histone lactylation levels [147]. Furthermore, "erasers," analogous to deacetylases, remove some or all lactate groups from target proteins, thereby interrupting the lysine lactylation cycle. This process prevents lysine residues on proteins from exerting lasting effects, effectively countering the "writers." Moreno-Yruela and colleagues identified HDAC1-3 and SIRT1-3 as key "erasers" in this context [155]. Finally, "reader" proteins specifically recognize these lactylation marks, influencing downstream signaling pathways

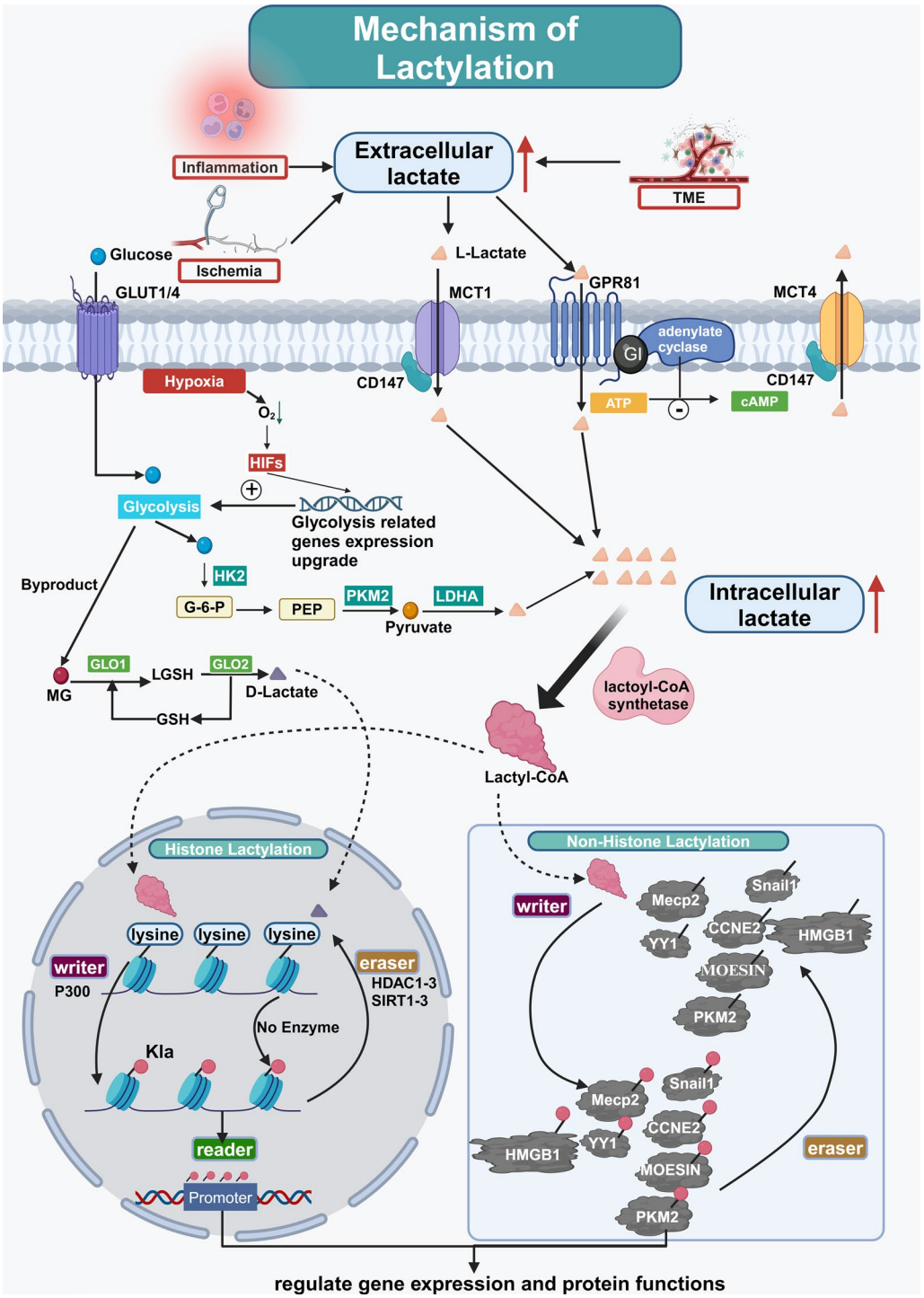

Fig. 4 The mechanism of lactylation. Extracellular lactate, elevated in response to factors such as inflammation, hypoxia, and ischemia, enters cells via MCT1 and GPR81. Under hypoxic conditions, HIFs upregulate glycolytic genes and inhibit the citric acid cycle, promoting L-lactate production. MG combines with glutathione via GLO1 to form LGSH, which GLO2 hydrolyzes to regenerate GSH and produce D-lactate. Intracellular lactate is converted into lactoyl-CoA, which drives lactylation of histone and non-histone proteins. The "writers" (e.g., p300) mediate lactylation on lysine residues, while "erasers" (e.g., HDAC1-3, SIRT1-3) remove these modifications. Lactylation finally regulate gene expression. (TME, tumor microenvironment; MG, methylglyoxal; GSH, glutathione; CD147, cluster of differentiation 147; GPR81, a G protein-coupled receptor that regulates lactate transport; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; Kla, lactylation.) Created using BioRender.com

and initiating various biological events [147, 156]. Additionally, lactate can be transferred to lysine residues on proteins through both enzymatic and non-enzymatic pathways. Similarly, Gaffney's research centered on protein translational modifications derived from methylglyoxal, a glycolytic byproduct. methylglyoxal rapidly combines with glutathione via glyoxalase 1 (GLO1) to form lactoyl-glutathione (LGSH), which is subsequently hydrolyzed by GLO2 to regenerate glutathione and produce D-lactate. Lactate derived from LGSH can undergo non-enzymatic acyl transfer to lysine residues on proteins, resulting in protein lactylation [148].

Mechanisms of non-histone lactylation

In addition to histone modifications, non-histone lactylation has emerged as a significant regulatory mechanism in various biological processes [157, 158]. Wang et al. reported that lactate accumulation during exercise enhances the lactylation of Mecp2 [159]. Furthermore, lactate enhances the lactylation of Snail1, promoting its nuclear translocation [160]. A study highlighted that lactylation of YY1 in microglial cells can upregulate the expression of FGF2, thereby influencing retinal neovascularization, potentially leading to vision loss [161]. Additionally, in hepatocellular carcinoma, SIRT3 mediates the lactylation of cyclin E2 (CCNE2), affecting its lactylation levels [162]. Yang et al. demonstrated that macrophages can absorb extracellular lactate to promote the lactylation of high mobility group box-1 (HMGB1), which is subsequently secreted via exosomes, increasing endothelial permeability and inducing further endothelial barrier dysfunction [163]. Gu et al. provided evidence that lactate regulates Treg cell generation through the lactylation of MOESIN at lysine 72, influencing related immunosuppressive functions [164]. Studies have suggested that decreased lactate levels reduce lactylation modifications on lysine residues within the ubiquitin–proteasome system (UPS), potentially affecting mechanisms underlying systemic lupus erythematosus [165]. Research by Wang et al. found that lactylation at lysine 62 of PKM2 inhibits the transition from tetramer to dimer, thereby enhancing PKM activity and facilitating the conversion of pro-inflammatory macrophages to a reparative phenotype [166].

Role of lactylation

Recent studies have confirmed that lactylation occurs in various cell types and plays crucial roles not only in regulating gene expression and cellular development but also in the tumor microenvironment (Fig. 5). Lactylation significantly impacts inflammation, fibrosis, cellular phenotype transitions, metabolism, aging, and the maintenance of cardiovascular function, demonstrating its unique and profound biological significance [150, 167–169].

In terms of gene expression, Chen et al. reported that lactate-induced lactylation of NBS1 enhances DNA repair mediated by homologous recombination [167]. Regarding cellular development, Dai et al. revealed that during neurogenesis and differentiation in mice, the levels of various histone lactylation increased, pre-activating neuronal transcription programs that promote the differentiation and maturation of neural stem cells [170]. Notably, Nian's research team found that during osteoblast differentiation, the expression of lactate dehydrogenase A (LDHA), intracellular lactate levels, and histone lactylation progressively increased [171]. In the context of tumors, numerous studies indicate that lysine lactylation is associated with the development of hepatocellular carcinoma, colorectal cancer, clear cell renal carcinoma, and ocular melanoma [172–176].

Inflammation

Elevated lactate levels are a characteristic feature of chronic inflammation. In the immune system, lactylation—particularly of lysine residues—plays a critical role, with growing evidence linking both histone and non-histone lactylation to inflammation [147, 163, 177, 178]. Some studies suggest that lactylation modifications may induce NKT cells to exhibit increased Foxp3 expression [179]. In tumor-infiltrating myeloid cells, lactylation promotes immune suppression primarily by upregulating the expression of methyltransferase-like 3(METTL3), which increases the levels of cytokines such as interleukin-10 [180]. Furthermore, the previously mentioned lactylation of PKM2, MOSEIN, and HMGB1 contributes to various inflammatory responses.

Fibrosis

Studies have shown that in liver fibrosis, hepatic stellate cells (HSCs) exhibit elevated lactate levels, and the activation of HSCs is a frequent occurrence associated with liver injury [181]. Interestingly, inactivated stellate cells are enriched in H3K18la within the promoter regions of specific genes associated with HSC activation and liver fibrosis, indicating a potential role for lactylation modifications in fibrosis [182]. Furthermore, research teams have observed that lactate induces histone lactylation at profibrotic gene promoters in macrophages, resulting in heightened profibrotic activity in lung tissue [183].

Cellular phenotype transition

Lactylation promotes the transition of NKT cells to Treg cells [179]. Additionally, lactylation of PKM can regulate macrophage polarization, resulting in the transition from pro-inflammatory to reparative phenotypes. [166]

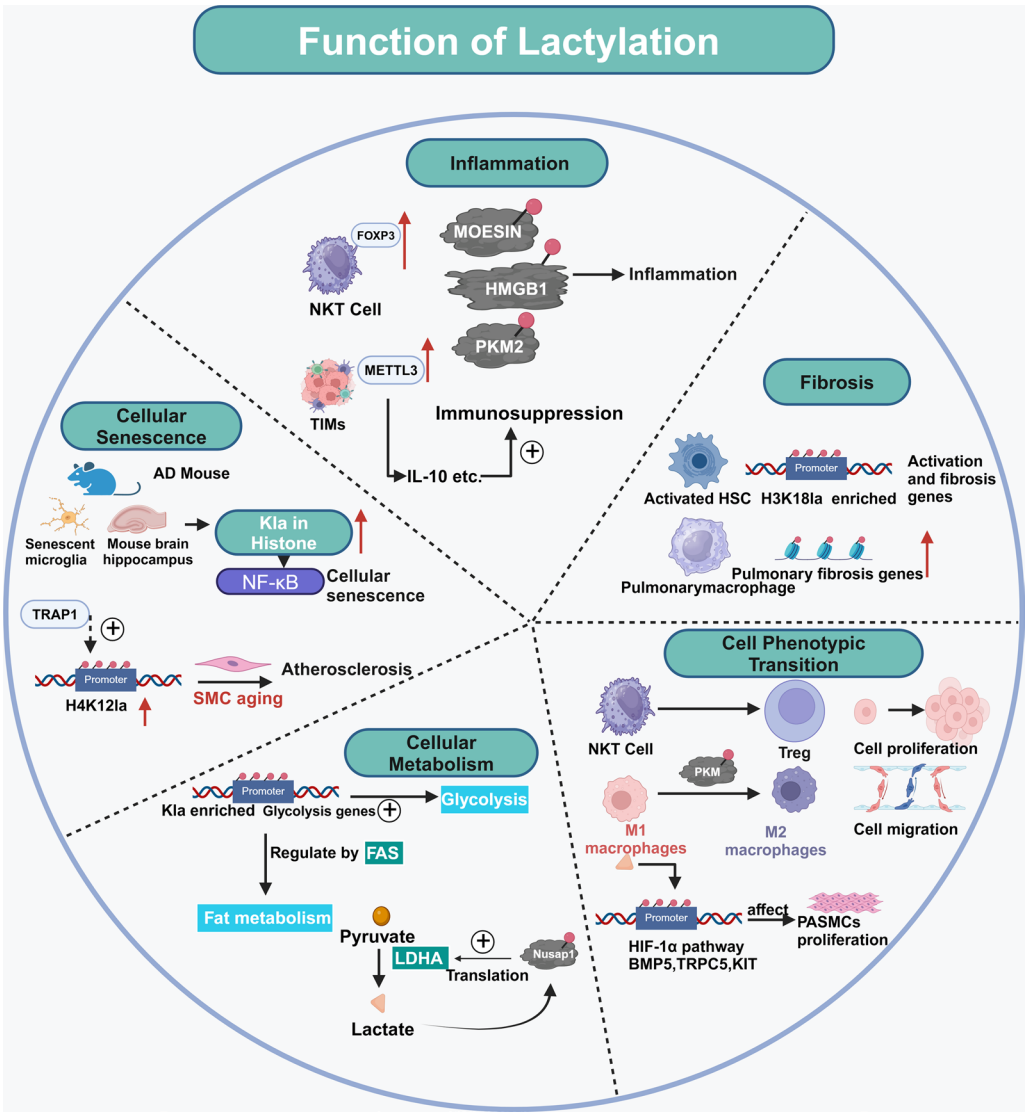

Fig. 5 The function of Lactylation. Lactylation significantly impacts inflammation, fibrosis, cellular phenotype transitions, cellular metabolism, cellular senescence. (FOXP3, forkhead box protein P3; NF-κB: nuclear factor-kappa B; TIMs, tumor-infiltrating myeloid cells; FAS, fatty acid synthase.) Created using BioRender.com

Research has shown that the accumulation of intracellular lactate increases the lactylation of histones at HIF-1α targets (such as BMP5, TRPC5, and KIT), thereby influencing PASMC proliferation [184]. Furthermore, existing literature indicates that lactylation leads to increased cell proliferation and migration [162, 176].

Cellular metabolism

Research indicates that lactylation of histones regulates glucose metabolism in various cell types, primarily by influencing glycolytic activity. For instance, elevated levels of H4K12la have been observed in microglia from a mouse model of Alzheimer's disease (AD), with lactylation modifications enriched at the promoters of glycolytic genes, thereby increasing glycolytic activity and impacting cellular metabolism [185]. A similar phenomenon has been noted in non-small cell lung cancer, where researchers identified increased histone lactylation levels near the promoters of hexokinase-1 (HK-1) and IDH3G through chromatin immunoprecipitation, affecting gene expression and regulating cellular metabolism [186]. Notably, research by Chen et al. indicates that lactate upregulates the expression of NUSAP1 through lysine lactylation modifications, thereby forming a NUSAP1-LDHA-glycolysis-lactate conduit loop. Consequently, lactylation modifications influence cellular

metabolism by regulating LDHA-mediated glycolysis, which plays a crucial role in the metastasis of pancreatic ductal adenocarcinoma [187]. Interestingly, in addition to glucose metabolism, lactylation modifications also play a role in lipid metabolism by influencing fatty acid synthase, thereby regulating cellular metabolism [188].

Cellular aging

An increasing body of evidence suggests that microglial aging plays a role in the pathogenesis of AD. One study indicated that, in naturally aged mice and AD model mice, levels of histone lysine lactylation were significantly upregulated in aging microglia and hippocampal tissue, stimulating the NFκB signaling pathway and promoting the senescence-associated secretory phenotype (SASP), thereby leading to cellular aging. This mechanism involves increased binding of H3K18la to the promoters of Rela (p65) and NFκB1 (p50) [189]. Another research team found that tumor necrosis factor receptor-associated protein 1 (TRAP1) can enhance vascular smooth muscle cell aging by increasing H4K12la levels [190].

Lactate and PAH

Lactylation, a recently recognized epigenetic modification, has garnered increased attention from researchers. Although definitive studies directly linking lactylation mechanisms to the pathogenesis of PAH are lacking, numerous studies have demonstrated a close relationship between glycolytic activity and the onset of PAH. As a byproduct of glycolysis, abnormalities in lactate homeostasis are believed to correlate with the development of PAH.

Glycolysis and PAH

Activation of glycolysis in PAH

Glucose metabolism primarily occurs through two pathways: glycolysis and oxidative phosphorylation, with lactate as the end product of glycolysis [8]. Evidence indicates that disruptions in glycolysis can result in imbalances in lactate levels. Research indicates that histone lysine lactylation is regulated by lactate levels and is a consequence of lactate accumulation [191]. Xiao et al. demonstrated that glycolysis plays a critical role in the proliferation of PASMCs. Inhibition of glycolysis can suppress the proliferation and migration of PASMCs, thereby alleviating or even reversing PAH in animal models [192]. Kovacs et al. found that the upregulation of fructose-2,6-bisphosphatase 3 leads to increased glycolysis and lactate levels, which, through ERK1/2-dependent phosphorylation of calcineurin, enhances collagen synthesis and PASMC proliferation, thereby contributing to vascular remodeling in PAH [193]. Similarly, Zhao et al. reported that elevated lactate levels promote HIF production by increasing fructose-2,6-bisphosphatase 3 expression, which leads to endothelial cell dysfunction. Damaged PAECs secrete growth factors and pro-inflammatory cytokines, stimulating PASMC proliferation [191]. Additionally, hypoxia further promotes HIF release, enhances glycolysis, and inhibits the tricarboxylic acid cycle, increasing lactate levels and subsequently HIF expression. Additionally, hypoxia may drive PAH development through activation of the PI3K/AKT/mTOR/HIF-1α signaling pathway [191]. Chen et al. demonstrated that hypoxia-induced mitochondrial reactive oxygen species inhibit HIF-1α hydroxylation, triggering glycolysis in PASMCs and lactate accumulation through the upregulation of the HIF-1α/PDK1 & PDK2/p-PDH-E1α axis. They further observed enhanced histone lactylation of HIF-1α target proteins, such as Bmp5, Trpc5, and Kit, which promotes PASMC proliferation [184]. METTL3, an m6A methyltransferase, is significantly upregulated in tumor-associated myeloid cells during lactate accumulation in the tumor microenvironment. Notably, METTL3 is also overexpressed in hypoxia-induced PAH, leading to excessive PASMC proliferation [180]. Zhang et al. found that inhibition of JMJD1C, a Jumonji domain-containing histone demethylase, reduces excessive accumulation of glycolytic enzymes (HK2, PGK1, LDHA) and lactate in the lungs of hypoxic mice. They confirmed that JMJD1C promotes PASMC proliferation and pulmonary vascular remodeling through the activation of STAT3 signaling, highlighting its potential role in regulating metabolic pathways and vascular remodeling in PAH [194]. This finding is corroborated by microarray analysis, suggesting a correlation between JMJD1C and PAH risk [195]. Smolders et al. identified increased glycolysis and endothelial dysfunction as critical factors in the pathophysiology of PAH. Their comparison of endothelial cells from chronic thromboembolic pulmonary hypertension (CTEPH) and PAH with healthy human pulmonary arterial endothelial cells (HPAECs) revealed significantly higher mRNA levels of glycolysis- and lactate-related enzymes (e.g., glucose transporter 1(GLUT1), HK2, LDHA) in PAH-ECs than in HPAECs. In contrast, CTEPH-ECs did not exhibit such an elevation. Additionally, oxidative phosphorylation-related proteins were elevated in PAH-ECs compared to CTEPH-ECs and HPAECs [196]. IL-7, a cytokine, has been shown to shift cellular metabolism from oxidative phosphorylation to aerobic glycolysis, commonly referred to as the Warburg effect. Dysregulation of IL-7 is associated with the development and progression of PAH [197].

Inhibition of glycolysis alleviates PAH

Balestra et al. demonstrated an increase in hexokinase activity, a critical enzyme in glycolysis, in rats with

monocrotaline-induced PAH [198]. This observation is consistent with Zhang et al.'s findings, which reported a metabolic shift toward glycolysis in PAH. Elevated glycolytic activity, characterized by increased levels of HK1 protein and mRNA, was detected in the right ventricle of PAH-affected animals [199]. miRNAs, small non-coding RNAs that regulate gene expression by targeting messenger RNAs for degradation or translational inhibition, have been implicated in cardiovascular diseases [200]. Luo et al. confirmed through both in vitro and in vivo experiments that miR-125a-5p inhibits glycolysis and PASMC proliferation by targeting HK-2, thereby alleviating PAH [201]. Similarly, Caruso et al. investigated miR-124 and found that its downregulation led to disrupted glycolysis and aberrant proliferation in PAECs from patients with IPAH. This dysregulation was attributed to the splicing factor polypyrimidine tract-binding protein 1 and pyruvate kinase muscle isoforms. Overexpression of miR-124 restored normal glycolytic function and cell proliferation in blood outgrowth ECs from hereditary PAH patients [202]. Li et al. identified Shikonin, a naphthoquinone compound derived from the traditional Chinese medicine 'comfrey,' as a potential treatment for monocrotaline-induced PAH in rats. The compound reduced pulmonary vascular remodeling and improved hemodynamics by inhibiting aerobic glycolysis through the downregulation of proteins such as PKM2, p-PKM2, p-ERK, GLUT1, and LDHA [203]. Michelakis reported that compared to healthy lungs, patients with PAH exhibit increased levels of pyruvate dehydrogenase kinase (PDK), an inhibitor of pyruvate dehydrogenase (PDH). This increase in PDK leads to enhanced glycolysis. Treatment with the PDK inhibitor dichloroacetate activates PDH and increases mitochondrial respiration, resulting in reduced mean pulmonary artery pressure and pulmonary vascular resistance, thereby improving lung function [204].

The Akt signaling pathway plays a significant role in the development of hypoxia-induced PAH [205]. Akt nitration activates glycolysis through Glut4 and LDHA. Varghese et al. reported that targeting Akt nitration with nitric oxide-conjugated peptides effectively prevented vascular proliferation in PAH. Treatment with nitric oxide-conjugated peptides inhibited the glycolytic pathway while activating the pentose phosphate pathway and gluconeogenesis, resulting in reduced lactate levels and alleviating vascular proliferation. 3-Bromopyruvate (3-BrPA), a pyruvate and lactate analog, has been demonstrated to exhibit anti-tumor activity by inhibiting key glycolytic enzymes such as HK2 and LDH [206–209]. Zhang et al. reported that 3-BrPA significantly reduced PAH in rats by inhibiting the expression of HK2 and the activity of LDH, resulting in decreased pulmonary arterial pressure and vascular resistance, as well as improved cardiac output. Additionally, 3-BrPA induced apoptosis in PASMCs and inhibited vascular remodeling and right ventricular hypertrophy [210]. Similar findings were reported by Chen et al., who demonstrated that hypoxic rats treated with 3-BrPA exhibited reduced expression of HK2 and decreased lactate levels compared to untreated hypoxic rats. Following hypoxic exposure, HK2 expression and lactate concentration increased in PASMCs; however, both were decreased after 3-BrPA administration. Therefore, they suggested that 3-BrPA inhibits PASMC proliferation and migration by suppressing glycolysis, effectively reversing vascular remodeling in rats with hypoxia-induced PAH [211]. Malenfant et al. highlighted that, in addition to lactate accumulation in the lungs, vasculature, and heart of PAH patients, mitochondrial dysfunction and metabolic impairment extend to skeletal muscles. Their study identified increased glycolytic activity in the skeletal muscles of PAH patients, indicating systemic metabolic disturbances [212]. Interestingly, Boehme's research revealed early PASMC overproliferation in pulmonary overcirculation, characterized by a unique metabolic profile independent of HIF-1α, PDHK1, or increased glycolytic flux [213]. Although the underlying mechanisms of this metabolic shift remain to be fully elucidated, these findings collectively suggest that the regulation of glycolysis affects PASMC proliferation and migration, thereby contributing to vascular remodeling. Overall, the degree of glycolytic activity appears positively correlated with vascular proliferation in PAH, suggesting that targeting glycolysis may influence the pathophysiology of the disease.

Lactate metabolism and PAH

Lactate, the final product of glycolysis, has been implicated in the dysregulation of lactate homeostasis in several studies related to PAH. Xu and colleagues conducted a plasma metabolomics analysis in adult patients with CHD associated with PAH. Through multivariate and univariate statistical analyses, as well as pathway analysis, they identified 28 metabolites from nuclear magnetic resonance spectra. The relative concentrations of these metabolites were analyzed, revealing distinct metabolic profiles in patients with PAH-CHD compared to those with CHD and healthy controls. The key metabolic markers identified included alanine, glucose, glycine, threonine, and lactate. Correlation analysis indicated that lactate levels were significantly associated with mean pulmonary artery pressure, pulmonary vascular resistance, and N-terminal pro-B-type natriuretic peptide [214]. Notably, a study by Morais et al. demonstrated that exercise training mitigated the cardiac metabolic remodeling induced by experimental PAH. In their PAH rat model,

increased glucose oxidation and lactate production were observed in the right ventricle [215]. Additionally, Ider et al. found elevated arterial lactate levels in premature calves with PAH compared to healthy controls [216]. Similar findings were reported by Deng et al. in a single-center retrospective study, where higher lactate levels were observed in patients with connective tissue disease-associated PAH and right heart failure who died from PAH progression compared to survivors [217]. Similarly, Nakamura et al. observed lactate accumulation in PAH, noting increased LDH mRNA, protein levels, and intracellular lactate concentrations in PASMCs from PAH patients under normoxic conditions, compared to non-PAH PASMCs. Interestingly, under hypoxic conditions, these parameters did not show significant increases in PASMCs from PAH patients compared to those from non-PAH patients, likely due to enhanced glycolytic activity in the non-PAH PASMCs under hypoxia [218]. Moreover, Izquierdo-Garcia et al., through metabolomic analysis and in situ molecular imaging of a PAH mouse model, reported significant alterations in the glycolytic pathway and increased lactate concentrations in the lungs and right ventricle [219]. LDH catalyzes the conversion of pyruvate to lactate during anaerobic glycolysis, a process that is detectable in serum. A positive correlation exists between lactate and LDH levels in the body. Several pathological conditions, including necrosis, hypoxia, tissue injury, and malignancies, can lead to elevated serum LDH (S-LDH) levels [220–222]. Hu et al. found that patients with IPAH who had higher S-LDH levels exhibited significantly lower survival rates compared to those with lower S-LDH levels, suggesting that elevated S-LDH could be a risk factor for mortality in IPAH patients [223]. Collectively, these studies suggest that lactate accumulation or the upregulation of related enzymes disrupts lactate homeostasis in PAH. However, additional fundamental research is necessary to clarify whether these lactate abnormalities directly contribute to the onset and progression of PAH through specific mechanistic pathways.

Lactylation and PAH

This paper specifically focuses on the relationship between lactylation and cardiovascular diseases. As noted previously, lactylation may play a critical role in the pathogenesis of PAH [157, 224, 225]. The role of lactylation modifications has been previously discussed, and these pathophysiological effects are intricately linked to the pathogenesis of PAH, encompassing inflammation, oxidative stress, DNA mutations and damage, and cellular aging. However, relevant research on their intrinsic relationship with PAH remains limited. Nonetheless, studies conducted to date have established connections between lactylation modifications and cellular phenotype transformation, cellular metabolism, fibrosis and inflammation in PAH (Fig. 6).

Studies have demonstrated that an imbalance in the M1/M2 macrophage ratio represents a key mechanism in the pathogenesis of PAH. Researchers observed an increase in M2 macrophage markers in the lung tissues of patients with IPAH. In a lactate-rich microenvironment, macrophages exhibited elevated levels of lactylation and underwent polarization towards the M2 phenotype [226]. In another study, high expression of the M2 macrophage polarization marker, mannose receptor I, was detected around the blood vessels of PAH patients. Similarly, PAH mice with low macrophage counts exhibited a reduced M1/M2 ratio and increased proliferation of PASMCs in culture media with low macrophage counts. Interestingly, researchers found that M2 macrophages secrete PDGF-BB and MMP9, which stimulate PASMC proliferation and migration. This suggests that lactylation may promote M2 macrophage polarization, thereby inducing PASMC proliferation and migration, and contributing to the development of PAH [227, 228]. Dysfunction and abnormal proliferation of PASMCs and PAECs are among the etiological factors of PAH. Xiao et al. noted that the Warburg effect plays a critical role in PDGF-induced PASMC proliferation, mediated through the PI3K/AKT/mTOR/HIF-1α pathway. Additionally, during PDGF-promoted PASMC proliferation, researchers observed an increase in intracellular lactate production and accumulation, which may enhance histone lactylation at HIF-1α targets, subsequently affecting the transformation of PASMC phenotypes and ultimately leading to remodeling of the pulmonary artery [184, 192]. Zhao et al. also found that lactate may promote the expression of METTL3 through H3K18 lactylation modifications, thereby influencing the expression of downstream genes [191]. Under hypoxic conditions, the N6-methyladenosine (m6A) binding protein YTHDF2 significantly increases in PASMCs. YTHDF2 recognizes METTL3 and promotes the degradation of PTEN, leading to excessive PASMC proliferation through the activation of the PI3K/AKT signaling pathway. Furthermore, lactylation has been detected in pulmonary fibrosis, a potential cause of hypoxic PAH [183]. Therefore, lactylation may contribute to the pathogenesis and progression of PAH by influencing fibrotic processes.

Lactylation and other cardiovascular diseases

ECs predominantly rely on aerobic glycolysis, also known as the Warburg effect, to meet their energy demands, even under aerobic conditions. Research indicates that more than 80% of adenosine triphosphate in ECs is generated through glycolysis, with lactate being one of the

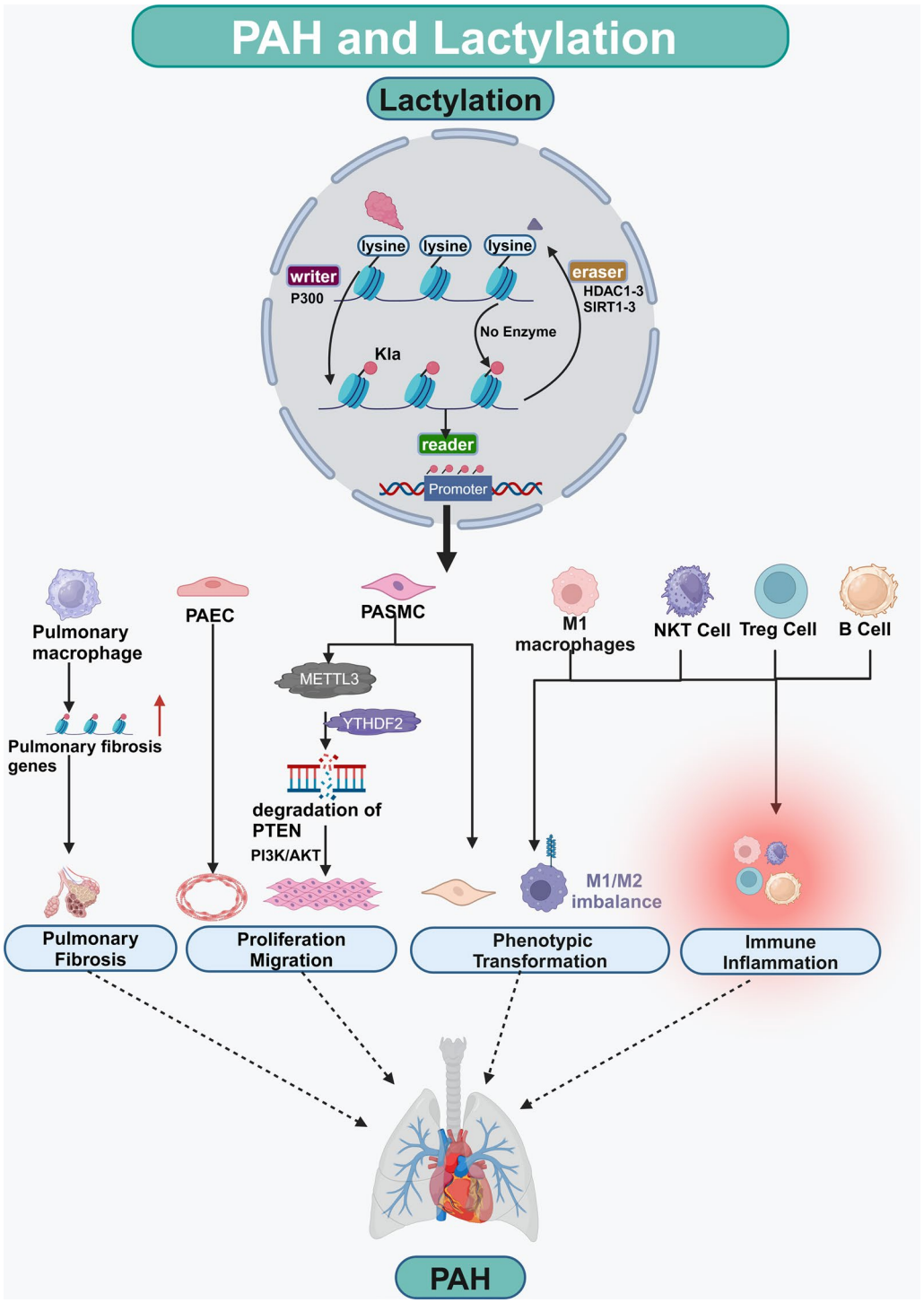

Fig. 6 PAH and lactylation. Lactylation, mediated by the 'writer' enzyme P300, influence PASMC proliferation, macrophage polarization, and immune responses. Key mechanisms include the promotion of pulmonary fibrosis, PASMC proliferation via METTL3/YTHDF2-induced PTEN degradation and PI3K/AKT pathway activation, and M1/M2 macrophage ratio imbalance can drive phenotypic transformation and inflammation. These processes contribute to vascular remodeling and immune dysregulation in PAH. Created using BioRender.com

end products of this metabolic pathway [229–231]. Studies have further suggested that the release of excess lactate from aging cardiomyocytes may stimulate increased glycolysis. This process can lead to elevated protein lactylation, which is associated with the progression of various cardiovascular diseases (Fig. 7) [232, 233].

Cardiovascular calcification

NR4A3, an orphan nuclear receptor, plays a critical regulatory role in atherosclerosis, particularly in processes induced by apolipoprotein A-IV [234]. Ma et al. demonstrated that *NR4A3* enhances glycolysis by directly binding to the promoter regions of the glycolytic genes *ALDOA* and *PFKL*, thereby initiating their transcription. Additionally, histone lactylation has been shown to promote medial calcification both in vitro and in vivo. The absence of *NR4A3* leads to reduced glycolytic activity, lower lactate production, and diminished histone lactylation during calcification. This finding suggests that NR4A3-mediated histone lactylation represents a novel

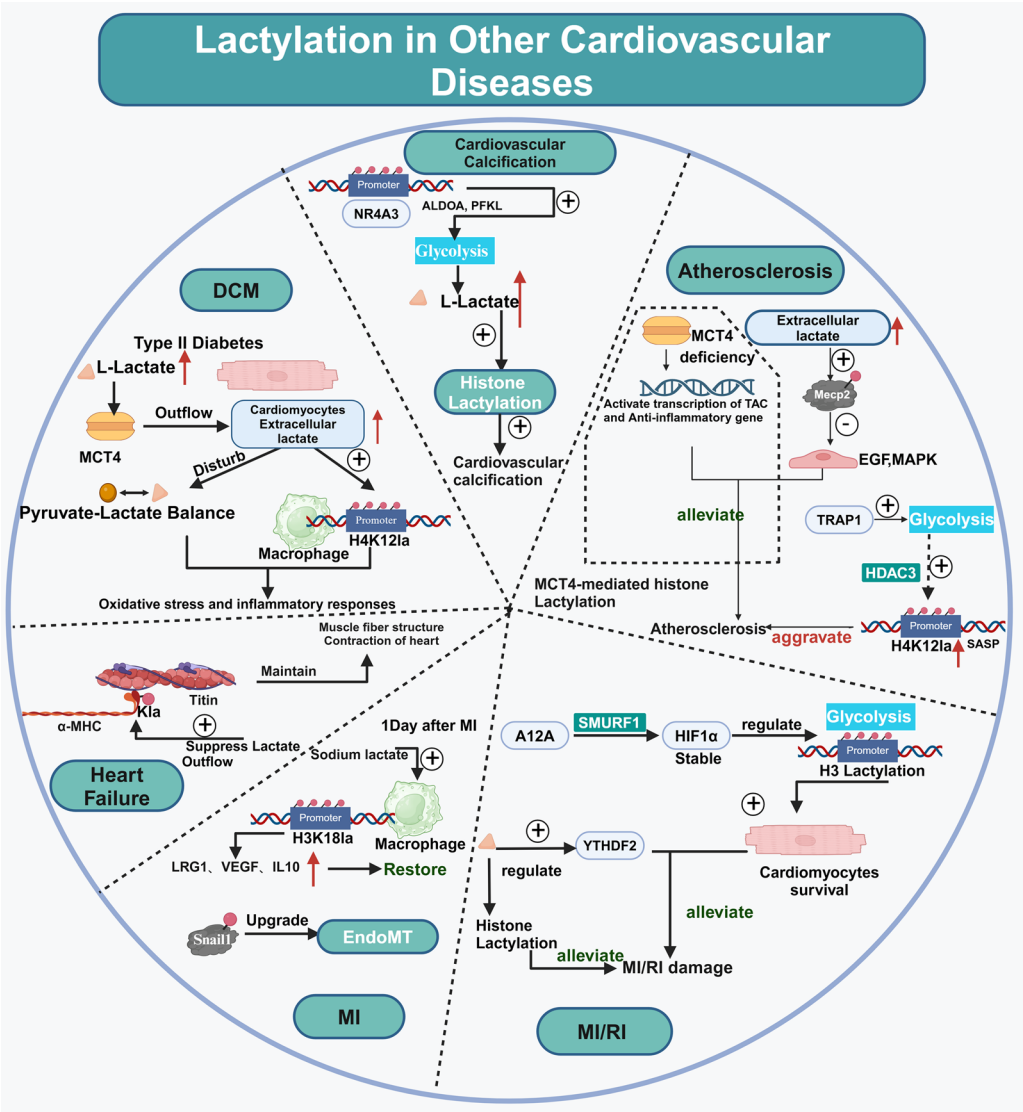

Fig. 7 Lactylation in other cardiovascular diseases. NR4A3 promotes glycolysis and histone lactylation, contributing to cardiovascular calcification. In atherosclerosis, MCT4 deficiency reduces lactylation, alleviating inflammation, while TRAP1 and HDAC3-mediated H4K12la aggravates it. In MI/RI, HSP A12A stabilizes HIF1α, enhancing H3la and cardiomyocyte survival. Elevated lactate efflux in diabetic cardiomyopathy increases H4K12 lactylation, inducing oxidative stress. In heart failure, α-MHC lactylation preserves muscle integrity, and in MI, sodium lactate-induced H3K18la promotes cardiac repair. (Abbreviations: EGF, epidermal growth factor; MAPK, mitogen-activated protein kinase; EndoMT, endothelial-to-mesenchymal transition; LRG1, leucine rich alpha-2-glycoprotein 1.) Created using BioRender.com

metabolic-epigenetic signaling pathway involved in arterial medial calcification [235]. Furthermore, Wang et al. corroborated the role of lactylation in cardiovascular calcification, reporting that andrographolide mitigates calcific aortic valve disease by modulating H3K18 lactylation modifications through p300, thereby reducing the extent of calcification [236].

Atherosclerosis

Zhang et al. elucidated a significant association between histone lactylation, mediated by MCT4, and the progression of atherosclerosis. Using gene manipulation and proteolytic targeting chimera technology, their research revealed that MCT4 deficiency alleviates atherosclerosis. This effect is mediated through the activation of transcriptional pathways for anti-inflammatory genes and tricarboxylic acid cycle genes, promoting local repair and restoring homeostasis [237]. Conversely, Wang et al. demonstrated that both physical exercise and exogenous lactate administration increase lysine lactylation of Mecp2. This modification inhibits the expression of epidermal growth factor and mitigates mitogen-activated protein kinase activity in ECs, thereby slowing the progression of atherosclerosis [159]. In the study by Li et al., overexpression of TRAP1 resulted in increased glycolysis, leading to elevated lactate levels. Subsequently, histone deacetylase HDAC3 enhances the level of H4K12 lactylation, promoting the transcription of newly formed SASP factors and exacerbating atherosclerosis [190].

Myocardial ischemia–reperfusion injury (MI/RI)

MI/RI is a pathophysiological phenomenon characterized by exacerbated tissue damage following the restoration of blood flow to the ischemic myocardium, which occurs subsequent to an acute myocardial infarction [238]. Evidence from various in vitro and in vivo studies indicates that epigenetic mechanisms, including histone modifications, DNA methylation, non-coding RNAs, and m6A methylation, play crucial roles in MI/RI [239]. Yu et al. demonstrated that heat shock protein A12A facilitates the stabilization of the HIF1α protein via Smurf1, thereby maintaining the balance of aerobic glycolysis and promoting histone H3 lactylation in cardiomyocytes. This process improves cell survival and offers protection against MI/RI injury [240]. In contrast, Xu et al. observed that inhibiting the N6-methyladenosine RNA-binding protein YTHDF2 alleviates acute damage and pathological remodeling associated with MI/RI. Lactate appears to modulate cardiomyocyte responses by enhancing protein lactylation and YTHDF2 expression, suggesting that reducing lactylation could be a promising therapeutic strategy for MI/RI [241]. Nevertheless, the divergent findings from these studies regarding the role of lactylation in MI/RI underscore the necessity for further research to resolve these inconsistencies.

Diabetic cardiomyopathy

Diabetic cardiomyopathy, a significant cause of mortality among diabetic patients, involves various complex pathophysiological mechanisms [242]. Ma et al. observed a significant elevation in lactate levels in individuals with type 2 diabetes, attributing this increase to the abnormal upregulation of MCT4 on the plasma membranes of cardiomyocytes, leading to excessive lactate efflux. This imbalance in lactate and pyruvate levels within cardiomyocytes triggers oxidative stress and inflammatory responses, exacerbating myocardial damage. Furthermore, they demonstrated that elevated lactate efflux enhances histone H4K12 lactylation in macrophages, thereby promoting an inflammatory microenvironment [243].

Heart failure

Studies indicate that lactylation of α-myosin heavy chain (α-MHC) plays a protective role in maintaining muscle fiber structure and function, potentially mitigating heart failure. Lactylation enhances the binding between α-MHC and titin, thereby preserving the integrity of muscle fiber structure and myocardial contractility. Consequently, restoring α-MHC lactylation and its interaction with titin through modulation of lactate levels could represent a potential therapeutic approach for heart failure. Notably, inhibiting lactate efflux may similarly achieve this effect [244, 245].

Myocardial infarction (MI)

Lactylation plays a protective role during MI, as clinical trials have demonstrated that administering sodium lactate within one day post-MI can reduce macrophage-mediated inflammatory responses, resulting in improved heart function [246]. Experimental evidence suggests that early remote activation of reparative transcription in monocytes following MI is mediated by H3K18 lactylation. This modification enhances the expression of key repair genes in macrophages, including leucine-rich α-2-glycoprotein 1, VEGF, and interleukin-10, which are crucial for recovery of heart function post-MI [247]. Furthermore, non-histone lactylation is implicated in the pathophysiology of MI as well. Research conducted by Fan et al. employed intraperitoneal injections of sodium lactate in MI model mice, revealing that lactate induces the lactylation of Snail1, subsequently promoting endothelial-to-mesenchymal transition following myocardial infarction [160]. This suggests that lactylation may be a crucial factor in mediating reparative processes during cardiac injury.

Future perspective

Lactylation, a novel form of protein translational modification, is still in the early stages of research; however, it has shown significant potential in biomedical research and clinical applications. Given the limited research on the regulatory mechanisms of lactylation in PAH, this paper primarily reviews the impact of abnormal glycolytic activity and lactate metabolism on PAH. Several studies have reported elevated lactate levels and glycolytic activity in PAH, contributing to PASMC proliferation, a key factor in the progression of the disease. Furthermore, lactylation also plays a role in other cardiovascular conditions, including vascular calcification, atherosclerosis, MI/RI, diabetic cardiomyopathy, heart failure, and myocardial infarction [232, 233].

Lactylation have made significant progress in tumor research, but there is a lack of related studies in PAH. The Warburg effect is an important metabolic process in tumor metabolism, and a similar phenomenon, namely aerobic glycolysis, has recently been observed in PAH. However, the specific mechanisms remain unclear. Lactate, a product of the Warburg effect, plays a crucial role in lactylation and PAH. Therefore, whether the Warburg effect induces the development of PAH through lactylation still needs further verification [230].

Studies have shown that the effects of lactylation include inflammation, oxidative stress, DNA damage, cellular aging, and fibrosis. Interestingly, these pathophysiological processes are closely associated with PAH. Future studies should focus on specific mechanistic pathways to explore how lactylation influence the onset and progression of PAH [150, 167–169].

Lactate levels regulated by glycolysis are associated with metabolic reprogramming, gene expression, histone lactylation, and non-histone lactylation, serving as epigenetic modification markers for glycolytic switches. Combining the epigenomics of histone lactylation sites with the metabolomics of lactate may reveal new molecular targets that regulate the expression levels of metabolic genes through epigenetic mechanisms, thereby altering the metabolome [248]. Additionally, the "writer" p300 and "eraser" HDAC1-3, SIRT1-3 involved in histone lactylation modifications have been confirmed, whereas studies on the related "reader" proteins remain insufficient. Future research should focus on the specific molecular mechanisms underlying histone lactylation modifications to identify more precise targets. Lactylation modifications of various non-histone and other proteins have been observed in multiple diseases, and future studies could explore their potential roles in PAH. TRAP1, through lactylation, promotes the transcription of newly formed SASP, leading to increased proliferation of vascular smooth muscle cells and exacerbating atherosclerosis. Thus, whether TRAP1 also plays a role in the pathogenesis of PAH warrants further investigation [190]. Studies have shown that NUSAP1 influences pancreatic ductal adenocarcinoma through lactylation modifications affecting glycolysis. Abnormal glycolysis in PAH has been observed in multiple studies; therefore, future research should investigate whether NUSAP1 can influence the onset of PAH through the NUSAP1-LDHA-glycolysis-lactate conduit loop [187].

Emerging therapeutic strategies that target lactylation and its associated signaling pathways show great potential for treating PAH. The primary strategy focuses on inhibiting glycolytic activity, The main molecules involved in the study are miR-125a-5p [201], miR-124 [202], Shikonin [203], NP [206–209], and 3-BrPA [210]. Although these molecules and compounds have demonstrated potential in experimental settings, their clinical efficacy has yet to be validated. Additionally, it remains unclear whether targeting glycolysis-related genes to improve PAH will exert effects by influencing lactylation modifications. Therefore, further studies are needed to elucidate the underlying mechanisms.

Lactate, a key metabolic intermediate and signaling molecule, plays a dual role in the progression of cardiovascular diseases. For instance, in conditions such as atherosclerosis and myocardial infarction, lactylation is considered a promoting factor in disease progression; however, in HF, lactylation is viewed as a protective factor. Currently, lactate is primarily viewed as a prognostic marker in clinical practice rather than a therapeutic target. Therefore, future research should focus on elucidating the specific effects of lactate levels on various pathophysiological responses, thereby clarifying the potential benefits and risks of lactate in clinical settings [244, 245].

The potential clinical applications of lactylation are substantial. Investigating the relationship between lactylation and PAH may uncover novel biomarkers linked to PAH. These biomarkers could be employed for early diagnosis, monitoring treatment responses, and assessing prognosis.

Conclusion

PAH is a rare and severe subtype of PH that affects thousands of patients globally, posing significant challenges for healthcare professionals. The underlying pathophysiology of PAH is exceedingly complex. Recent research has indicated that lactylation, a novel form of epigenetic modification, along with its associated signaling pathways, plays a critical role in the pathogenesis of PAH and other cardiovascular diseases. Moreover, the role of lactate metabolism in the progression of PAH has been emphasized. Future research should concentrate

on elucidating the specific mechanisms of lactylation in PAH to facilitate innovative therapeutic and diagnostic approaches, ultimately allowing for more effective management of this complex condition. In-depth mechanistic studies may identify key genes and proteases associated with PAH, paving the way for the development of small-molecule drugs and biologics targeting these pathways, thereby offering new strategies for disease treatment.

Abbreviations

PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
PAECs	Pulmonary arterial endothelial cells
CHD	Congenital heart disease
IPAH	Identified idiopathic pulmonary arterial hypertension
PASMCs	Pulmonary artery smooth muscle cells
ECs	Endothelial cells
MCUC	Mitochondrial calcium uniporter complex
MCT	Monocarboxylate transporter
miRNAs	MicroRNAs
IL-6	Interleukin-6
TNF-α	Tumor necrosis factor-alpha
NF-κB	Nuclear factor-kappa B
HDACs	Histone deacetylases
PPHN	Persistent pulmonary hypertension of the newborn
NO	Nitric oxide
eNOS	Endothelial nitric oxide synthase
SOD2	Superoxide dismutase 2
HIF-1	Hypoxia-inducible factor 1
Tregs	Regulatory T cells
H3K18la	Lactylation of histone 3 lysine 18
GLO1	Glyoxalase 1
LGSH	Lactoyl-glutathione
CCNE2	Cyclin E2
HMGB1	High mobility group box-1
UPS	Ubiquitin–proteasome system
PKM2	Pyruvate kinase M2
LDHA	Lactate dehydrogenase A
HSCs	Hepatic stellate cells
AD	Alzheimer's disease
SASP	Senescence-associated secretory phenotype
TRAP1	Tumor necrosis factor receptor-associated protein 1
CTEPH	Chronic thromboembolic pulmonary hypertension
HPAECs	Human pulmonary arterial endothelial cells
HK1	Hexokinase-1
PDK	Pyruvate dehydrogenase kinase
PDH	Pyruvate dehydrogenase
3-BrPA	3-Bromopyruvate
S-LDH	Serum LDH
α-MHC	α-Myosin heavy chain
MI/RI	Myocardial ischemia–reperfusion injury
MI	Myocardial infarction
GLUT	Glucose transporter
METTL3	Methyltransferase-like 3
PARP-1	Poly(ADP-ribose) polymerase 1
GLO2	Glyoxalase 2
m6A	N6-methyladenosine
HK2	Hexokinase-2
WHO	World health organization
KCNK3	Member 3 of the potassium channel subfamily K
CCL2/MCP-1	C–C Motif Chemokine Ligand 2
CD20	Cluster of differentiation 20
HIV	Human immunodeficiency virus
PVOD	Pulmonary veno-occlusive disease
PCH	Pulmonary capillary haemangiomatosis
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFmrEF	Heart failure with mid-range ejection fraction
PA	Pulmonary artery
EEC	Erythropoietin-independent erythroid colony
Mito	Mitochondrial
BMPR2	Bone morphogenetic protein receptor type 2
16αOHE1	16α-Hydroxyestrone
DNMT	DNA methylation
Me	Methylation
FOXP3	Forkhead box protein P3
TIMs	Tumor-infiltrating myeloid cells
FAS	Fatty acid synthase
EGF	Epidermal growth factor
MAPK	Mitogen-activated protein kinase
EndoMT	Endothelial-to-mesenchymal transition
LRG1	Leucine rich alpha-2-glycoprotein 1
TME	Tumor microenvironment
MG	Methylglyoxal
GSH	Glutathione
CD147	Cluster of differentiation 147
GPR81	A G protein-coupled receptor that regulates lactate transport
ATP	Adenosine triphosphate
cAMP	Cyclic adenosine monophosphate
Kla	Lactylation

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Author contributions
Y.H. H and T.Y. P contributed to the study's conception and design. T.Y. P wrote the manuscript. J.M. L, X.L. Z and C.Z. completed the review editing. All authors revised the article and approved the final version.

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Declarations

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Publisher's Note

Yu-hu He is a Researcher and Ph.D. supervisor in the Department of Cardiology at Xiangya Second Hospital. His research focuses on cardiovascular diseases, particularly in the areas of pulmonary hypertension and vascular biology. In recent years, Dr. He has authored over 10 publications as the first or corresponding author in high-impact journals, including Circulation Research (IF = 23), American Journal of Respiratory and Critical Care Medicine (IF = 30), Journal of Clinical Investigation, and Arteriosclerosis, Thrombosis, and Vascular Biology. Dr. He has received several prestigious grants, including the National Natural Science Foundation of China (NSFC) Excellent Young Scientists Fund, two NSFC General Program grants, and one Youth Program grant. He also leads two projects funded by the Hunan Provincial Natural Science Foundation and has co-authored a popular science book as an associate editor. His academic contributions have earned him notable awards, such as the OCC-East Rising Star Award and the ATS Gong Lansheng Young Investigator Award (First Prize).