

Metabolic Reprogramming Intermediates of Glucose Regulate Macrophage Polarization: An Important Direction for Ameliorating Pulmonary Vascular Remodeling

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Abstract: Pulmonary vascular remodeling (PVR) is a key pathological basis for various lung diseases and is centered on macrophage-driven pathological vascular remodeling. Macrophage functional polarization is closely related to metabolic reprogramming, a process that not only encompasses energy supply but also dictates cellular function through metabolic intermediates. To bridge the knowledge gap between metabolic regulation and clinical translation in PVR, this review focuses on key metabolites produced during glucose metabolism: pyruvate, citrate, succinate, and itaconate. These intermediates are not merely metabolic byproducts; rather, they directly influence the pathological processes of vascular endothelial cells, smooth muscle cells, and the extracellular matrix by modulating the polarization of macrophages. This review systematically elucidates the precise regulatory mechanisms of these metabolic signals, with the aim of providing new diagnostic and therapeutic targets for PVR. It emphasizes the immense potential of targeting metabolic intermediates for future precision medicine, ultimately promoting a paradigm shift in PVR therapy from traditional anti-proliferative interventions to an innovative model based on metabolic reprogramming.

Keywords: pulmonary vascular remodeling, macrophage polarization, glycolytic reprogramming, pyruvate, citrate, succinate, itaconate

Introduction

Pulmonary vascular remodeling (PVR), characterized by pathological alterations in the structure and function of pulmonary vessel walls, primarily manifests as vascular wall thickening and lumen narrowing. These changes lead to increased pulmonary vascular resistance and pulmonary artery hypertension (PAH), which can ultimately progress to right heart failure and death.^{1,2} As a common pathological feature in various pulmonary diseases, including PAH, acute respiratory distress syndrome (ARDS), and chronic obstructive pulmonary disease, PVR involves multiple processes such as endothelial cell dysfunction, abnormal proliferation of smooth muscle cells, and extracellular matrix (ECM) deposition.^{3,4} In recent years, macrophages have emerged as key immune effector cells driving the development of PVR, given their high plasticity and rapid responsiveness to microenvironmental changes.^{5,6}

Depending on microenvironmental stimuli, macrophages can polarize into either pro-inflammatory M1 or anti-inflammatory/pro-repair M2 phenotypes. The balance between these polarization states is crucial for the pathogenesis of PVR. Research has demonstrated a strong link between macrophage polarization and their metabolic pathways, with metabolic reprogramming being particularly pronounced under hypoxic and inflammatory conditions.^{7,8} Specifically, M1 macrophages rely on glycolysis for a rapid energy supply to fuel their immune responses, whereas M2 macrophages

predominantly utilize oxidative phosphorylation (OXPHOS) and fatty acid oxidation to support their anti-inflammatory and tissue repair functions.^{9–11} These findings highlight that metabolic reprogramming is not merely about energy supply but serves as a core determinant of macrophage functional phenotype conversion.

Furthermore, intermediate metabolites generated during glucose metabolic reprogramming, such as succinate, citrate, pyruvate, and itaconate, are no longer viewed simply as byproducts of energy production. Instead, they function as critical signaling molecules.^{12–14} These metabolites can directly influence macrophage polarization and function by modulating epigenetic modifications, such as histone acetylation, or by activating signaling pathways like HIF-1 α . Their effects extend further to the vessel wall, promoting PVR by driving smooth muscle cell proliferation, endothelial cell phenotypic transformation, and abnormal ECM deposition⁶ (Figure 1). This review aims to systematically explore the precise regulatory role of glucose metabolism intermediates on macrophage polarization and their subsequent impact on PVR pathogenesis, in an effort to provide new theoretical support for developing targeted immunometabolic intervention strategies.

Macrophage Polarization and Glycolytic Reprogramming: Metabolic Characteristics and Regulatory Mechanisms of M1/M2 Phenotypes

Glycolytic metabolic reprogramming refers to the process by which cells select and regulate their energy metabolism pathways in response to specific microenvironmental cues and external stimuli. This process not only involves changes in energy supply but also entails the generation of metabolic intermediates, the adjustment of metabolic pathways, and the reconstruction of regulatory networks. For macrophages, glucose metabolic reprogramming is fundamental to their polarization, functional execution, and participation in various physiological and pathological processes. Current research indicates that based on differences in their immune functions, polarized macrophage subtypes are broadly classified into classically activated M1 macrophages and alternatively activated M2 macrophages.¹⁵

Under physiological conditions, macrophages predominantly utilize the tricarboxylic acid (TCA) cycle and OXPHOS for energy production. However, under conditions of hypoxia or surging energy demand, such as in rapidly proliferating cells, they switch to glycolysis as the main energy source. In the context of PVR, abnormal blood flow, local hypoxia, and the continuous release of inflammatory mediators collectively alter the microenvironment, activating hypoxia-inducible

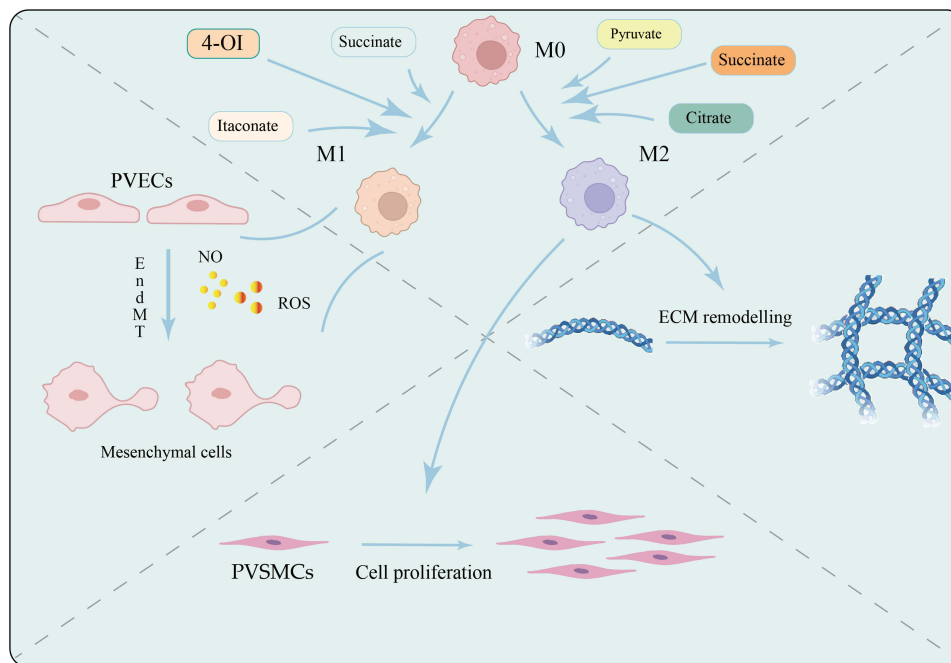


Figure 1 Metabolic intermediates of glycolysis in macrophages regulate their polarization states (M1 vs M2), orchestrating crosstalk among pulmonary vascular endothelial cells, smooth muscle cells, and immune cells, ultimately driving the progression of pulmonary. Created in BioRender. Junlan, T. (2025) <https://BioRender.com/cqjmnah>.

factor (HIF-1 α). Concurrently, inflammatory signals (eg, TNF- α , IL-1 β) and oxidative stress signals also participate in regulating cellular metabolism. This results in a critical phenomenon: even in the presence of sufficient oxygen, macrophages preferentially utilize glycolysis over mitochondrial OXPHOS for energy production.⁶ This metabolic shift not only provides energy for the polarization process but also, through its metabolic products and associated signaling pathways, dictates the direction of macrophage polarization and their corresponding biological functions.¹⁶ Of note, macrophage polarization exhibits temporal dynamics. An animal model study by Fan et al demonstrated a transient increase in M1 macrophages during the early stage, which are subsequently replaced by M2 macrophages. The latter, by continuously secreting pro-proliferative factors such as IL-4 and IL-13, accelerate the progression of the disease. In summary, the polarization state of macrophages and their metabolic reprogramming dynamically interact throughout the disease course, with glucose metabolic reprogramming serving as both a consequence and a driver. Therefore, by exploring the distinct roles of glucose metabolic reprogramming in macrophage polarization, the following sections of this review will provide a detailed exposition of the core mechanisms and regulatory networks linking macrophage polarization and glucose metabolic reprogramming.

Metabolic Characteristics of M1 Macrophages

M1 macrophage polarization is triggered by various cytokine stimuli and accompanied by a core metabolic reprogramming that is characterized by significantly enhanced glycolysis and pentose phosphate pathway (PPP) activity.¹⁷ This metabolic shift involves a progressive transition of cellular energy metabolism from OXPHOS to glycolysis, alongside an interruption of TCA cycle. Glycolysis not only provides rapid energy for M1 macrophages but also regulates immune responses through intermediate metabolites such as citrate and succinate, which facilitates the rapid proliferation and pro-inflammatory cytokine secretion necessary for combating pathogens. This metabolic reprogramming is precisely regulated by both metabolic factors like HIF-1 α and PKM2 and non-metabolic molecular signals. For instance, eRNA has been shown to act as a signaling molecule that participates in M1 macrophage activation and is closely associated with the expression of pro-inflammatory genes.¹⁸ This synergistic interplay between non-metabolic signals and core metabolic reprogramming is essential for maintaining the pro-inflammatory M1 phenotype. The reduced activity of isocitrate dehydrogenase and succinate dehydrogenase in the TCA cycle of M1 macrophages leads to the accumulation of metabolic intermediates, including succinate and itaconate, which act as important signaling molecules in addition to their metabolic roles.¹⁷ Notably, succinate accumulation can stabilize HIF-1 α by inhibiting succinate dehydrogenase (SDH), thereby further promoting glycolysis and enhancing the expression of pro-inflammatory factors like IL-1 β .

Enhanced glycolysis necessitates an increased supply of glucose, which is typically achieved by upregulating the expression of glucose transporters. This funnels more glucose-6-phosphate (G-6-P) into the PPP. The robust activity of the PPP promotes the generation of NADPH and nucleotide precursors, which are essential for supporting antioxidant responses and rapid proliferation.¹⁹ Furthermore, M1 macrophages not only upregulate aerobic glycolysis but also stimulate glycogen synthesis. Carbon tracing experiments have shown an increase in PCK1-mediated phosphoenolpyruvate (PEP) synthesis, with a portion of this PEP flux being directed toward glycogen synthesis. The G-6-P derived from glycogenolysis then enters the PPP. As a crucial branch of glycolysis, the PPP is highly active in M1 macrophages, where it generates reactive oxygen species (ROS) via NADPH oxidase to maintain reduced glutathione (GSH) levels. This mechanism is critical for countering oxidative stress and plays a key role in the inflammatory response.²⁰

Regarding the underlying regulatory mechanisms, inflammatory cytokine stimulation upregulates hexokinase mRNA levels, which in turn promotes glycolysis.²¹ Research indicates that the mammalian target of rapamycin complex 1 (mTORC1) mediates glycolysis-induced activation of the NLRP3 inflammasome via hexokinase, thereby regulating the secretion of IL-1 β and IL-18 by M1 macrophages.²² Furthermore, the expression of pyruvate kinase M2 (PKM2) is elevated in M1 macrophages, where it tends to exist as a dimer. This dimer can translocate to the nucleus and interact with HIF-1 α , promoting the expression of glycolytic enzymes such as PFKFB3 and LDHA while also upregulating the transcription of pro-inflammatory factors like IL-1 β and IL-6.²³ As a key regulator of glycolysis, hypoxia-inducible factor 1 α (HIF-1 α) demonstrates enhanced stability and activity upon activation of mTOR signaling. This in turn further promotes the expression of glycolysis-related proteins and the accumulation of succinate, thereby sustaining the pro-inflammatory phenotype of M1 macrophages.^{24,25}

Metabolic Characteristics of M2 Macrophages

In contrast to M1 macrophages, M2 macrophages are more geared towards anti-inflammatory and tissue repair functions, with their primary energy sources being oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) and a lower dependence on glycolysis. Due to their metabolic flexibility, M2 cells can derive energy from both glucose and fatty acid metabolism, which maintains the integrity of the TCA cycle and allows pyruvate to enter the cycle to support energy metabolism for their anti-inflammatory and tissue repair functions. Studies have shown that while glucose metabolism is not completely suppressed in IL-4-induced M2 macrophages, a certain level of glycolytic activity is maintained, although their energy is predominantly reliant on fatty acid oxidation. It is widely believed that fatty acid oxidation is the main energy source during macrophage polarization. Interestingly, in the context of early IL-4 stimulation, glucose metabolism is more significant, suggesting that glycolysis also plays an important role in M2 polarization.²⁶ Furthermore, OXPHOS generates abundant ATP to meet the energetic demands of M2 macrophages for maintaining cellular homeostasis and tissue repair. Research indicates that as long as OXPHOS maintains sufficient activity, macrophage M2 polarization may not require glycolytic stimulation.²⁷

In M2 macrophages, glucose is metabolized via glycolysis to produce pyruvate, which enters the TCA cycle as a substrate for OXPHOS, thereby supporting mitochondrial respiration. Concurrently, IL-4 enhances glucose metabolism through the AKT and mTORC1 signaling pathways, promoting glucose uptake by macrophages. It also upregulates the activity of the pyruvate dehydrogenase complex (PDC), which boosts the conversion of pyruvate to acetyl-CoA, providing an ample energy source for the TCA cycle and OXPHOS.²⁸ Moreover, the expression pattern of pyruvate kinase M2 (PKM2) in M2 macrophages differs from that in M1 cells; it predominantly exists in a tetrameric form. This tetrameric PKM2 is more likely to promote the entry of pyruvate into the TCA cycle rather than engaging in pro-inflammatory signaling pathways. However, the specific regulatory mechanism between glycolysis and OXPHOS during M2 macrophage activation remains to be fully elucidated.

Regarding FAO, it is a dominant pathway in M2 macrophages, promoting their function and polarization by regulating fatty acid metabolism and anti-inflammatory responses.²⁷ In recent years, the relationship between FAO and inflammasomes has emerged as a new focal point in the field of immunometabolism. The inflammasome is a crucial intracellular multiprotein complex that is primarily involved in activating inflammatory responses, particularly in driving the release of pro-inflammatory cytokines.

Crosstalk Between Macrophages and Key Cells in Pulmonary Vascular Remodeling

PVR refers to the dynamic and pathological changes in the pulmonary artery vessel wall, encompassing alterations in both cellular components and the extracellular matrix. This process is a key pathological feature of numerous pulmonary vascular diseases, leading to increased vascular resistance and, ultimately, right heart failure.² PVR involves multiple cell types and molecular mechanisms, including endothelial cell dysfunction, smooth muscle cell proliferation and migration, and extracellular matrix remodeling.¹ In the early stages of pulmonary vascular injury, an inflammatory response characterized by the infiltration of immune cells (macrophages, T/B lymphocytes) and the release of pro-inflammatory cytokines (IL-6, IL-13, TNF- α) induces endothelial dysfunction and abnormal smooth muscle cell proliferation. This, in turn, triggers the vascular wall thickening and fibrosis associated with the remodeling process. As a crucial component of the innate immune system, macrophages not only play a pivotal role in inflammatory responses but also directly and indirectly influence PVR pathogenesis through metabolic regulation, cytokine secretion, and intercellular signaling. The lung contains two primary types of macrophages, which are categorized by their anatomical location: interstitial macrophages (IMs) and alveolar macrophages (AMs), distributed respectively in the lung interstitium (the connective tissue surrounding vessels and airways) and on the alveolar surface.²⁹ Macrophage origin further distinguishes them as either tissue-resident or monocyte-derived. The former originates from the embryonic yolk sac or fetal liver and maintains pulmonary homeostasis via self-renewal, while the latter is recruited to the lungs from peripheral blood monocytes under specific stimuli and subsequently differentiates into macrophages.^{29,30} Notably, macrophages exhibit high plasticity, functionally polarizing in response to microenvironmental signals. This is particularly evident in IMs

under pathological conditions. Single-cell transcriptome sequencing by Liu et al revealed that monocytes can replenish resident AMs that are depleted by inflammatory reactions, and then gradually mature into bone-marrow-derived macrophages.³¹ In their study, Kumar et al noted a significant increase in the number of abnormally proliferating perivascular IMs in pulmonary hypertension, whereas the number of AMs remained unchanged.³² Furthermore, Qiu et al used single-cell sequencing to demonstrate a significant increase in AMs following hypoxia and identified MHCIIhiLYVE1loCCR2hi IMs as the most prominent subpopulation. They further showed that inhibiting this subtype could alleviate the progression of PH.³³ These results collectively suggest that IMs may play a more critical role in the pathological process of pulmonary vascular remodeling.

More importantly, these shifts in cell numbers are typically accompanied by a change in their functional phenotype. Under disease conditions, macrophages can be stimulated by bacterial lipopolysaccharide (LPS) and interferon- γ (IFN- γ) to undergo M1 activation.³⁴ Activated M1 cells, in turn, can induce T helper 1 (Th1) lymphocytes to release more pro-inflammatory factors like IFN- γ ,³⁵ and further amplify the inflammatory cascade by secreting a variety of pro-inflammatory cytokines and chemokines (eg, IL-1 β , IL-6, TNF- α , and IL-12). In contrast, M2 macrophages, activated by signals such as IL-4 and IL-13, primarily function to suppress inflammation and promote tissue repair.³⁶ Throughout disease progression, the early stage is often dominated by M1 macrophages, but as the disease advances, the proportion of M2 macrophages gradually increases and they assume a critical role.³⁷ Consequently, the polarization balance between M1 and M2 macrophages is central to regulating the inflammatory microenvironment in PVR, as it governs the initiation, maintenance, and resolution of the inflammatory response (Figure 2).

Regulation of Endothelial Function by M1/M2 Macrophages

Endothelial cells, the primary cell type lining the pulmonary vasculature, are crucial for maintaining vascular homeostasis and regulating vessel tone. Under normal conditions, they maintain vascular permeability through tight junctions. However, inflammatory cytokines (eg, TNF- α , IL-1 β) and oxidative stress can disrupt these junctions, leading to a loss of barrier function and increased vascular permeability.^{38,39} This compromised barrier allows monocytes to be recruited to

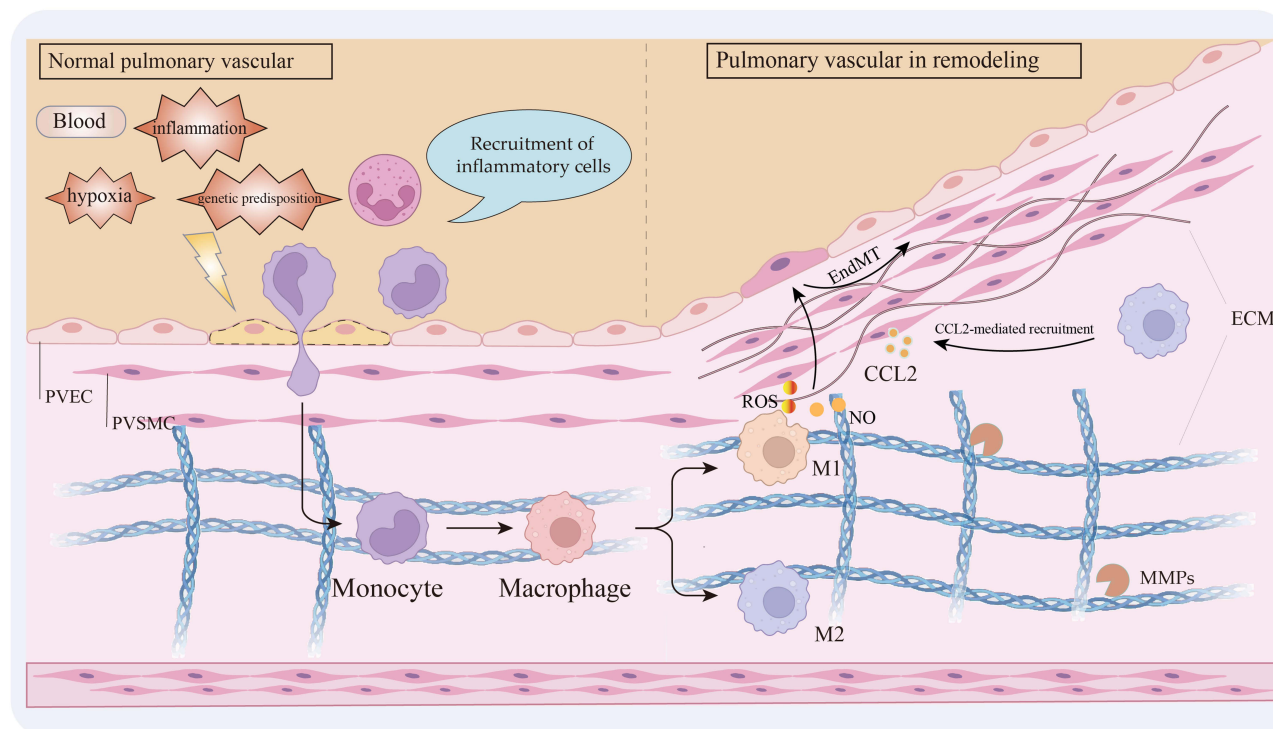


Figure 2 Under conditions such as hypoxia, inflammation, and genetic susceptibility, immune cells including monocytes are recruited and transmigrate across the pulmonary endothelium, where they differentiate into macrophages and polarize toward either the M1 or M2 phenotype. Both polarization states contribute to the progression of pulmonary vascular remodeling. Created in BioRender. Junlan, T. (2025) <https://BioRender.com/j9l0pnb>.

the damaged vessel wall by chemokines (eg, CCL-2), which are typically released by vascular endothelial cells, smooth muscle cells, and other immune cells.⁴⁰ Endothelial cell injury and apoptosis are key initiating factors throughout the pathological process of PVR. Upon their migration and activation into macrophages at the site of injury, a bidirectional regulatory crosstalk with endothelial cells emerges that continues to drive disease progression.

Upon migration to the injury site, monocytes differentiate into polarized M1 or M2 macrophages, establishing a complex regulatory network with endothelial cells. In the early stages of PVR, M1 macrophages produce a significant amount of cytotoxic mediators, including nitric oxide (NO) and reactive oxygen species (ROS),⁴¹ While these mediators play a protective role in clearing pathogens, their over-activation can cause oxidative stress and apoptosis in vascular endothelial cells, compromising the endothelial barrier and thereby exacerbating tissue damage and vascular remodeling. Concurrently, M1 macrophages can activate and upregulate the expression of adhesion molecules (eg, ICAM-1 and VCAM-1), enhancing the adhesion and infiltration of monocytes to the damaged area and further amplifying the inflammatory response.⁴² In addition to secreted cytokines, macrophages can also regulate endothelial function by releasing non-metabolic molecules such as extracellular eRNA. Studies have demonstrated that macrophage-derived eRNA can be taken up by vascular endothelial cells, inducing apoptosis and barrier dysfunction.⁴³ Furthermore, during the pathogenesis of PVR, the role of macrophages extends beyond initiating inflammation and damaging endothelial cells; they can also induce endothelial cells to undergo a phenotypic transition.⁴⁴ When exposed to stimuli such as inflammation, oxidative stress, or hypoxia, endothelial cells are induced to undergo Endothelial-to-Mesenchymal Transition (EndMT).⁴⁵ During this transition, endothelial cells lose their characteristic markers (eg, VE-cadherin, CD31) and begin to express mesenchymal cell markers like α -SMA and fibronectin. This phenotypic shift not only compromises the endothelial barrier and promotes the abnormal proliferation and migration of smooth muscle cells, but also provides a new pathological cell population that drives pulmonary vascular remodeling. Notably, EndMT may directly contribute to PAH by transforming endothelial cells into smooth muscle-like cells with higher proliferative and migratory potential. This notion is supported by clinical and experimental findings, including the observation of EndMT markers in both PAH patients and the vascular lesions of BMPR2 mutant rats.⁴⁶

The interaction between endothelial cells and macrophages during EndMT is especially crucial. On one hand, EndMT cells can regulate macrophage polarization by secreting specific factors. Multiple studies, including those in mouse models and in vitro cell culture experiments, have demonstrated that in pancreatic ductal adenocarcinoma, EndMT cells secrete the chaperone HSP90 α , which induces M2 macrophage polarization and further HSP90 α secretion to promote tumor growth.⁴⁷ Conversely, other studies in mice, both in vitro and in vivo, have shown that CD163+ macrophages release pro-inflammatory cytokines rather than mediating an anti-inflammatory response. These macrophages activate intracellular signaling pathways within endothelial cells, leading to an apoptosis-prone EndMT phenotype and identifying NF- κ B as a key pathway responsible for CD163+ macrophage-induced EndMT formation.^{44,48,49}

In summary, the interaction between endothelial cells and macrophages in PVR forms a complex bidirectional regulatory network. Endothelial injury attracts and activates macrophages via the secretion of chemokines and the expression of adhesion molecules. In a reciprocal manner, macrophages modulate endothelial cell function and phenotypic transformation by secreting bioactive molecules and metabolic products. Mechanistic studies of this interaction not only enhance our understanding of PVR pathogenesis but also provide a theoretical basis for exploring novel therapeutic targets.

The Effect of Macrophage Polarization on Smooth Muscle Cell Proliferation and Phenotype

The interaction between smooth muscle cells (SMCs) and macrophages is a critical factor in the pathological progression of PVR. These two cell types not only directly participate in vascular structural changes but also play significant roles in the development of the disease.

Under normal physiological conditions, SMCs are located in the tunica media of blood vessels, where they provide mechanical strength and stability to the vasculature through interactions with the extracellular matrix. Concurrently, their contractile and relaxation capabilities regulate blood flow and pressure. However, under pathological conditions, inflammatory factors (eg, IL-6) and growth factors (eg, platelet-derived growth factor, PDGF) induce excessive proliferation of vascular

SMCs by activating signaling pathways such as MAPK and PI3K/Akt,^{50,51} These cells then migrate to the intimal layer, initiating a phenotypic switch from a contractile phenotype with low proliferative capacity to a synthetic phenotype characterized by significantly enhanced proliferation and migration. This transformation further exacerbates vascular lumen narrowing.⁵²

During PVR, SMCs not only undergo their own phenotypic transformation but also recruit macrophages to local inflammatory or injury sites by secreting chemokines like CCL2, thereby amplifying the local immune response. The link between chemokines and macrophage recruitment and activation has been demonstrated in clinical patients and animal models: models deficient in specific chemokines show a significant reduction in PVR, suggesting a core role for the SMC-macrophage interaction in disease progression.⁵³ The relationship between M2 macrophages and SMCs is particularly prominent, as M2 macrophages promote the proliferation of pulmonary artery SMCs (PASMCs) and vascular remodeling by secreting pro-angiogenic factors such as VEGF and PDGF- β .³⁷ Research by Abid et al has shown that M2 macrophages cooperate with PASMCs via CCR2/CCR5-mediated signaling pathways to promote PASMC proliferation and migration.⁵⁴ The pro-proliferative effect of M2 macrophage culture supernatant on PASMC proliferation was significantly attenuated by blocking CCR2 and CCR5, indicating that the CCR2/CCR5 signaling pathway plays a key role in this process.⁵⁴ Furthermore, CCR5 is expressed in endothelial cells, SMCs, and macrophages of PH patients and is also upregulated in rodent models of chronic hypoxia. Conversely, mice lacking CCR5 and exposed to hypoxia exhibit reduced PASMC proliferation and do not develop pulmonary hypertension.⁵⁵ These findings suggest that M2 macrophages not only function by secreting anti-inflammatory factors but also likely participate in the pathological progression of PVR through direct communication with PASMCs.

In summary, the interaction between PASMCs and macrophages is a key mechanism driving disease progression. PASMCs secrete chemokines that recruit macrophages to the lesion site. M2 macrophages then further promote PASMC proliferation and migration through the secretion of pro-angiogenic factors and the activation of the CCR2/CCR5 signaling pathway. This series of intercellular interactions highlights the critical pathological basis for the cooperative roles of PASMCs and M2 macrophages in PVR progression.

Macrophage Polarization and Extracellular Matrix Remodeling

The extracellular matrix (ECM), composed of various matrix proteins such as collagen, elastin, and glycosaminoglycans, plays a crucial role in maintaining vascular structure, elasticity, and stability. In PVR, macrophages interact with the ECM to regulate local inflammation and fibrosis, thereby driving vascular remodeling. ECM metabolic dysregulation also plays a key role in this process, with excessive deposition of matrix proteins, dysregulated degradation, and increased stiffness. These changes can regulate cell behavior via mechanotransduction signals, forming a pathological positive feedback loop.^{56,57}

Macrophages regulate local inflammation and fibrosis progression through their interaction with the ECM. On one hand, ECM components such as fibronectin, laminin, and glycosaminoglycans can act as chemoattractants for macrophages, promoting their migration to injury sites. Upon migration to these areas, macrophages exacerbate local inflammatory responses by secreting various inflammatory factors (eg, TNF- α , IL-1 β , IL-6),⁵⁸ On the other hand, macrophages regulate the dynamic balance of the ECM during remodeling by secreting matrix metalloproteinases (MMPs) and their inhibitors (TIMPs).⁵⁹ The dynamic regulation of the ECM is critically dependent on the balance between MMPs and TIMPs. Excessive MMP activity coupled with insufficient TIMP levels results in abnormal ECM degradation. This process also releases growth factors stored within the matrix (eg, VEGF, TGF- β), further exacerbating vascular pathological changes.⁶⁰

In regulating vascular remodeling, different macrophage polarization phenotypes have distinct effects on ECM metabolism. M2 macrophages interact with T helper 2 (Th2) cells to secrete anti-inflammatory and pro-repair factors such as IL-10, TGF- β , CD206, Arg-1, and CCL-18. This action both suppresses M1 pro-inflammatory factor production and mitigates tissue damage while also promoting ECM deposition and vascular wall repair, thereby alleviating abnormal vascular permeability.^{15,61} However, the over-activation of M2 macrophages can lead to fibrosis and abnormal ECM deposition. Through their regulation of TGF- β and other ECM-related factors, these cells promote the deposition of Type I and Type III collagen, increasing vascular wall stiffness and ultimately driving pathological vascular remodeling.⁶² Additionally, MMP-2 and MMP-9 secreted by M1 macrophages can degrade collagen and fibronectin. This action provides space for smooth muscle cell migration and releases matrix-stored growth factors (eg, VEGF), further accelerating the remodeling process.⁶³

In summary, macrophages regulate endothelial cell function, smooth muscle cell proliferation, migration, and phenotypic changes, and also influence ECM metabolic balance. This intricate pathological network exacerbates vascular wall thickening and stiffness while driving a positive feedback loop of pathological inflammation and tissue remodeling that accelerates PVR progression. Single-cell RNA sequencing to investigate the mechanisms by which different polarized macrophage phenotypes contribute to PVR not only offers a new perspective for understanding the pathogenesis of diseases like pulmonary hypertension but also presents potential therapeutic strategies for the targeted regulation of macrophage, smooth muscle cell, and endothelial cell phenotypic transitions.

The Regulatory Role of Glucose Metabolism Intermediates in Macrophage Polarization States

Macrophages play a crucial role in inflammation, immune regulation, and tissue repair, and the reprogramming of glucose metabolism (including pathways such as glycolysis and OXPHOS) is closely linked to their polarization states, which further influence the progression of PVR. The metabolites of glucose metabolism not only provide energy for cells but also play significant roles in cell signaling, immune responses, and tissue repair (Figure 3 and Table 1)

Pyruvate

Pyruvate, the final product of glycolysis, is also a key intersection point for multiple biosynthetic pathways, and its metabolic fate profoundly impacts cellular function. In the pathological state of pulmonary vascular remodeling PVR, local hypoxia and inflammatory stimuli significantly enhance the glycolytic rate in macrophages, leading to the production of large amounts of pyruvate.

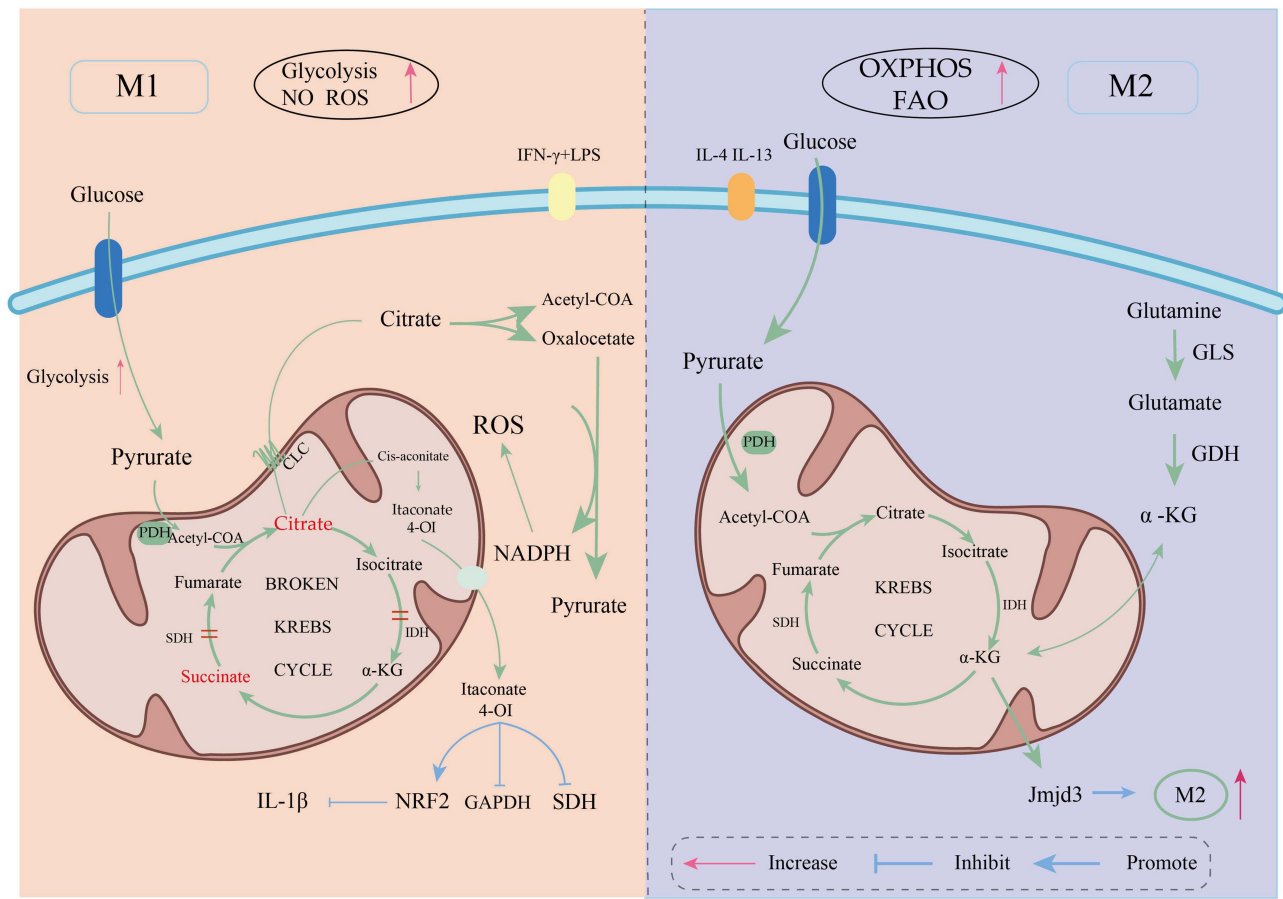


Figure 3 The metabolic differences between M1 and M2 macrophages.

Table 1 The Regulatory Role of Metabolic Intermediates in Macrophage Polarization and Inflammation

Metabolite	Mechanism	Synthesis	Effects on Macrophage Polarization	Inflammatory	References
Pyruvate	The end product of glycolysis	Pyruvate Kinase	Acetyl-CoA promotes histone acetylation and epigenetic modifications, thereby enhancing the pro-inflammatory response of M1 macrophage	Increased NF- κ B; Increased IL-1 β , TNF- α	[63]
Lactic acid	Derived from pyruvate	Lactate Dehydrogenase	Increased M2 Polarization	Inhibits inflammation	[64]
Citrate	TCA Cycle Intermediate Metabolites	Citrate Synthase	Acetyl-CoA regulates the expression of pro-inflammatory genes in M1-macrophages through histone acetylation	Increased ROS, NO and Prostaglandin	[63,65,66]
Succinate	TCA Cycle Intermediate Metabolites	Succinate dehydrogenase	High concentrations of succinate stabilize HIF-1 α by inhibiting PHD, Increased M1 polarization.	In different microenvironments, it can exhibit both pro-inflammatory and anti-inflammatory expression	[67,68]
Malate	TCA Cycle Synthesis	Fumarase	Malate promotes M2 macrophage polarization via SOCS2, exerting anti-inflammatory and tissue repair effects, while suppressing pro-inflammatory responses.	Anti-inflammatory expression	[69,70]
α -Ketoglutarate	TCA Cycle Synthesis; Glutamine Metabolism	Isoctrate Dehydrogenase	Increased anti-inflammatory and M2 gene expression by aKG-Jmjd3 pathway	Anti-inflammatory expression	[71]
Itaconate, 4-octyl itaconate (itaconate derivative)	Catalyzed by the IRG1 enzyme	Cis-Aconitate decarboxylase	Inhibit inflammatory cytokine production in M1	Activation of the anti-inflammatory program; Activation of NRF2 inhibits the production of IL-1 β	[72-74]
Fumarate	TCA Cycle Synthesis	Succinate Dehydrogenase		Inhibits KDM5 histone demethylases, increasing H3K4me3 levels and promoting TNF and IL-6 expression	[75]

Pyruvate primarily follows two metabolic fates. On one hand, it can enter the mitochondria and be catalyzed by the pyruvate dehydrogenase complex (PDC) to enter the TCA cycle, generating citrate and subsequent metabolites. This process increases the level of acetyl-CoA in the cytoplasm, promoting histone acetylation and related epigenetic modifications. These epigenetic changes help activate the transcription of pro-inflammatory genes, thereby enhancing the inflammatory response of M1 macrophages;⁷⁶ On the other hand, under the condition of enhanced aerobic glycolysis in M1 macrophages, pyruvate is converted into lactate in the cytoplasm through the catalysis of lactate dehydrogenase (LDH). Lactate not only serves as a signaling molecule, playing a role in intracellular and extracellular signal transduction with key immune regulatory functions, but increasing evidence also suggests that lactate acts as a metabolic regulator of macrophages, closely linked to their polarization. A 2019 study demonstrated that lactate can induce histone lactylation, which enhances the expression of M2 genes during the M1 polarization phase of macrophages.^{64,77} This finding offers a new perspective for intervening in the reciprocal transformation of macrophage polarization states in disease conditions. In the context of PVR, enhancing the expression of M1-associated genes and suppressing the

proportion and activity of M2 macrophages during the later stages of disease progression may represent a viable strategy to attenuate vascular remodeling. This metabolic diversion mechanism determines the energy utilization patterns and functional phenotypes of macrophages under distinct microenvironmental conditions, underscoring the pivotal role of glucose metabolism reprogramming in immune regulation.

Notably, the balance and regulation of pyruvate metabolism involve multiple key catalytic enzymes and regulatory factors. For instance, pyruvate dehydrogenase kinase (PDK) inhibits the activity of the PDC via phosphorylation, thereby directing pyruvate toward lactate production. In mammals, the PDK family comprises four main isoenzymes (PDK1–PDK4), each exhibiting distinct regulatory properties and tissue-specific expression patterns—features that are also relevant to the regulation of macrophage polarization.⁷⁸ PDK1 deficiency has been shown to attenuate LPS-induced glycolysis, reduce the number of M1 macrophages, and suppress the production of associated pro-inflammatory mediators such as IL-6, IL-12, IL-1 β , and iNOS. Concurrently, it promotes the activation of M2 macrophages.^{79,80} PDK2 suppresses macrophage activation and M1 polarization through the VSIG4–PI3K/Akt/STAT3 signaling pathway;⁸¹ PDK4 promotes M1 macrophage polarization through the HIF-1 α –PDK4 signaling axis.⁸² The combined activity of PDK4 and PDK2 synergistically promotes M1 macrophage polarization⁸³ (Table 2).

In summary, under pro-inflammatory stimulation and upregulation of the Warburg effect, pyruvate—as the end product of glycolysis and a central node in cellular energy metabolism—undergoes metabolic branching toward either mitochondrial oxidation via the TCA cycle or cytosolic conversion into lactate. These divergent pathways not only directly influence cellular energy supply but also modulate macrophage polarization through mechanisms such as acetylation-dependent epigenetic regulation, signaling pathway activation, and microenvironmental acidification. Targeting key regulatory enzymes such as PDK and LDH thus presents a promising therapeutic strategy for modulating macrophage function.

Citrate Metabolism

Citrate is not only a critical intermediate in TCA cycle but also serves as a key signaling molecule involved in the regulation of cellular functions and epigenetic modifications.⁸⁴ In normal cells, citrate participates in the TCA cycle to support ATP production. However, in macrophages activated by pro-inflammatory stimuli, disruption of the TCA cycle leads to intracellular accumulation of citrate.^{17,85}

The citrate accumulated in the mitochondria must be transported to the cytoplasm through the citrate transporter (SLC25A1, also known as CIC) located on the mitochondrial inner membrane. This transport process is dependent on the concentration gradient.⁸⁶ Once in the cytoplasm, citrate is cleaved by ATP citrate lyase (ACLY) into acetyl-CoA and oxaloacetate.⁸⁷ This metabolic pathway is a critical hub for metabolic epigenetics and can regulate the polarization of M1/M2 macrophages.⁸⁸ Studies have shown that silencing CIC or ACLY significantly reduces the production of ROS, NO, and prostaglandins, suggesting that citrate efflux plays an important role in pro-inflammatory responses.⁸⁴ During the activation of M1 macrophages, both the mRNA and protein expression levels of CIC and ACLY are significantly increased.⁸⁹ Both enzymes, as key regulators of macrophage-mediated inflammatory responses, are crucial for the production of inflammatory mediators. They influence immune cell recruitment, the progression of inflammation, and even vascular dilation.⁹⁰ In summary, regulating the CIC/ACLY axis may offer a potential therapeutic strategy for alleviating pulmonary vascular remodeling by influencing macrophage polarization. However, ACLY plays crucial roles

Table 2 The Impact of Pyruvate Dehydrogenase Kinase (PDK) on Macrophage Polarization

PDK	Metabolic Pathways	Effects on Macrophage Polarization	References
PDK1	Regulation of Glycolysis	Increased M1 Polarization, Inhibits M2 Polarization	[79]
PDK2	VSIG4-PI3K/Akt/STAT3 Pathway	Inhibits M1 Polarization	[80]
PDK4	HIF-1 α -PDK4 Pathway	Increased M1 Polarization	[81]
PDK2-PDK4	PDK-PDH-Lactic acid Pathway	Increased M1 Polarization	[82]

in various tissues, and targeting ACLY expression specifically in macrophages within the lung tissue remains a significant challenge. This represents a major obstacle for the further clinical translation of this strategy.

Acetyl-CoA participates in the reactions of histone acetyltransferases, leading to increased histone acetylation levels. This modification alters chromatin structure, thereby regulating the expression of pro-inflammatory or anti-inflammatory genes.⁹¹ This mechanism plays a crucial role in regulating macrophage polarization, particularly the balance between M1 and M2 phenotypes. Under pro-inflammatory conditions, the increase in cytosolic acetyl-CoA levels is often associated with enhanced histone acetylation, which facilitates the activation of a range of pro-inflammatory genes (such as IL-1 β , TNF- α , etc), promoting M1 macrophage polarization and its inflammatory response. Conversely, in anti-inflammatory or repair environments, relatively lower acetyl-CoA availability favors the maintenance of M2 macrophage function.⁹²

Similarly, oxaloacetate, produced from citrate breakdown, plays multiple roles. It can be converted into malate through intracellular enzymatic reactions, and under the action of malate dehydrogenase, it generates pyruvate and NADPH. This provides the cell with reducing power, supporting fatty acid synthesis and maintaining redox balance.⁹³ NADPH, as a crucial reducing cofactor, not only participates in biosynthetic reactions but also plays a key role in combating oxidative stress. This is essential for maintaining normal cell function and regulating macrophage phenotypes. Oxaloacetate, by supporting NADPH production, helps regulate ROS levels and intracellular signaling, indirectly influencing macrophage polarization.⁹⁴

Therefore, in the context of PVR, metabolic reprogramming triggered by local hypoxia and inflammatory stimuli leads to citrate efflux into the cytoplasm, where it is broken down by ACLY to generate acetyl-CoA and oxaloacetate. Together, these metabolites form a dual regulatory system. Acetyl-CoA promotes the expression of pro-inflammatory phenotypes by regulating histone acetylation and lipid metabolism, while oxaloacetate regulates NADPH levels and the redox state, influencing cellular energy balance and signaling. This system jointly determines the direction of macrophage polarization towards M1 or M2 phenotypes. This mechanism plays a crucial role in local inflammation, tissue repair, and the progression of PVR, providing new theoretical insights and therapeutic targets for metabolic interventions in related diseases.

Itaconate and Its Derivatives

Itaconate was first synthesized in 1836, and at that time, it was primarily used for industrial purposes.⁹⁵ With ongoing research, it has been discovered that itaconate plays a significant role in immune regulation. Subsequently, researchers identified that the enzyme encoded by the *Irg1* gene is responsible for the synthesis of itaconate in macrophages. This gene was recognized as encoding the enzyme that catalyzes the decarboxylation of cis-aconitate (an intermediate of the TCA cycle) to produce itaconate.⁹⁶ Researchers have used techniques such as gene knockout models (*Irg1*^{-/-}) to analyze the role of itaconate and its derivatives in macrophages, investigating their regulatory mechanisms in inflammatory responses.^{12,72}

Itaconate exerts anti-inflammatory effects through various mechanisms, one of which is by inhibiting SDH to reduce ROS generation in mitochondria. Studies have shown that itaconate shares a similar structure with maleic acid and can competitively inhibit SDH, thereby reducing LPS-induced ROS production. This effect has been validated in mouse bone marrow-derived macrophages (BMDMs).⁹⁷ However, itaconate's effectiveness as an SDH inhibitor is relatively weak, as experimental results show that only at high concentrations does itaconate significantly inhibit SDH. This suggests that SDH inhibition is not the sole mechanism underlying itaconate's anti-inflammatory effects.⁷³ In addition to its inhibition of SDH, studies have shown that due to the structural similarity between itaconate and malate, itaconate can be transported from the mitochondrial inner membrane to the cytoplasm via common carriers.⁷³ This process subsequently activates the NRF2 pathway to regulate the antioxidant response.⁷⁴ This process subsequently activates the NRF2 pathway to regulate the antioxidant response,⁹⁸ thereby further inhibiting ROS production and the generation of the pro-inflammatory cytokine IL-1 β . -octylitaconate (4-OI), a derivative of itaconate, alkylates the cysteine residues of GAPDH, thereby inhibiting its enzymatic activity and activating anti-inflammatory programs.⁹⁹ This mechanism further underscores the role of itaconate and its derivatives in regulating macrophage inflammatory responses. Specifically, 4-OI not only reduces ROS levels in macrophages stimulated by LPS but also inhibits IL-1 β production through NRF2 activation, thereby highlighting its potential in mitigating inflammatory responses.⁷⁴ Notably, itaconate also exhibits a negative feedback regulation with the type IFN signaling pathway. IFN- β

induces the expression of Irg1 and the production of itaconate, while the itaconate derivative 4-OI can attenuate the expression of IFN-dependent genes by inhibiting the IFN signaling pathway.¹⁰⁰ Interestingly, although itaconate accumulates in macrophages after M1 polarization and retains its anti-inflammatory effects, studies have shown that the reduction of IRG1 and itaconate is essential for M2 macrophage polarization. This finding further supports the inhibitory role of itaconate when it is excessively activated during immune responses,¹⁰¹ It also provides a novel approach to alleviating vascular remodeling by modulating M2 macrophage polarization.

Based on the aforementioned studies, itaconate alleviates inflammation by inhibiting SDH, activating NRF2-mediated antioxidant pathways, and negatively regulating IFN signaling, thereby reducing inflammation-associated ROS production and the expression of pro-inflammatory cytokines. Given the close association between the development of pulmonary vascular remodeling (PVR) and inflammation, oxidative stress, and cellular metabolic abnormalities, these mechanisms suggest that itaconate and its derivatives may mitigate endothelial cell damage and SMCs hyperproliferation by modulating the local immune microenvironment in the lungs and balancing M1 and M2 macrophage polarization. This, in turn, may inhibit or reverse pathological vascular remodeling. Although most studies to date have focused on the effects of itaconate in macrophages, the precise mechanisms underlying its role in the interplay between lung inflammation and vascular remodeling remain incompletely understood. Further *in vitro* and *in vivo* experiments are needed to explore the therapeutic potential and mechanisms of itaconate in diseases associated with PVR.

Succinate and α -Ketoglutarate

Within the context of PVR, the significance of succinate in the reprogramming of macrophage glucose metabolism is increasingly recognized. Upon macrophage activation, glycolysis is upregulated, leading to enhanced succinate production, which subsequently inhibits succinate dehydrogenase activity and suppresses succinate-mediated inflammation. Traditionally regarded as an intermediate in the TCA cycle and a substrate for the mitochondrial electron transport chain, succinate has now been identified as a signaling molecule. It exerts its effects by binding and activating its specific receptor, SUCNR1 (G protein-coupled receptor 91), thereby participating in processes such as inflammation and immune activation.^{102,103} Meanwhile, in the TCA cycle, succinate is derived from the conversion of α -ketoglutarate (α -KG), and these two metabolites are closely linked in cellular metabolic pathways. During macrophage activation, the concentrations of succinate and α -KG influence each other, collectively regulating cellular energy metabolism and the inflammatory response.

Intracellular succinate oxidation is closely linked to the increase in mitochondrial membrane potential. In LPS-activated macrophages, the shift towards glycolysis reduces mitochondrial ATP synthesis, leading to a significant increase in mitochondrial membrane potential. This elevated membrane potential, in conjunction with succinate oxidation, promotes the generation of mitochondrial ROS. As signaling molecules, ROS activate HIF-1 α , thereby enhancing the expression of pro-inflammatory genes.¹⁰⁴ α -ketoglutarate (α -KG) inhibits M1 macrophage activation while promoting M2 macrophage activation. It exerts anti-inflammatory effects by mediating both metabolic and epigenetic reprogramming.⁷¹ Studies have shown that measuring the α -KG/succinate ratio reveals that macrophages stimulated with IL-4 exhibit a higher α -KG/succinate ratio compared to those treated with LPS. Manipulating this ratio allows for the customization of macrophage immune responses.¹⁰⁵ Additionally, when macrophages are stimulated by pro-inflammatory factors such as LPS, partial reprogramming of the TCA cycle leads to succinate accumulation within the cells. High concentrations of succinate can inhibit PHDs, which depend on α -KG and oxygen for catalysis. As succinate levels rise, PHD activity is competitively inhibited, resulting in the stabilization of HIF-1 α . This stabilized HIF-1 α translocates to the nucleus, where it forms heterodimers and binds to hypoxia response elements (HREs), thereby initiating the transcription of a series of downstream genes.^{67,104,106} The stabilization of HIF-1 α further promotes the expression of pro-inflammatory cytokines, which can be considered a key function of succinate as a signaling marker.²¹ SUCNR1 is a G protein-coupled receptor and serves as the specific receptor for extracellular succinate,¹⁰³ Succinate primarily mediates its signaling through the Di and Gq signaling pathways. Upon binding to SUCNR1, succinate activates downstream signaling cascades, such as the cAMP/PKA and PLC/IP3/Ca²⁺ pathways, thereby modulating macrophage inflammatory responses.⁶⁸ SUCNR1 exhibits a markedly paradoxical role in pro- and anti-inflammatory signaling, with its effects being significantly influenced by environmental factors. During early inflammation or hypoxia, the activation of SUCNR1 can induce the production of inflammatory factors (eg, IL-1 β and TNF- α), thereby

enhancing the macrophage inflammatory response and exacerbating M1 macrophage-mediated vascular damage. This suggests a pro-inflammatory role for SUCNR1 in the early stages of PVR, which drives vascular inflammation.^{68,107} Conversely, other studies have shown that extracellular succinate, through binding to this receptor, activates the PKA–CREB–KLF4 signaling pathway. This enhances IL-4-induced anti-inflammatory gene expression, such as Arg1, Mrc1, Fizz1, and IL-10, and consequently suppresses the expression of pro-inflammatory factors like IL-1 β , IL-6, Tnf, and Nos2.¹⁰⁸ This mechanism suggests that under specific conditions, SUCNR1 may promote M2 polarization or mediate the resolution of inflammation. Furthermore, LysM-Cre SUCNR1 $^{fl/fl}$ mice (with myeloid-specific SUCNR1 deletion) exhibit a stronger inflammatory response and metabolic dysfunction under both steady-state and high-fat diet conditions. This implies that the absence of SUCNR1 leads to a predominant pro-inflammatory macrophage phenotype,^{16,108} The high expression of SUCNR1 in M2 macrophages, which are generated from primary human monocyte cultures with a combination of IL-4 and IL-13, in stark contrast to M1 macrophages, strongly suggests a critical role for SUCNR1 in the M2 polarization process.¹⁰⁹

In summary, succinate's role is multifaceted: it promotes an increase in mitochondrial membrane potential, induces ROS generation, and stabilizes HIF-1 α . This, in turn, activates a cascade of downstream pro-inflammatory gene expression, thereby aggravating the local inflammatory environment. The changing balance between succinate and α -KG also participates in regulating macrophage phenotypic transformation, offering a new regulatory perspective for maintaining metabolic homeostasis and immune balance. The dual role of SUCNR1 consequently makes its function in PVR more intricate. The specific functional tendencies of SUCNR1 at different stages of PVR (eg, from early inflammation to late fibrosis), and the mechanisms by which it is regulated in a given microenvironment to mediate either pro- or anti-inflammatory responses, remain to be fully elucidated. This complexity makes SUCNR1 a multifaceted regulatory node. A precise understanding of its role in PVR will be instrumental in developing more stage-specific intervention strategies.

Conclusion and Outlook

PVR is a central pathological process in various pulmonary vascular diseases, including pulmonary arterial hypertension. Its essence lies in the dynamic reconstruction of the vascular wall structure, involving endothelial cell dysfunction, SMCs proliferation and phenotypic transformation, as well as abnormal deposition and degradation of the ECM. According to the 2022 pulmonary hypertension diagnostic guidelines, pulmonary hypertension is a global health issue, with a prevalence of 1% in the global population, particularly higher in individuals over 65 years of age.² However, the treatment of PVR-related diseases is still in its early stages, with no specific therapeutic approaches currently available. Existing medications—such as oral endothelin receptor antagonists (bosentan, ambrisentan, macitentan),^{110,111} oral type 5 phosphodiesterase inhibitors (sildenafil and avanafil, which exert vasodilatory and antiproliferative effects on pulmonary artery smooth muscle cells),¹¹² and the oral soluble guanylate cyclase stimulator Riociguat (which has direct vasodilatory effects)⁶⁵—primarily target endothelial dysfunction and abnormal SMC proliferation.

This review systematically elucidates how intermediate metabolites from glucose metabolic pathways are no longer merely byproducts of energy metabolism but serve as crucial signaling molecules that directly determine macrophage polarization and, in turn, influence PVR progression. Our key findings include: (1) The accumulation of succinate and citrate is a hallmark of M1 polarization. Succinate promotes inflammatory gene expression by stabilizing HIF-1 α . Citrate efflux into the cytoplasm is converted into acetyl-CoA by ACLY, which then directly enhances the transcription of pro-inflammatory genes via histone acetylation, aggravating endothelial damage and vascular inflammation. (2) Pyruvate and its downstream product, lactate, serve as key metabolic hubs that regulate M1/M2 conversion and inflammation resolution by modulating PDK family activity and histone lactylation. (3) Itaconate, an endogenous metabolite, possesses potent anti-inflammatory effects. It negatively regulates M1 polarization and inflammatory responses by inhibiting SDH or activating the NRF2 signaling pathway, suggesting its potential value in attenuating PVR.

Despite the significant progress made in understanding these metabolic regulatory mechanisms, translating these findings into precision therapies for PVR faces formidable challenges. Future research should prioritize addressing the following knowledge gaps and translational barriers:

1. The Challenge of Tissue- and Cell-Specific Delivery: Many metabolic enzymes (eg, ACLY) are widely expressed across systemic tissues. The primary clinical translational barrier is how to specifically deliver metabolites or metabolic enzyme inhibitors to IMs while avoiding off-target effects on other organs or on Ams within the lung. Therefore, there is an urgent need to develop novel targeted delivery systems (such as nanocarriers or conjugated antibodies) that target ACLY, PDK, or itaconate derivatives to enable precise intervention on macrophages at the PVR lesion site.
2. The Mechanisms of Dynamic Pathology and Cellular Crosstalk: Most existing research is based on static models, and a systematic analysis of macrophage polarization and metabolic features throughout the dynamic progression of PVR is lacking. Concurrently, the mechanism by which macrophages paracrine regulate endothelial cells and PASMCs via metabolites remains unclear. To address this, it is crucial to combine single-cell RNA sequencing and metabolomics techniques to analyze the metabolic profiles of macrophages at different disease stages. Furthermore, developing more physiologically relevant pulmonary vascular organoid or microfluidic models is necessary to simulate and verify the direct paracrine effects of macrophage metabolites on vascular wall cells.
3. The Validation and Translation of Clinical Biomarkers: The changes in metabolic intermediates (eg, succinate, itaconate) in the plasma or lung tissue of PVR patients have not been validated on a large scale as biomarkers for disease diagnosis or prognostic assessment. Therefore, in clinical cohorts, it is imperative to perform metabolomic analysis of plasma and exhaled breath condensate (EBC) from PVR patients to validate the biomarker potential of intermediates like succinate and citrate. This will promote precision phenotyping and personalized therapy based on immunometabolic dysregulation.

In conclusion, a deeper understanding of the regulatory mechanisms of glucose metabolic intermediates on macrophage polarization will open new directions for PVR treatment. This will drive a paradigm shift in the field, moving from traditional anti-proliferative interventions to an innovative model of targeted immunometabolic regulation.

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Disclosure

The authors report no conflicts of interest in this work.

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