Glycolysis modulation: New therapeutic strategies to improve pulmonary hypertension (Review)

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Abstract. Pulmonary hypertension (PH) is a progressive life-threatening cardiopulmonary vascular disease involving various pathological mechanisms, including hypoxia, cellular metabolism, inflammation, abnormal proliferation and apoptosis. Specifically, metabolism has attracted the most attention. Glucose metabolism is essential to maintain the cardiopulmonary vascular function. However, once exposed to a noxious stimulus, intracellular glucose metabolism changes or switches to an alternative pathway more suitable for adaptation, which is known as metabolic reprogramming. By promoting the switch from oxidative phosphorylation to glycolysis, cellular metabolic reprogramming plays an important role in PH development. Suppression of glucose oxidation and secondary upregulation of glycolysis are responsible for various features of PH, including the proliferation and apoptosis resistance of pulmonary artery endothelial and smooth muscle cells. In the present review, the roles and importance of the glucose metabolism shift were discussed to aid in the development of new treatment approaches for PH.

Contents

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1. Introduction

Pulmonary hypertension (PH) refers to increased pressure (>20 mmHg) in the pulmonary arteries. Based on its etiology, pathophysiology and treatment, PH can be divided into five clinical groups: Pulmonary arterial hypertension (PAH, group I), PH in secondary to left-sided cardiac disease (group II), PH resulting from chronic lung illness (group III), chronic thromboembolic PH (group IV), and unclear and/or multifactorial PH (group) (1). Different etiologies are attributed to different forms of PH. Although variations are observed among the different forms, pulmonary vascular remodeling is the predominant pathological change characterizing the disease (2). Improved vascular remodeling is important for PH treatment. Various targeted agents used to treat PH have significantly improved the exercise tolerance and quality of life of patients with PH; however, the mortality rate remains high (3). Only limited treatment options are available for PH, with no therapies that can effectively reverse the late structural

vascular changes associated with PH. This chronic, progressive and multi-causal condition affects ~1% of the global population, with most >65 years of age, and >50% of the affected patients exhibiting comorbid heart failure (HF) (4). Therefore, understanding the pathogenesis of PH is necessary to develop novel therapeutic modalities.

Over the years, numerous mechanisms have been elucidated, from vasodilation, vasoconstriction and endothelial dysfunction to more sophisticated regulatory mechanisms of cellular signaling pathways, such as hypoxia, metabolism, proliferation, apoptosis, aging and inflammation (Fig. 1). In 2020, five popular topics associated with PH (hypoxia, cellular metabolism, inflammation, abnormal proliferation and personalized medicine) were discussed, highlighting the challenges and treatment opportunities at the 62nd Thomas L. Petty Aspen Lung Conference (5). Metabolic abnormalities, including abnormalities in the metabolism of glucose, fatty acids, glutamine, and arginine, are universal features of PH widely observed in the lungs and hearts of patients with PH and in the pulmonary vascular cells isolated from patients with PH and PH rodent models (6-10). Glucose metabolism, the hub of cellular energy metabolism, is involved in numerous metabolic pathways and plays an important role in PH development. In the present review, the roles of cellular metabolism in PH development were discussed, focusing on the impact of impaired glucose metabolism on the pulmonary vasculature. Furthermore, prospective therapeutic techniques were outlined based on the discussed translational findings.

2. Glucose metabolism in PH

Glucose is the primary energy source for most eukaryotic cells. Initially, glucose undergoes glycolysis in the cytoplasm, where it is metabolized into pyruvate, yielding modest quantities of the high-energy molecules, ATP and NADH. In the presence of sufficient oxygen, pyruvate derived from glycolysis is further converted to acetyl-CoA in the mitochondria, which undergoes the tricarboxylic acid cycle and redox reactions along the electron transport chain, known as oxidative phosphorylation (OXPHOS). This process leads to the binding of the terminal electron acceptor, molecular oxygen, to produce more ATP. However, in the absence of sufficient oxygen, pyruvate does not undergo OXPHOS and instead generates lactate via anaerobic respiration to produce two ATP molecules (Fig. 2) (11). The net ATP generated from OXPHOS of one glucose molecule is 32, which is almost 16-times more than that generated from glycolysis and meets the energy requirements for cell metabolism and proliferation.

In 1924, Warburg *et al* (12) observed an interesting phenomenon, in which tumor cells exhibited a preference for glycolysis to promote proliferation, regardless of the presence of sufficient oxygen. This phenomenon for energy supply that requires neither oxygen nor mitochondria is known as the 'Warburg effect' and is characterized by high glucose uptake, lactate secretion and anaerobic energy production (13). At each stage of the cell cycle, proliferating cells require nutrients, energy and biosynthetic machinery to replicate proteins, lipids and nucleic acids. Hence, proliferating cells adopt a metabolic approach different from that of the non-proliferating cells (5). The metabolic preference of rapidly proliferating cancer cells for low ATP production is possibly because glycolysis generates ATP more rapidly and efficiently than the more intricate OXPHOS process. Furthermore, glycolysis uses the most abundant extracellular nutrient, glucose, to synthesize glucose-derived molecules crucial for sustaining cell proliferation and biomass production via essential biosynthetic pathways (14). Energy metabolism without mitochondria prevents apoptosis induced by mitochondrial dysfunction (6,15). The Warburg effect is observed in >80% of all cancers, and this metabolic shift from complex OXPHOS to relatively simple glycolysis promotes rapid cell proliferation, and overcoming this effect is a key focus of cancer research (16). Similar to cancer, PH is a highly lethal condition characterized by excessive proliferation and apoptotic resistance in specific cell types, including fibroblasts, pulmonary artery endothelial cells (PAECs), and pulmonary artery smooth muscle cells (PASMCs); it is also described as 'cancer' of the cardiovascular diseases (17). Numerous studies have investigated the relationship between abnormal glucose metabolism and development of PH to facilitate its treatment.

3. Adaptive metabolic shift in PH contributes to cell proliferation

Although vasodilators are important for PH management, current research indicates that proliferative vascular remodeling, rather than vasoconstriction, is the underlying cause of PH (18). Pulmonary vascular remodeling is essential for PH development and causes histopathological changes similar to those in cancer, with the aberrant proliferation and apoptotic resistance of PAECs and PASMCs as the central components. The Warburg effect is a contributing factor to PH, as its characteristic features, such as high glucose uptake, lactate secretion, and anaerobic energy production, are associated with PH (19,20). In patients with PH, positron emission tomography (PET) shows significantly increased fluorodeoxyglucose [(^{18}F)FDG] uptake by the lungs and right ventricle (21,22). Marsboom *et al* (23) and Zhao *et al* (24) reported that elevated [^{18}F]FDG uptake by the lungs is due to increased uptake of [^{18}F]FDG by PAECs and PASMCs. Blood outgrowth endothelial cells of patients with heritable PAH (HPAH) and idiopathic PAH (IPAH) carrying the bone morphogenetic protein receptor 2 (*BMPR2*) mutation exhibit significantly higher lactate secretion than that by the control cells. Lactate levels are also high in the supernatants of HPAH and IPAH cells (25). Furthermore, ATP production is significantly higher in PAH PASMCs than in non-PAH PASMCs under hypoxia, suggesting increased anaerobic energy production in PAH (26). Numerous studies on patients with PH and rodent models have reported impaired glucose OXPHOS and/or a shift to glycolysis in PAECs (23,27,28) and PASMCs (8,29,30), which are highly dependent on glycolysis to promote proliferation. This metabolic shift helps to maintain cellular energy homeostasis and reduce the dependency of cells on oxygen, making it easier for the cells to survive in a hypoxic environment (31). Increased glycolysis is always accompanied by the inhibition of OXPHOS, which reduces the exposure to the mitochondrial pro-apoptotic substances, reactive oxygen species (ROS) and cytochrome C, thereby inhibiting apoptosis (6). Therefore, metabolic shift to glycolysis promotes proliferation and apoptosis resistance in PAECs and PASMCs, representing an attractive therapeutic approach for PH (Fig. 3).

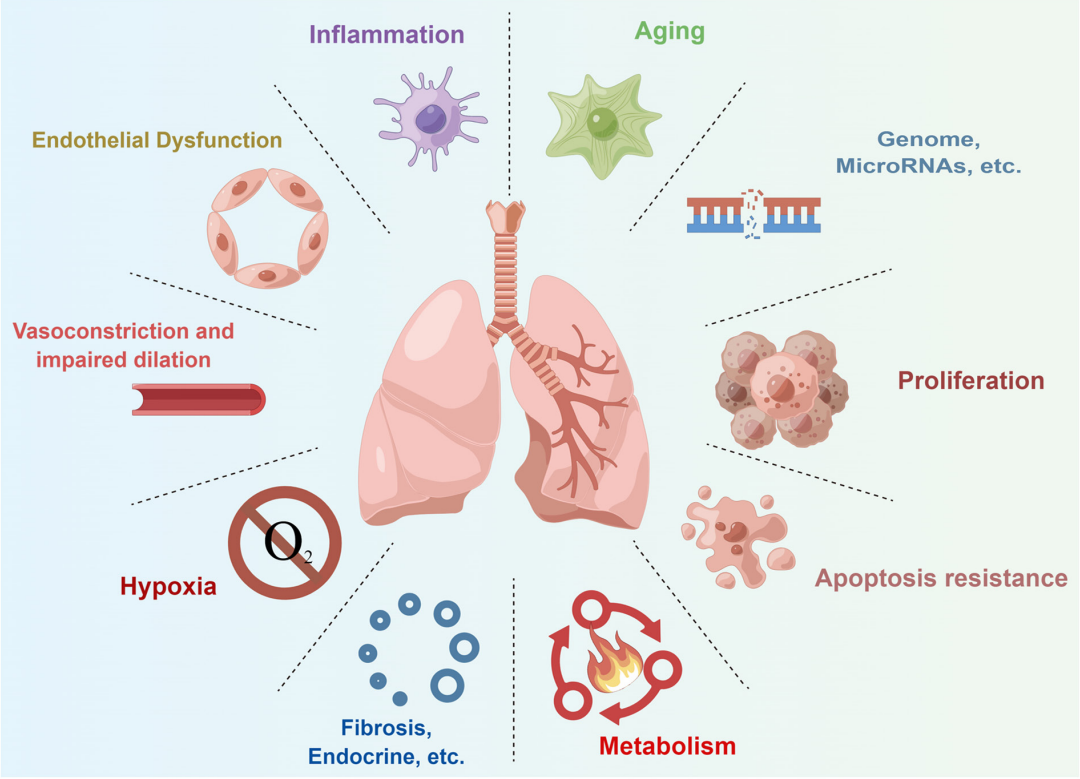

Figure 1. Some of the main mechanisms that contribute to the development of PH, of which metabolism is currently one of the most focused topics of research. The figure was created using Figdraw (www.figdraw.com).

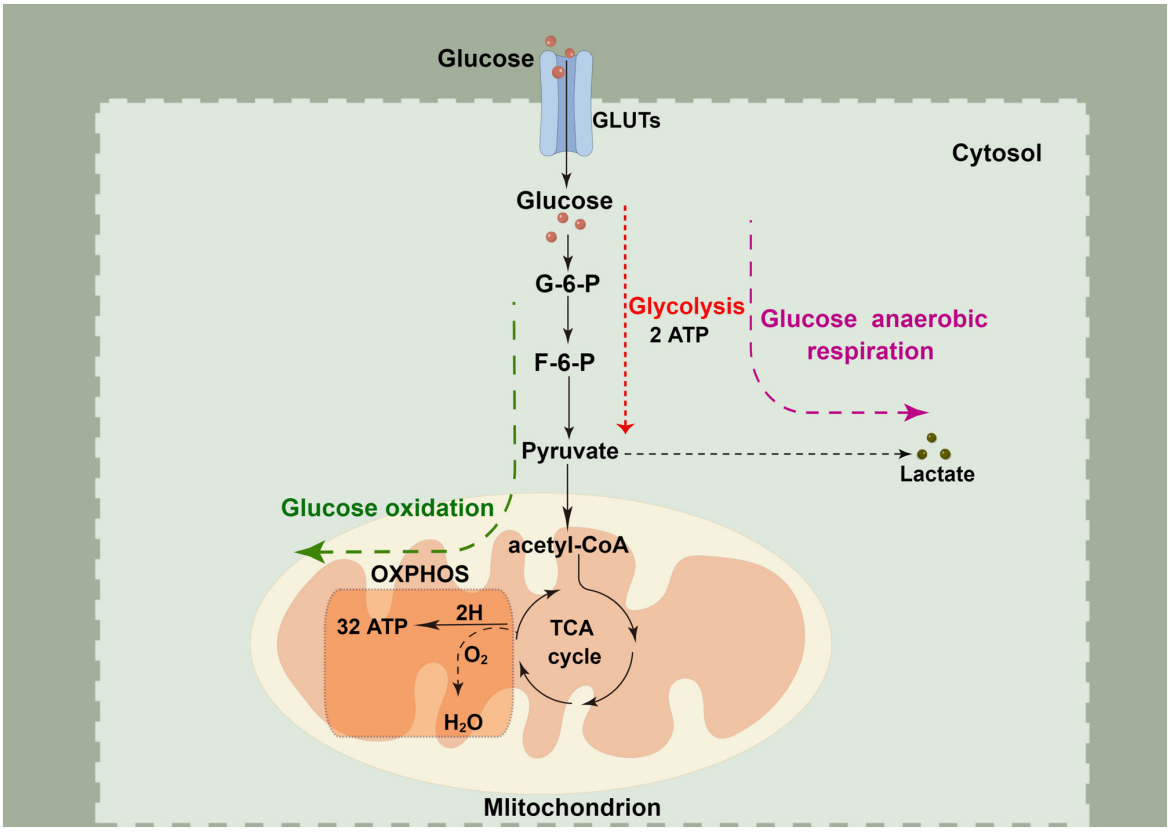

Figure 2. A simplified diagram of cellular glucose metabolism. Glycolysis takes place in the cytosol and converts glucose to pyruvate with the production of 2 ATP molecules. In the absence of sufficient oxygen, glycolysis does not proceed to oxidative phosphorylation. Instead, anaerobic respiration occurs and lactate is produced. Under aerobic conditions, pyruvate enters the TCA cycle to produce 32 ATP molecules. G6P, Glucose-6-phosphate; F6P, fructose-6-phosphate; F1,6BP, fructose-1,6-Bisphosphate; ATP, adenosine triphosphate; TCA, tricarboxylic acid; OXPHOS, oxidative phosphorylation. The figure was created using Figdraw (www.figdraw.com).

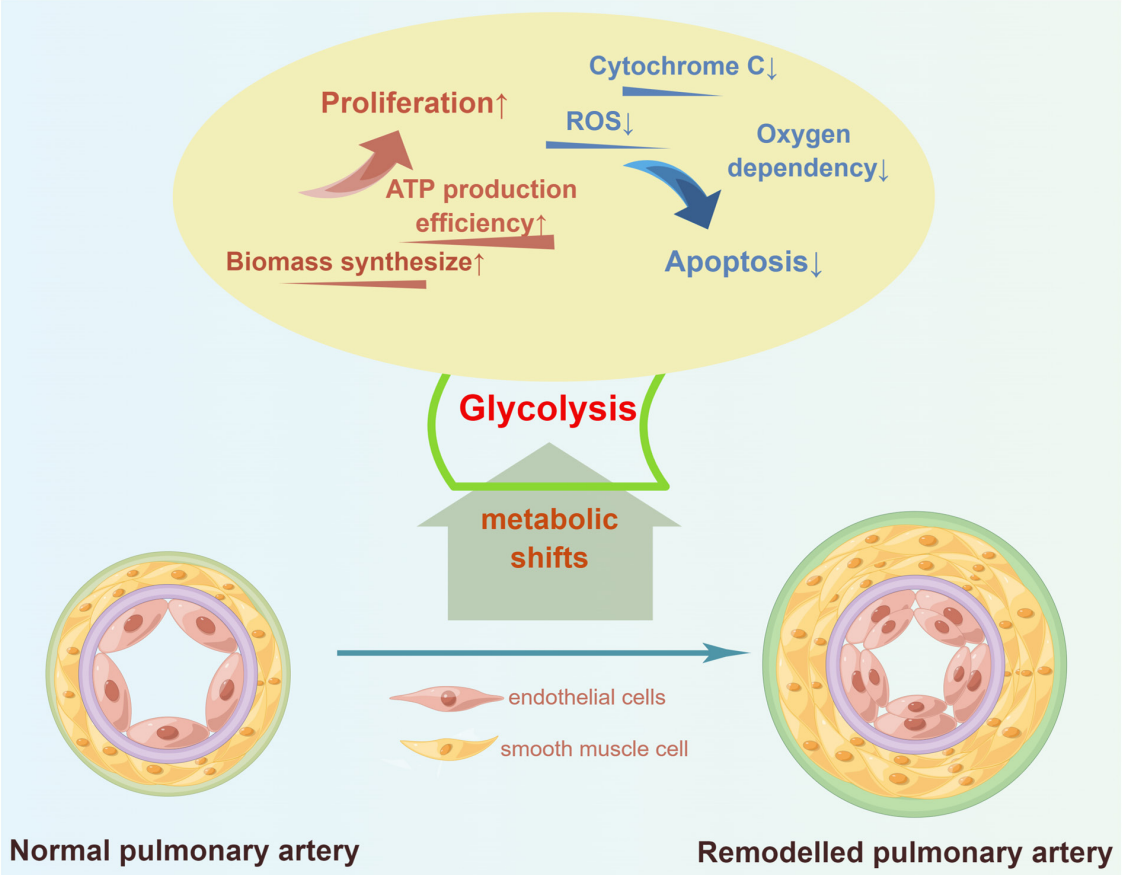

Figure 3. Mechanisms of glycolysis that contribute to cell proliferation. The high rate and efficiency of ATP production by glycolysis and its contribution to the biosynthesis of glucose sources. Glycolysis reduces cellular dependence on oxygen and reduces the production of pro-apoptotic substances (ROS and cytochrome C). ATP, adenosine triphosphate; ROS, reactive oxygen species. The figure was created using Figdraw (www.figdraw.com).

4. Metabolic shift mechanism in PH

The precise molecular and biochemical changes that drive the metabolic shift in PH remain unknown. Several essential regulatory pathways have been identified. Specifically, stability of hypoxia-inducible factor (HIF)-1α under hypoxia or normoxia is the primary mechanism involved in the metabolic shift in PH (32).

5. HIF-1α drives the metabolic shift to glycolysis

HIF-1α is one of the two subunits that assemble HIF-1. Under normoxic conditions, prolyl hydroxylase (PHD) uses O_2 as a substrate to hydroxylate the proline residue in HIF-1α, triggering its binding to von Hippel-Lindau and subsequent degradation by the proteasome. Under hypoxia, PHD activity is reduced, leading to HIF-1α stabilization and nuclear translocation. In the nucleus, HIF-1α binds to constitutively expressed HIF-1β to form the HIF-1 complex, which recruits cofactor proteins to HIF-binding sites in the hypoxia response element and activates the transcription of multiple target genes involved in cell proliferation, angiogenesis, survival and metabolic processes (33-35).

Activation of HIF-1α is closely related to the metabolic shift in PH. HIF-1α activation plays a crucial role in driving glycolysis by modulating various glycolysis-related enzymes, including glucose transporters (GLUTs) (23,36,37), pyruvate dehydrogenase (PDH) kinase 1 (PDK1) (38), hexokinase 1/2 (HK1/2) (39) and lactate dehydrogenase A (LDHA) (40,41). Specifically, upregulation of PDK1 by HIF-1α is a critical mediator linking intracellular hypoxia to the metabolic shift. PDK1 inactivates PDH, a key enzyme for glucose oxidation (GO) in the mitochondria, yielding pyruvate that cannot be catabolized to acetyl-CoA and is accumulated in the cytoplasm to undergo anaerobic respiration and produce lactate. Glycolysis produces ATP with high efficiency but low output; therefore, HIF-1α mediates the entry of large amounts of glucose into the cytosol for glycolysis by upregulating the levels of GLUTs, HK2 and LDHA to maintain energy homeostasis (42).

In addition to hypoxia, numerous factors contribute to the upregulation of HIF-1α under normoxic conditions. These include mitochondrial abnormalities (6), ROS (43), metal ions (44), nitric oxide (NO) production (27) and mechanical stretch (45), all of which act as significant inducers of HIF-1α in pulmonary vascular cells (Fig. 4). Mitochondria are the cellular oxygen sensors that affect HIF-1α activity and regulate cellular glucose metabolism by regulating the intracellular redox status through the superoxide dismutase 2 (SOD2)-H_2O_2-HIF-1α-PDK-PDH pathway (46,47). In PH, epigenetic silencing of *SOD2* in mitochondria leads to decreased ROS (H_2O_2) production, resulting in pseudo-hypoxia in cells, which causes abnormal activation of HIF-1α (48). Iron is a cofactor for numerous enzymes, including PHD. Iron deficiency increases morbidity and mortality in IPAH (49). In experimental PH, feeding rats an iron-deficient diet induces the accumulation of HIF-1α and promotes the upregulation of

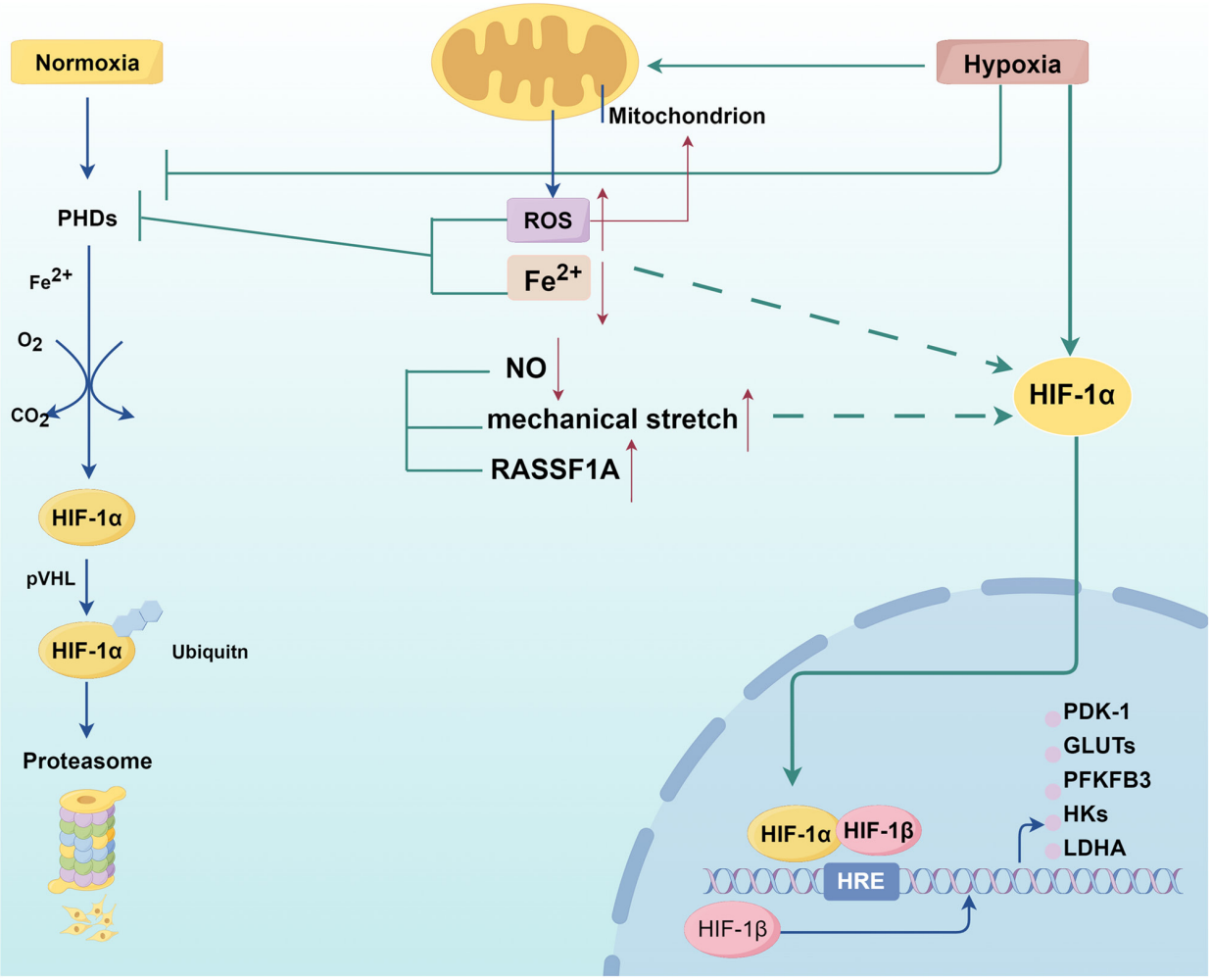

Figure 4. Mechanisms of HIF-1α stabilization. In addition to hypoxia, HIF-1α was significantly stabilized and increased nuclear translocation in pulmonary vascular cells by ROS, metal ions, NO generation, mechanical stretch and RASSF1A, which enhanced the transcription of enzymes involved in glycolysis. The figure was created using Figdraw (www.figdraw.com).

GLUT1, HK1 and PDK1 levels in their pulmonary arteries, but iron replacement therapy (carboxymethyl ferrous, 75 mg/kg) reduces the pulmonary artery pressure (PAP) and alleviates pulmonary artery remodeling (44). Endothelin 1, a potent vasoconstrictor, induces stabilization of the glycolytic switch HIF-1α under normoxia by promoting ROS production and calcium-dependent dephosphorylation of the receptor for activated C kinase 1, leading to inhibition of PHD2 activity (50,51). NO generated by endothelial cells is essential for vascular homeostasis, as evidenced by the lack of NO in conditions associated with cardiopulmonary vascular diseases (52). By preventing the stabilization of HIF-1α by increasing PHD-mediated degradation, NO also modulates the cellular response to hypoxia (53). Fijalkowska *et al* (27) reported that reduced NO production leads to the loss of HIF-1α inhibition in PAECs under normoxic conditions, thus contributing to the glycolytic shift. Previously, another mechanism contributing to the stabilization of HIF-1α has been reported in PASMCs. Ras association domain family 1A enhances HIF-1α stability and nuclear entry, leading to the trans-activation of target genes *PDK1*, *HK2*, and *LDHA* (54). In addition to the aforementioned chemical triggers, mechanical stretch was identified by Wedgwood *et al* (45) as an independent regulator of HIF-1α. Mechanical stretch of PASMCs leads to mitochondrial complex III-mediated ROS formation, which inhibits PHD2 and activates HIF-1α (45).

These studies highlight the importance of the HIF-1 system in facilitating the metabolic shift, known as the Warburg effect, in pulmonary vascular cells. Although hypoxia is an important factor, it is not an absolute necessity for this effect. Therefore, interventions aimed at inhibiting the activity of HIF-1α or its downstream targets show potential as PH therapy.

6. Role of the Notch signaling pathway in PH metabolic shift

Notch belongs to a family of single-channel transmembrane receptor proteins. Four different Notch receptors (Notch1-4) have been identified in mammals and can bind to five different ligands: Three Delt-like (DLL1, DLL3 and DLL4) and two Jagged (Jag1 and Jag2) ligands (55). After ligand engagement, the Notch receptor is cut by γ-secretase, releasing the Notch intracellular domain (NICD), which is transported to the nucleus as it modulates nuclear localization signals. In the nucleus, NICD binds to the DNA-binding protein, CSL (also known as the recombination signal sequence-binding

protein Jκ), which controls numerous cellular processes, including cell growth, development, proliferation and apoptosis, via the transcription of Notch targets (HEY1, HES1 and Myc) and their downstream targets; this is an important pathway that determines the cell fate (56,57). Notch1 and Notch3 levels are upregulated in PAECs and PASMCs and mediate their proliferation and apoptosis resistance, which are involved in the progression of PH (58,59). A functional link is observed between Notch signaling and cellular metabolism; hyperactivated Notch undergoes a glycolytic switch in several cells (60-62). Under 5% O_2, Notch1-HES1 enhances the glycolytic pathway by inactivating p53 and activating NF-κB signaling. Notch1-HES1 also enhances glycolysis by directly binding to the promoters of key enzymes in glycolysis, such as GLUT1, GLUT3 and fructose-2,6-biphosphatase 3 (PFKFB3), to promote their transcription and expression (5,63). Moriyama *et al* (64) reported that treatment with DAPT (a Notch inhibitor) increases the activities of PDH and COX IV (key enzymes of OXPHOS) and inhibits the activity of LDH in hADMPCs, reinforcing the important role of Notch in cellular metabolic shift. In addition to acting independently, Notch promotes cellular metabolic shift through synergistic effects with HIF-1α. Activation of Notch1 significantly increases HIF-1α transcriptional activity, and knockdown of HIF-1α partially attenuates glycolysis induced by Notch1, suggesting that the cellular glycolytic pathway is regulated by Notch signaling and HIF-1α in coordination (65).

7. Mammalian target of rapamycin (mTOR) signaling pathway promotes metabolic shift in PH

mTOR, an atypical serine/threonine protein kinase that is a member of the phosphatidylinositol kinase-related kinase protein family, consists of two functional multi-protein complexes: mTORC1 and mTORC2. mTORC1 is sensitive to rapamycin and consists of mTOR, raptor (an mTOR-associated regulatory protein), and mLST8 (also known as GßL), whereas mTORC2 is insensitive to rapamycin and consists of mTOR, Rictor (an mTOR chaperone that is insensitive to rapamycin) and mLST8 (66). Both cooperate to integrate various extracellular signals, such as nutrients, energy and growth factors, and participate in biological processes, such as gene transcription, protein translation and ribosome synthesis, which play important roles in cell growth, apoptosis, autophagy and metabolism (67,68).

mTOR activation is a key regulator of pulmonary vascular remodeling in PH (69,70). In 2014, Goncharov *et al* (8) first reported the involvement of mTOR as a coordinator of energy metabolic shifts in the pathogenesis of PH. Their study showed that mTORC2 was required for increased ATP production, proliferation and survival of IPAH PAVSMCs. Inhibition of mTORC2 by Rictor siRNA reduces glycolysis-dependent proliferation and survival of IPAH PAVSMCs (8). mTOR drives aerobic glycolysis and reprograms cellular glucose metabolism by directly or indirectly modulating the expression of glycolytic enzymes (71,72). Firstly, mTORC1 enhances the transcription and expression of glycolytic enzymes [GLUT1, HK2, PFKFB3 and pyruvate kinase M2 (PKM2)] by directly regulating the activity of two key transcription factors, HIF-1α and Myc, resulting in the upregulation of glycolysis (73-76). Secondly, similar to the Notch pathway, mTORC1 promotes glycolysis by indirectly increasing the transcriptional activity of HIF-1α by regulating the signal transducer and activator of transcription 3 and forkhead box K1 (77,78). mTORC2 promotes glycolysis via the phosphoinositide 3-kinase/Akt/forkhead box O pathway (79). Considering the important role of mTOR in cellular metabolic reprogramming, mTOR inhibitors are widely used to treat various tumors. However, their therapeutic role in PH remains uncertain and represents a great challenge owing to the complex signaling crosstalk between mTORC1 and mTORC2.

8. Fat mass and obesity-associated (FTO) promotes glycolysis in PH

FTO genes have obesity-associated alleles located on chromosome 16q12.2 and are associated with dietary intake, appetite regulation and energy metabolism (80,81). In 2007, FTO protein was identified as an RNA demethylase (82). Methylation of the nitrogen atom at the 6th adenine on the RNA chain is the most common mRNA modification that regulates gene expression during the translation of proteins. Since Jia *et al* (83) identified N6-methyladenosine (m6A) in nuclear RNA as the primary substrate of FTO protein and clarified that FTO proteins are RNA m6A demethylases, FTO-RNA epigenetic modifications have been widely investigated. FTO protein plays important regulatory roles in tumors (84), hypertrophic cardiomyopathy (85), HF (86) and PH (87,88) through demethylation modifications of RNA m6A. FTO increases the activity of transcription factors c-Jun, JunB and C/EBPb via m6A demethylation modification, promotes the expression of the glycolysis-related enzymes phosphofructokinase, phosphoglycerate mutase 1 and HK1, and facilitates glycolysis-dependent cell proliferation in cancer (89). Furthermore, MDA-MB-231 cells transfected with miFTO inhibitors show significantly reduced HK1 and PKM expression, which result in significantly decreased ATP and lactate levels (90). These findings suggest that FTO regulates cellular glycolysis through the demethylation of RNA m6A. In line with the cancer theory of PH, several studies have explored the role of FTO in PH. In monocrotaline (MCT)-induced PH (MCT-PH) rats, the expression of FTO in the lung tissue was significantly reduced, accompanied by an increase in m6A methylation levels. The researchers then extracted lung tissue RNA for methylated RNA immunoprecipitation sequencing, and a total of 3,298 differentially methylated m6A sites were screened based on false discovery rate ≤0.0001 and fold change ≥2. Kyoto Encyclopedia of Genes and Genomes pathway analysis showed that differentially methylated m6A sites were enriched in the glycolytic/glycogenic pathway, in which the mRNA m6A levels of key glycolytic enzymes HK3, glucose-6-phosphate isomerase, LDHA and PKM were significantly upregulated (88). These results suggested that FTO may affect the translation or transcription of key glycolytic enzymes by regulating mRNA m6A levels and may be involved in the development of PH.

9. Glucose-fatty acid cycle in PH

Fatty acid oxidation (FAO) is a main source of ATP production; however, it produces less ATP than that by GO with the

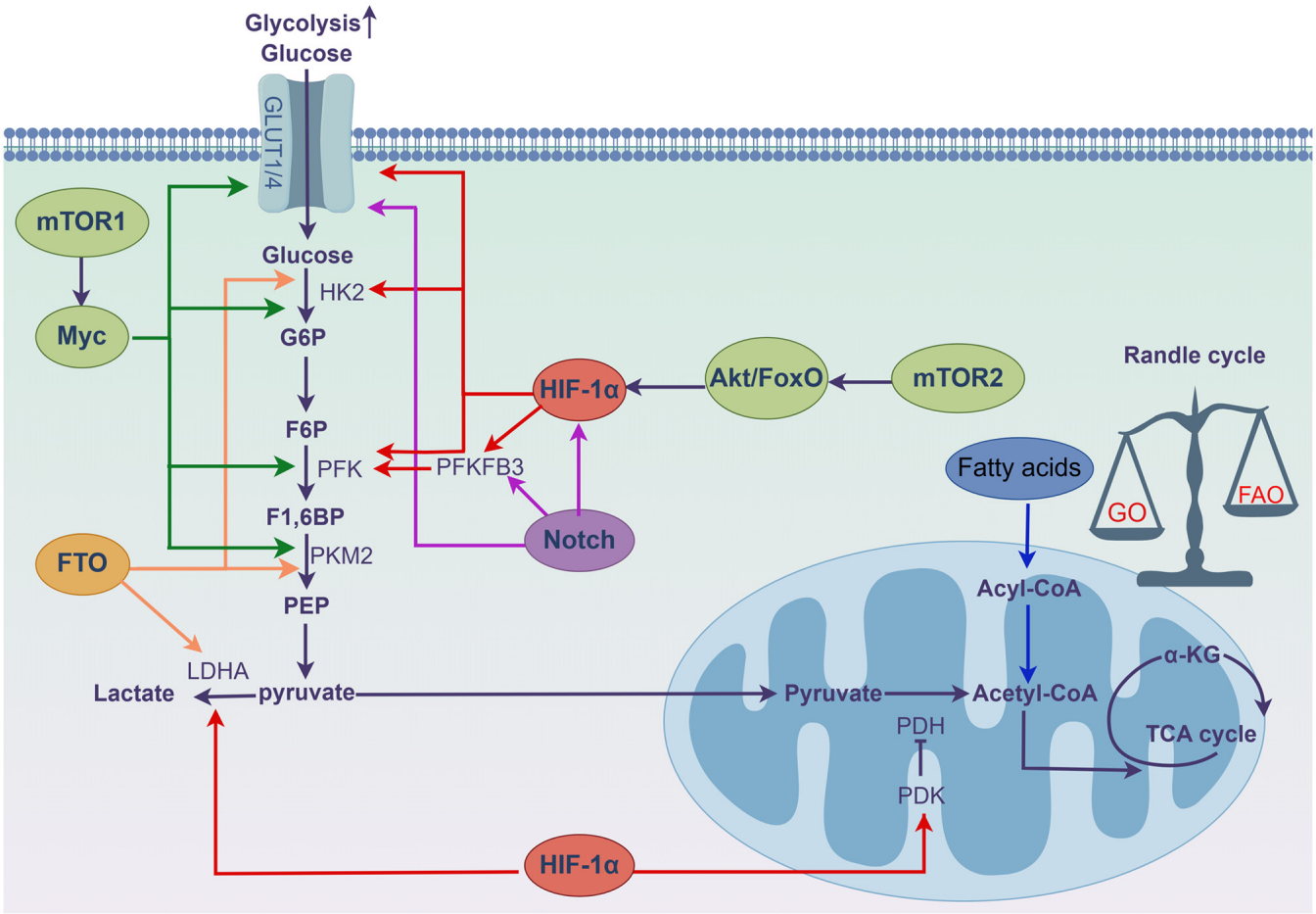

Figure 5. Mechanisms of metabolic shift in PH. Several pathogenic factors are involved in the metabolic reprogramming of pulmonary vascular cells by affecting the expression of key enzymes in the glycolytic pathway through signaling pathways such as HIF-1α, Notch, mTOR and FTO. In addition, an imbalance in the glucose-fatty acid cycle is also an important mechanism for metabolic shifts. The figure was created using Figdraw (www.figdraw.com).

same oxygen consumption. Therefore, under normal conditions, most cells rely on GO as their main energy source, except for rapidly proliferating cells. There is a reciprocal regulation of fatty acid and glucose metabolism, characterized by a competitive relationship in which the dominance of one can lead to the inhibition of the other, as evidenced by the increase in the proportion of acetyl CoA produced from FAO that inhibits PDH activity, leading to the suppression of GO, which is known as the glucose-fatty acid or Randle cycle (91-93). FAO levels are elevated in patients with PH and rodent models of PH (9,94). A non-targeted metabolomic analysis performed on 21 patients with IPAH and 31 age-, body mass index-, and sex-matched normal controls showed that FAO metabolites are significantly upregulated in patients with IPAH compared with those in the normal controls, suggesting that FAO is more abundant in IPAH (95). Malonyl coenzyme A decarboxylase is an important FAO regulatory enzyme that degrades malonyl-CoA to acetyl-CoA and reduces the inhibitory effect of malonyl-CoA on carnitine acyltransferase-1, the rate-limiting enzyme of FAO. Malonyl coenzyme A decarboxylase knockout mice are protected from hypoxic PH, and targeting carnitine acyltransferase-1A with oxyfenicine attenuates Su/Hx-induced PH in rats (96). All these effects of improving PH by interfering with FAO are achieved through the regulation of the Randle cycle, where FAO inhibition promotes GO, drives cells from glycolysis to GO, and inhibits rapid cell proliferation. In summary, FAO inhibition prevents glycolysis by shifting the metabolism from FAO to GO, thereby facilitating PH treatment (Fig. 5).

10. Potential therapeutic effects of targeting glycolysis in PH

Glycolytic pathway exerts significant impact on PH, serving as a target for PH treatment. Drugs targeting the key genes and enzymes in the glycolytic pathway significantly improve PH in rodents. Currently, some pharmacological agents targeting glycolysis are undergoing clinical trials.

Influence of HIF-1α on glycolysis has been extensively studied, with numerous studies focusing on pharmacological agents targeting PHD or HIF-1α. Inhibitors that directly or indirectly affect HIF-1α can be divided into five main groups: Inhibitors that reduce *HIF* mRNA expression, such as EZN-2968; inhibitors that prevent HIF-1α protein expression, such as 2-methoxyestradiol (2-ME2); inhibitors that enhance the degradation of HIF-1α protein, such as apigenin and bisphenol A; inhibitors that inhibit the dimerization of HIF-1α and HIF-1β, such as acriflavine and doxorubicin; and inhibitors of DNA binding of HIF-1, such as echinomycin (97-99). Currently, clinical trials of HIF-1α inhibitors are primarily

Table I. A summary of studies targeting HIF-1α in cell or animal model of PH.

First author, year	Drugs	Intervention	Model	PA remodeling (or cell proliferation *in vitro*)	RVSP	RVHI	(Refs.)
Chen *et al*, 2016	R59949	PHD2 activator	C57BL/6, Hx	↓	↓	↓	(102)
	-	SMC-specific knockout of PHD2	C57BL/6, Hx	↑	↑	↑	
Wang *et al*, 2016	-	EC specific knockout of PHD2	C57BL/6	↑	↑	↑	(103)
Han *et al*, 2021	Echinomycin	HIF-1α inhibitor	PASMC, Hx	↓	-	-	(104)
Dessouroux *et al*, 2008	DHEA	HIF-1α inhibitor	HPASMC, Hx	↓	-	-	(105)
Arai *et al*, 2021	Tagitinin C	HIF-1α inhibitor	HPASMC, Hx	↓	-	-	(20)
Ball *et al*, 2014	-	smooth muscle-specific knockout of HIF-1α	Mice, Hx	↓	-	↓	(106)
Docherty *et al*, 2019	2-ME2	HIF-1α inhibitor	SD-rats, Hx	↓	↓	↓	(107)
He *et al*, 2020	Apigenin	HIF-1α inhibitor	Rats, Hx	↓	↓	↓	(108)
Jiang *et al*, 2018	Topotecan	HIF-1α inhibitor	*Wistar rats,* Hx	↓	↓	↓	(109)
Koulmann *et al*, 2006	Cyclosporin A	HIF-1α inhibitor	Rats, Hx	-	↓	↓	(110)
Kurosawa *et al*, 2019	Celastramycin	HIF-1α inhibitor	Rats, MCT and Su/Hx	↓	↓	↓	(111)
Abud *et al*, 2012	Digoxin	HIF-1α inhibitor	C57BL/6, Hx	↓	↓	↓	(112)

Hx, hypoxia; Su/Hx, SU5416 + hypoxia; MCT, monocrotaline.

focused on the treatment of cancer, with no clinical trials related to PH currently registered on the Clinical Trials.gov registry. However, as a signaling messenger, HIF-1α performs numerous important physiological functions, and its inhibition may lead to adaptive metabolic disorders in multiple organs and tissues (33). In a phase II trial, patients with metastatic renal cell carcinoma were divided into two treatment arms based on whether they stopped or continued sunitinib treatment. Patients in treatment arm A received 1,500 mg panzem (2-ME2) thrice daily, whereas those in treatment arm B received a comparable dose of panzem plus sunitinib at the highest tolerated dose for the patient. However, this study was halted after 17 patients experienced treatment toxicity in both arms, resulting in fatigue (60%), diarrhea (53%), elevated aspartate aminotransferase (41%), decreased appetite (35%), joint and muscle pain (35%), and lack of objective response to treatment (100).

In a previous study, inhibition of the Notch signaling pathway via gene ablation caused myocardial hypertrophy and HF in adult mice (101), which severely limited the development of PH pharmacological drugs targeting HIF-1α or Notch. Therefore, investigation of downstream glycolytic targets is important for novel drug development for PH. Numerous inhibitors prevent or reverse PH in various cellular and animal models of hypoxia, MCT and Su/Hx (Table I).

11. Glycolytic enzymes as attractive targets for PH therapy

Several enzymes are involved in glycolysis. Glycolysis is the main metabolic pathway for energy production in the pulmonary vascular cells of patients with PH, and glycolytic enzyme expression is increased in PH (25,113,114). Therefore, targeting glycolysis-related molecules, such as GLUT1, PFKFB3 and PDK1, is a promising strategy for PH treatment.

12. GLUT inhibition prevents PH development

Glucose uptake is the first and most critical step of glucose metabolism. GLUTs (also known as sodium-glucose co-transporters) are a large group of membrane proteins that facilitate glucose transport across the plasma membrane of mammalian cells. To date, 14 members of the GLUT family have been identified, of which GLUT1-4 are the most widely studied and extremely important to maintain the normal physiological functions in humans; their abnormal expression and function can lead to various diseases (115-117). GLUT1-4 mRNA and protein levels are significantly increased in the lungs, along with glycolysis, in rodent models of PH (118-121). Empagliflozin and dapagliflozin (GLUT2 inhibitors) significantly attenuate pulmonary vascular remodeling, right ventricular (RV) systolic pressure (RVSP) and RV hypertrophy index in rodents with PH (121,122). The Universitaire Ziekenhuizen KU Leuven in Belgium is currently conducting a clinical trial (NCT05731466) to investigate the effects of GLUT2 inhibitors on RV-arterial coupling in patients with HF with preserved ejection fraction and PH. A prospective randomized multi-center open-label study previously investigated whether GLUT2 inhibitors improve the left ventricular (LV) pump function and reduce the increase in LV filling pressure (LVFP) and RVSP during exercise in patients with type 2 diabetes mellitus. The study revealed that the addition of dapagliflozin at a daily dose of 5 mg to conventional treatment significantly improved both RVSP and LVFP during exercise in patients with type 2 diabetes mellitus over a 6-month period (123). This

study highlighted the potential use of GLUT2 inhibitors for PH treatment.

13. Roles of HKs and 2-deoxyglucose (2-DG) in PH therapy

HKs play a critical role in glucose metabolism regulation by catalyzing the first irreversible step of glycolysis. In mammals, four HK isozymes (HK1-4) have been identified. HK1-3 are associated with the metabolic shift in PH, and HK2 is the most extensively studied, whose inhibition exhibits potential for PH therapy (124,125). Moreover, 3-bromopyruvate (3-BrPA), a pyruvate analog targeting HK2, significantly improves PH induced by hypoxia, MCT and Su/Hx in rodents (126-128). In addition to inhibiting the glycolytic pathway, 3-BrPA also causes the opening of the mitochondrial permeability transition pore and release of the pro-apoptotic molecule, CytoC, into the cytoplasm by inhibiting the binding of HK2 to the mitochondria, causing apoptosis via caspase 3 activation, which alleviates pulmonary vascular remodeling and RV hypertrophy in animals with PH (129,130). However, studies on 3-BrPA for PH treatment are currently in early stages. Therapeutic studies on the HK2 selective inhibitors, ketoconazole and posaconazole, have entered phase I clinical trials (NCT03763396). Considering the promising results observed in experimental PH studies in rodents, 3-BrPA can be a promising drug for PH treatment after further pharmacological, toxicological and clinical studies.

Notably, 2-DG is a glucose analog that enters the cytoplasm through a deceptive mechanism; it mimics glucose to trick the cells into internalizing it (131). On the one hand, 2-DG competes with glucose for HK2, thereby inhibiting glycolysis. On the other hand, unlike normal glucose, 2-DG is unable to generate energy via subsequent catabolism, resulting in cell starvation and inhibition of cell proliferation and other metabolic processes (132). It also suppresses PASMC proliferation, which plays an important role in improving PH (114,133). After completing the phase I study, 2-DG entered the phase II study for prostate cancer (NCT00633087); however, this study was stopped early due to slow progress and insufficient data to measure outcomes. Therefore, further research is essential to facilitate the application of 2-DG for PH treatment.

In addition to being a potential therapeutic agent, 2-DG is a prospective diagnostic strategy to monitor the pulmonary vasculature. [^{18}F]FDG is a fluorinated derivative of 2-DG, in which the hydroxy group at the 2nd position of glucose is replaced by the radioisotope, ^{18}F. In patients with PH, lung [^{18}F]FDG uptake on PET imaging is positively correlated with the condition severity (134,135).

14. Antagonism of PFKFBs alleviates PH

Fructokinase 6-phosphate kinase 1 (PFK1), the second rate-limiting enzyme of glycolysis catalyzing the formation of fructose-1,6-bisphosphate from fructose 6-phosphate (F6P), is regulated by PFKFB3 (136). PFKFB3 does not play a direct role in the catalytic mechanism of glycolysis. However, it is responsible for the synthesis of fructose 2,6-bisphosphate, which is a potent allosteric activator of PFK1. By catalyzing the conversion of F6P, PFKFB3 significantly enhances the catalytic activity of PFK1. Therefore, PFKFB3 is critical for glycolysis regulation (137). Similar to HK2 levels, PFKFB3 levels are significantly increased in the lung tissues of patients with PAH and rodent models. Knockdown of *PFKFB3* or use of its small molecule isoenzyme inhibitor, 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3-PO), significantly reduces the proliferation of PASMCs and PAECs, attenuates vascular remodeling, and ameliorates PAH by inhibiting glycolysis (28,113,138). However, efficacy of 3-PO as a therapeutic intervention for PH is currently being investigated in experimental studies with cellular and animal models.

15. Targeting PKM2 in PH

In total, four pyruvate kinase isoenzymes are present in mammals: Pyruvate kinase M1, M2, L, and R (139). Among these, PKM2 is an important regulator of anaerobic metabolism and a potential therapeutic target for PH (140,141). PKM2 exists in two forms: Low-activity dimer and high-activity tetramer. Dimeric form of PKM2 plays a critical role in the final rate-limiting step of the glycolytic pathway by facilitating the production of pyruvate and ATP (142,143). In addition to its primary enzymatic function, dimeric form of PKM2 translocates to the nucleus and functions as a transcriptional co-activator, enhancing the activity of various transcription factors, such as HIF-1α and signal transducer and activator of transcription 3, subsequently increasing the expression levels of GLUT1, HK2 and LDHA (144-146). Targeted inhibition of PKM2 ameliorates MCT- and supra-coronary aortic banding-induced PH in rodents (119,147). However, current research on PKM2 inhibitors for PH treatment remains in its early stages.

16. Effect of PDK1 inhibitor on PH

PDH catalyzes the production of acetyl-CoA from pyruvate, which is the central link between cytoplasmic glycolysis and the mitochondrial tricarboxylic acid cycle. As a downstream target of HIF-1α, PDK phosphorylates PDH, leading to its inactivation, which results in pyruvate accumulation in the cytoplasm, facilitating glycolysis. PDK levels are significantly higher in PH lung tissues than in the healthy lung tissues (42,148). PDK inhibitor dichloroacetate (DCA) ameliorates PH caused by hypoxia (149), MCT (150) and serotonin transporter overexpression (151) by restoring OXPHOS in the glycolytic tissues of rodent models. Importantly, unlike HK2 and PFKFB3 inhibitors, DCA has yielded promising results in PH clinical trials. In 2010, Imperial College London and University of Alberta in Canada conducted a phase I two-center clinical trial of the efficacy of DCA for PH (NCT01083524). A total of 30 patients with advanced IPAH were enrolled and continuously administered oral DCA (3.0-12.5 mg/kg twice daily) for 16 weeks. At the follow-up, DCA significantly reduced the pulmonary vascular resistance and PAP and improved the exercise tolerance in patients (42). The first-in-human study of a mitochondria-targeting drug in PH revealed PDK as a druggable target causing hemodynamic improvement in genetically susceptible patients, thus facilitating the establishment of precision medicine approaches for PH. However, extensive clinical trials are necessary to assess the efficacy and safety of such drugs.

Table II. A summary of studies targeting glucose metabolism in cell or animal model of PH.

First author, year	Drugs	Intervention	Model	PA remodeling (or cell proliferation *in vitro*)	RVSP	RVHI	(Refs.)
Chowdhury *et al*, 2020	Empagliflozin	GLUT2 inhibitor	SD-rats, MCT	↓	↓	↓	(121)
Wu *et al*, 2022	Dapagliflozin	GLUT2 inhibitor	SD-rats, MCT	-	↓	-	(166)
Tang *et al*, 2022	Dapagliflozin	GLUT2 inhibitor	SD-rats, MCT	↓	↓	↓	(122)
Zhang *et al*, 2019							
Liu *et al*, 2020	3-BrPA	HK-2 inhibitor	SD-rats, MCT	↓	↓	↓	(127, 128)
Chen *et al*, 2018	3-BrPA	HK-2 inhibitor	SD-rats, Hx	↓	↓	-	(126)
Lu *et al*, 2019	2-DG	HK-2 inhibitor	IPAH PAVSMC	↓	-	-	(133)
Luo *et al*, 2020	miR-125a-5p	HK-2 inhibitor	SD-rats, MCT	↓	↓	↓	(167)
Wang *et al*, 2021	-	PFKFB3 knock out	Myeloid-specific PFKFB3-deficient mice, Su/Hx	↓	↓	↓	(138)
Cao *et al*, 2019	-	PFKFB3 knock out	Endothelial PFKFB3-knockout mice, Su/Hx	↓	↓	↓	(28)
	3-PO	PFKFB3 inhibitor	SD-rats, Su/Hx	↓	↓	↓	
Kassa *et al*, 2021	3-PO	PFKFB3 inhibitor	C57BL/6, Hx	↓	-	↓	(168)
Li *et al*, 2023	Shikonin	PKM2 inhibitor	SD-rats, MCT	↓	↓	↓	(119)
Xiong *et al*, 2022	Shikonin	PKM2 inhibitor	SD-rats, PH induced by supra-coronary aortic banding (SAB)	↓	↓	↓	(147)
	Small interfering RNA	small interfering RNA-targeting PKM2	SD-rats, PH induced by supra-coronary aortic banding (SAB)	↓	↓	↓	
Michelakis *et al*, 2002	DCA	PDK1 inhibitor	SD-rats, Hx	↓	↓	↓	(149)
McMurtry *et al*, 2004	DCA	PDK1 inhibitor	Rats, MCT	↓	↓	↓	(150)
Guignabert *et al*, 2009	DCA	PDK1 inhibitor	Mice overexpressing 5-HTT specifically in the SMCs	↓	↓	↓	(151)
Qi *et al*, 2019	FDCA	PDK1 inhibitor	Rats, MCT	↓	↓	↓	(169)

PA, pulmonary artery; RVSP, right ventricular systolic pressure; RVHI, right ventricular hypertrophy index; Su/Hx, SU5416 + hypoxia; MCT, monocrotaline.

17. Trimetazidine (TMZ) and ranolazine activate the Randle cycle to improve the RV function in PH

A reciprocal relationship is observed between FAO and GO that is the core of the Randle cycle. The Randle cycle is also observed in PH. Preventing FAO from producing acetyl-CoA limits glycolysis by increasing PDH activity and enhancing GO via the Randle cycle. TMZ, an inhibitor of mitochondrial enzyme long-chain 3-ketoacyl CoA thiolase, increases GO and inhibits FAO by activating the Randle cycle and is widely used to treat angina pectoris (152), myocardial infarction (153,154) and HF (155). Parr*a et al* (156) reported that treatment of HPASMCs with TMZ inhibits the increase in the mRNA levels of glycolysis markers (*HK2*, *PFKFB3* and *GLUT1*) and suppresses hypoxia-induced HPASMC proliferation. Moreover, TMZ-induced FAO inhibition triggers the accumulation of long-chain fatty acids in the cytoplasm (lipotoxicity), resulting in endoplasmic reticulum stress, ultimately leading to cell death and alleviation of pulmonary vascular remodeling and RV hypertrophy (157-159). A phase II clinical trial (NCT02102672) sponsored by the Pontificia Universidad Catolica de Chile evaluated the efficacy of TMZ in improving the RV function, remodeling and functional class in patients with PAH. Over the course of 3 months, participants in the study received TMZ at a dose of 35 mg twice daily in addition to conventional PAH-specific therapy. The Pontificia Universidad Catolica de Chile sponsored a phase II clinical trial (NCT02102672) to evaluate the efficacy of TMZ in improving

Table III. A summary of clinical trials of drugs targeting glucose metabolism.

Drugs	Disease	Mechanism	Phase	NCT Num.
Iron sucrose	HPAH	Enhanced degradation of HIF	Not applicable (Interventional)	NCT00952302
Iron supplement	PAH	Enhanced degradation of HIF	Not applicable (Interventional)	NCT01446848
Dapagliflozin	PAH/CTEPAH	GLUT-2 inhibitor	Phase 2	NCT05179356
Empagliflozin	IPAH	GLUT-2 inhibitor	Phase 2	NCT05493371
Dapagliflozin	HFpEF-PH	GLUT-2 inhibitor	Not applicable (Interventional)	NCT05731466
Ketoconazole				
Posaconazole	Brain tumor	HK-2 inhibitor	Early Phase 1	*NCT03763396*
2-DG	Prostate cancer	HK-2 inhibitor	Phase 1 Phase 2	*NCT00633087*
Dichloroacetate Sodium	PAH	PDK1 inhibitor	Phase 1	NCT01083524
Trimetazidine	Precapillary PAH	3-KAT inhibitor	Phase 2/Phase 3	NCT03273387
Trimetazidine	PAH	3-KAT inhibitor	Phase 2	NCT02102672
Ranolazine	PAH	FAO inhibitor	Phase 1 Phase 4	NCT01757808
			Phase 4	NCT02829034
				NCT01839110
Ranolazine	PAH Associated with LVDD	FAO inhibitor	Phase 4	NCT02133352
Ranolazine	Angina, PAH	FAO inhibitor	Phase 3	NCT01174173

HPAH, heritable pulmonary arterial hypertension; CTEPAH, chronic thromboembolic pulmonary hypertension; HFpEF-PH, heart failure with preserved ejection fraction pulmonary hypertension; LVDD, left ventricular end diastolic dimension.

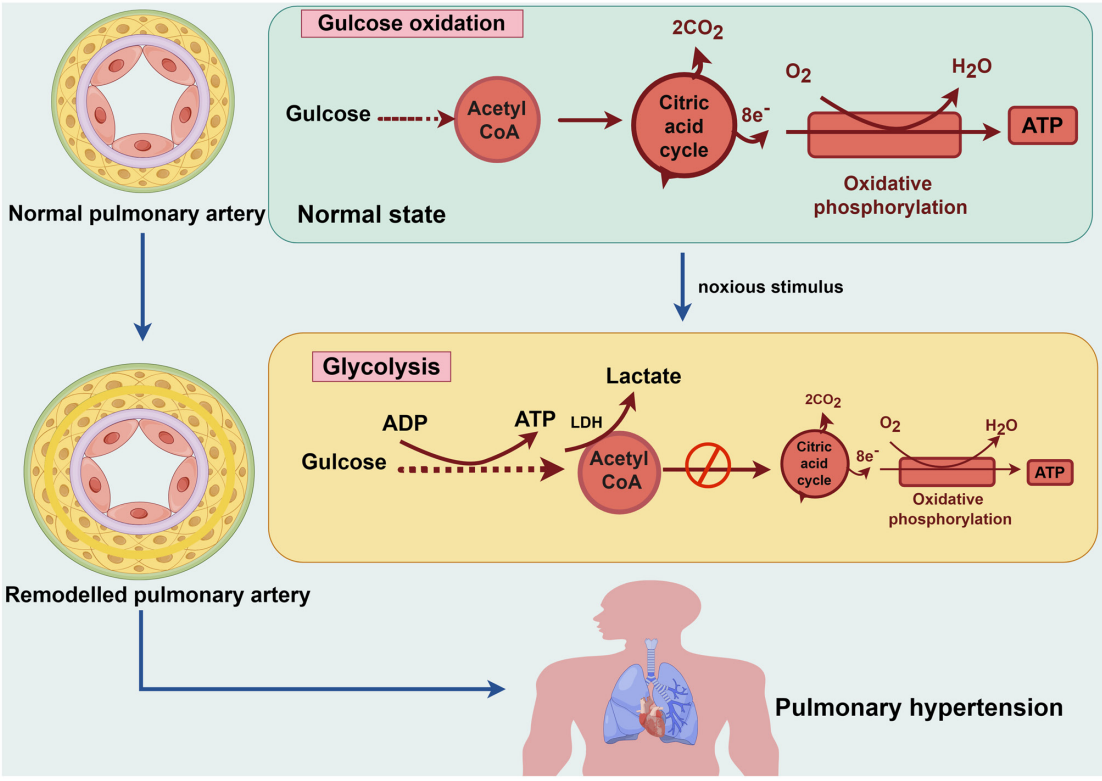

Figure 6. A graphical summary of the present review. The figure was created using Figdraw (www.figdraw.com).

the RV function, remodeling and functional class in patients with PAH. Patients in the TMZ group exhibited a significant decrease in the RV diastolic area, significant increase in the 6-min walking distance, and modest but significant improvement in RV remodeling (160). The aforementioned study serves as a valuable reference for the application of TMZ to treat PH.

Ranolazine is an anti-anginal and anti-ischemic drug that inhibits sodium-dependent calcium overload in the myocardium without affecting the heart rate or blood pressure (161). Additionally, ranolazine partially inhibits FAO (162). However, unlike TMZ, ranolazine does not influence FAO-associated enzymes; instead, it stimulates GO by activating PDH (163,164). Ranolazine also increases ATP production, reduces the expression of glycolytic mediators, such as GLUT1, HKI and LDHA, and decreases lactate production in a rat pulmonary artery banding model (91). Cardiac function significantly improves after ranolazine treatment. A randomized, double-blind, placebo-controlled, multi-center, phase IV clinical trial assessing the effects of ranolazine on RV dysfunction in patients with PAH using cardiovascular magnetic resonance was sponsored by the University of Pennsylvania (NCT01839110 and NCT02829034). The participants orally received ranolazine (500 mg twice daily) with stable PAH-specific treatment, which was subsequently increased to 1,000 mg twice daily after 2 weeks and continued for a total of 26 weeks. Only 9 patients completed the follow-up cardiovascular magnetic resonance imaging, and six completed the placebo arm. Notably, ranolazine only improves the RV function in precapillary PAH and has no significant effect on other forms of PH (165). Therefore, further large-scale studies are necessary to confirm the efficacy of ranolazine for PH treatment. Previous studies and clinical trials focusing on glucose metabolism are summarized in Tables II and III, respectively.

18. Conclusion

To date, most studies on PH have focused on vasoconstriction, dilation and endothelial dysfunction. Recent studies have revealed the significance of metabolic dysregulation and reprogramming in driving excessive proliferation and apoptosis resistance in pulmonary vascular cells, thereby leading to pulmonary vascular remodeling. Metabolic shift is observed in both patients with PH and animal models. Targeting glycolysis-related pathways has been effective in mitigating PH, suggesting the role of metabolic reprogramming in PH pathogenesis (Fig. 6). Furthermore, some clinical studies have shown that modulation of cellular glucose metabolism reduces the pulmonary vascular resistance and PAP and improves exercise tolerance and RV function in patients with PH. In addition to its mechanistic significance, glycolytic alterations in PH can be used to develop a diagnostic approach based on the pulmonary vasculature. PET using [^{18}F]FDG as a radiotracer can provide valuable information on the pulmonary vascular and RV metabolic status, thereby aiding in the diagnosis and management of PH. However, fundamental questions remain regarding the interplay between mitochondrial dysfunction and metabolic switching and their combined roles in PH pathogenesis. Therefore, further investigation of the roles of metabolic abnormalities and mitochondrial dysfunction in PH pathogenesis are necessary for the development of novel therapeutic approaches for this condition.

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Authors' contributions

MC and WL conceived and designed the entire review and wrote the paper. MC, HL, YLi and YLuo assisted with literature collection and figure drawings. YH, XS and WL reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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