





Review

LDHA Regulates the Inflammatory Response in Acute Lung Injury Through Metabolic Reprogramming of Vascular Muscle Cells

Di Lian^{1,†}, Xinlin Fu^{2,†}, Lixin Xie^{1,*}, Shoulong Deng^{3,*}¹College of Pulmonary and Critical Care Medicine, Chinese PLA General Hospital, 100853 Beijing, China²College of Animal Science and Technology, China Agricultural University, 100193 Beijing, China³NHC Key Laboratory of Human Disease Comparative Medicine, Institute of Laboratory Animal Sciences, Chinese Academy of Medical Sciences and Comparative Medicine Center, Peking Union Medical College, 100021 Beijing, China*Correspondence: xielx301@126.com (Lixin Xie); dengshoulong@cnilas.org (Shoulong Deng)

†These authors contributed equally.

Academic Editor: Esteban C. Gabazza

Submitted: 3 March 2025 Revised: 9 May 2025 Accepted: 13 May 2025 Published: 16 January 2026

Abstract

Acute lung injury (ALI) is a severe condition characterized by an inflammatory response and increased vascular permeability, with its pathological mechanisms closely associated with the dysfunction of vascular smooth muscle cells (VSMCs). The present study investigates the molecular mechanisms through which lactate dehydrogenase A (LDHA) influences the inflammatory response in ALI by modulating VSMC metabolic reprogramming. It was observed that under pathological conditions, hypoxia and the inflammatory microenvironment significantly upregulate LDHA expression in lung VSMCs via the activation of the hypoxia-inducible factor (HIF) signaling pathway. The LDHA-mediated Warburg effect not only provides energetic support to VSMCs but also exacerbates inflammatory responses through both direct and indirect mechanisms. This review highlights the critical role of LDHA as a metabolic-inflammatory nexus in ALI and offers a theoretical foundation for targeting LDHA to regulate metabolic reprogramming as a means to mitigate the progression of ALI. Future research will further investigate the specific mechanisms by which LDHA regulates VSMC metabolic reprogramming and will seek to identify effective intervention strategies.

Keywords: ALI; LDHA; smooth muscle cell; inflammation

1. Introduction

Acute lung injury (ALI) is characterized as an acute, diffuse inflammatory condition of the lungs, precipitated by a variety of intra- and extra-pulmonary pathogenic factors of non-cardiogenic origin. This condition can lead to severe hypoxemia and acute respiratory failure, potentially progressing to the critical illness, known as acute respiratory distress syndrome (ARDS). The reprogramming of glucose metabolism is intricately associated with immune responses and inflammatory processes. Study indicates that sepsis link to hyperlactatemia; during septic ALI, macrophages recruited and activated by lipopolysaccharides (LPS) exhibit enhanced glycolysis, which further exacerbates the inflammatory response and worsens oxidative stress, leading to progression of ALI and potentially ARDS or even death, suggesting that glycolytic inhibition is a potent anti-inflammatory strategy for the treatment of ALI [1]. ARDS is a critical respiratory condition characterized by an unclear pathogenesis, a lack of effective pharmacological treatments, and a low quality of life and survival rate for affected individuals. Currently, the incidence of new ALI cases worldwide exceeds three million annually, with clinical meta-analyses revealing a mortality rate of 43%. Furthermore, up to 50% of survivors experience significant pulmonary dysfunction. Persistent inflammation,

coupled with the loss of vascular barrier integrity, results in pulmonary edema and multiorgan dysfunction, which are significant contributors to the elevated mortality associated with ALI and ARDS. The pulmonary vascular system, due to its extensive surface area, is particularly susceptible to the activation of inflammatory responses. In the context of ALI, the infiltration of inflammatory cells and the release of inflammatory mediators, along with increased tissue metabolic activity, lead to a heightened demand for oxygen. Additionally, inflammation-induced vasoconstriction further diminishes oxygen supply to the affected regions of the lung, resulting in hypoxemia. This hypoxic state subsequently triggers the overexpression of HIF, which directly promotes the upregulation of LDHA and the degradation of Inhibitor of kappa B zeta ($I\kappa B-\zeta$). These molecular changes contribute to the reprogramming of cellular metabolism and the exacerbation of inflammatory responses.

Vascular endothelial cells (VECs) constitute a layer of mononuclear cells situated between the bloodstream and the vascular wall tissues. These cells are capable of secreting a variety of vasoactive substances through autocrine, endocrine, and paracrine mechanisms, thereby playing crucial roles in regulating vascular tone, inhibiting the proliferation of smooth muscle cells, and modulating inflammatory responses within the vascular wall. The struc-



tural and functional integrity of VECs is essential for the maintenance of vascular wall function and lung homeostasis. Under homeostatic conditions, VECs remain quiescent and exhibit antioxidant and anti-inflammatory properties. However, during inflammatory events, VECs participate in the interplay between local and systemic immune responses and serve as significant targets for inflammatory processes. This involvement can enhance innate immune responses through the production and release of cytokines and chemokines, including the activation of the NF- κ B signaling pathway and the pro-inflammatory factors interleukin-6 (IL-6) and interleukin-8 (IL-8). The expression of pro-inflammatory factors such as IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) can be activated, positioning VECs as a secondary cascade of chain reactions in response to inflammation [2].

VECs are influenced by various factors that prompt them to lose their original characteristics and undergo significant alterations in polarity, morphology, and function. This process leads to their transformation into mesenchymal cells, such as fibroblasts and smooth muscle cells, a phenomenon known as endothelial-to-mesenchymal transition (EndMT) [3]. Pyruvate dehydrogenase kinase (PDK) phosphorylates pyruvate dehydrogenase complex (PDH) during EndMT, which inhibits the mitochondrial catabolism of pyruvate in endothelial cells, resulting in the reduction of endothelial pyruvate by lactate dehydrogenase (LDH) reduces pyruvate from endothelial cells to lactate, resulting in a paradigm shift in the energy metabolism of VECs.

Abnormal communication between VECs and VSMCs is a critical factor in the initiation and progression of vasculopathic alterations. In ALI, lung epithelial cells and vascular endothelial cells leads to diffuse interstitial and alveolar edema, progressive hypoxemia, and respiratory distress, which subsequently triggers hypoxic pulmonary vasoconstriction (HPV) [4]. Although early HPV is a protective immune response, persistent inflammation and hypoxia can result in the hyperproliferation of VSMCs, thickening of the vascular wall, and ultimately the development of ARDS. Nitric oxide and carbon monoxide in VECs indirectly induce vasodilation and modulate the inflammatory response through crosstalk between VECs and VSMCs, while also promoting the proliferation and migration of VSMCs. The knockdown of vesicle-associated membrane protein 3 (VAMP3) and synaptosomal-associated protein 23 (SNAP23) in endothelial cells has been shown to inhibit the proliferation, migration, and phenotypic transformation of smooth muscle cells co-cultured with endothelial cells. Furthermore, microRNA-126-3p secreted by endothelial cells enhances the proliferation and dedifferentiated phenotype of smooth muscle cells, contributing to the thickening of the neointima in arterial vessels in murine models [5].

VSMCs are a highly differentiated cell type characterized by the expression of various proteins associated with vascular contraction, including smooth muscle myosin heavy chain (SMMHC) and alpha-smooth muscle actin (α -SMA). In their physiological state, VSMCs are referred to as contractile VSMCs, which constitute approximately 90% of the vascular mesenchymal layer and exhibit low capacities for proliferation, migration, and secretion. Despite their high level of differentiation, VSMCs are not terminally differentiated and retain significant phenotypic plasticity. In response to inflammatory stimuli, there is a noted decrease in the expression of contractile phenotypic proteins and an increase in the expression of secretory phenotypic proteins, such as Kruppel-like factor 4 (KLF4) and Osteopontin (OPN). Consequently, these cells are classified as secretory (synthetic) VSMCs, which do not participate in vasoconstriction but instead play a role in regulating vascular remodeling [6]. It also secretes a variety of inflammatory factors, such as interleukins (ILs), tumor necrosis factor- α (TNF- α), and monocyte chemoattractant protein-1 (MCP-1).

During vascular injury, VSMCs migrate from the mesentery to the intima in response to growth factors secreted by endothelial cells, resulting in intimal hyperplasia and restenosis. To mitigate excessive proliferation, nitric oxide (NO) and prostacyclin (PGI₂) released by endothelial cells inhibit the over-proliferation and migration of VSMCs, thereby maintaining the stability of the vessel wall. Furthermore, VSMCs may undergo phenotypic transformation, adopting a myofibroblast-like phenotype that is more conducive to tissue repair, characterized by enhanced proliferation and increased secretion of extracellular matrix (ECM). Consequently, investigating the interactions between vascular smooth muscle cells and vascular endothelial cells in the context of inflammatory responses and cell proliferation during the development of ALI is an effective way to ameliorate the adverse prognosis associated with ALI and to prevent vessel wall thickening.

2. Function and Expression of LDHA in Vascular Smooth Muscle Cells

2.1 Biological Functions of LDHA

The human *LDHA* gene is localized on chromosome 11, 11p15.4, and encodes a protein containing 332 amino acids, including 24 splice variants and several unknown pseudogenes [7]. LDHA is expressed predominantly in skeletal muscle and has a high affinity for pyruvate, preferentially converting pyruvate to lactate while converting nicotinamide adenine dinucleotide (NADH) to NAD⁺ [8]. During conditions of hypoxia or high-intensity exercise, skeletal muscle generates elevated levels of lactic acid through the action of LDHA and subsequently releases it into the bloodstream. This lactic acid is then transported throughout the body, including to the lungs, via the circulatory system. In the lungs, smooth muscle cells uptake lactic acid from the blood, utilizing it as an energy source.

The clearance of lactate produced by skeletal muscle occurs in the liver through the Cori cycle. Conversely, lactate generated by VSMCs in the lungs exerts direct effects on local immune cells, such as macrophages, and endothelial cells, thereby establishing a positive feedback loop that exacerbates the progression of ALI [9], which is important for us to explore the relationship of lactate and LDHA, and the inflammatory response, to the inflammatory response in the lungs. Lactate and LDHA are intricately associated with the inflammatory response in the lungs. Recent studies have demonstrated that the regulatory effects of LDHA primarily manifest through transcriptional regulation, post-transcriptional regulation, and post-translational modifications [10]. LDHA is mainly found in the cytoplasm, but it is also present in the nucleus of some tumor cells. It has been reported that tyrosine residues of LDHA appear in the nucleus after phosphorylation, suggesting that LDHA may have a unique function in gene transcription and RNA stability.

LDH is classified within the 2-hydroxy oxidoreductase family. In humans, LDH is encoded by three genes: LDHA, LDHB, and LDHC. Notably, LDHC is specifically expressed in testicular tissues, while LDHA and LDHB are ubiquitously expressed across various tissues and are recognized as some of the most abundant proteins found in the cytoplasm [11]. LDH functions as a homo- or heterotetramer composed of two subunits, LDHA (M) and LDHB (H), which are encoded by the respective LDHA and LDHB genes. Among the different isoforms, LDH-5 (4M) exhibits the highest catalytic efficiency in the conversion of pyruvate to lactate [12].

The promoter region of the LDHA gene encompasses multiple transcription factor binding sites and is subject to regulation by various transcription factors. Hypoxia-inducible factor-1 (HIF-1) interacts with the hypoxia-responsive element (HRE) to activate LDHA expression. Additionally, the proto-oncogene c-Myc forms a heterodimer with myc-associated factor X (MAX), which subsequently binds to the E-box within the LDHA promoter, thereby enhancing LDHA expression [12]. Furthermore, forkhead box protein M1 (FOXM1) directly binds to the LDHA promoter region, modulating the transcriptional regulation of the LDHA gene, a process that is crucial for aerobic glycolysis and tumorigenesis in patients with pancreatic cancer [13]. Moreover, KLF4 is involved in the regulation of epithelial and mesenchymal gene expression, which is significant for cell proliferation and differentiation. Research indicates that KLF4 exhibits a negative correlation with LDHA expression level [14].

LDHA was directly regulated by factors such as HIF-1, c-Myc, FOXM1, and KLF4, suggesting that LDHA plays a significant role in cellular phenotypic transformation, cell proliferation, and apoptosis [15]. Additionally, the pro-inflammatory effects exhibited by VSMCs in inflammatory contexts, mediated by elevated lactate production, fur-

ther underscore its critical involvement in cellular energy metabolism. Nevertheless, research concerning the role of LDHA in cell proliferation remains insufficient, revealing numerous gaps in the current understanding. Investigating how LDHA regulates inflammatory responses, cell proliferation, and vascularization in ALI is a novel and significant area for future research.

2.2 LDHA Expression in Vascular Smooth Muscle Cells and Its Regulatory Mechanism

Recombinant LDHA is a pivotal enzyme in the glycolytic pathway, significantly influencing the proliferation, migration, and metabolic processes of VSMCs. The lactate microenvironment generated by LDHA activity facilitates the transition of VSMCs from a contractile phenotype to a secretory phenotype, thereby enhancing their proliferation and migration, as well as promoting the secretion of ECM. This process contributes to the thickening of the vascular wall and an increase in pulmonary vascular resistance [16]. The modifications of LDHA, specifically crotonylation and monoubiquitination, were found to be elevated in proliferating VSMCs and neovascular endothelium. The crotonylation occurred at lysine 5 (K5), while monoubiquitination was observed at lysine 76 (K76). The crotonylation at K5 enhanced LDHA activity and increased intracellular lactic acid levels by facilitating its tetramer formation, thereby promoting cellular growth. Conversely, the monoubiquitination at K76 contributed to cell proliferation by mediating mitochondrial division and enhancing VSMC migration [16,17].

In a mouse ALI model, the knockdown of LDHA in VSMCs significantly decreased lung edema and neutrophil infiltration while enhancing the oxygenation index [18]. Conversely, LDHA in lung VSMCs exacerbated alveolar injury by promoting lactate accumulation, directly activating the NF- κ B and signal transducer and activator of transcription 3 (STAT3) pathways, and inducing the release of pro-inflammatory factors such as IL-6 and TNF- α [19].

Metabolic reprogramming of vascular smooth muscle cells is a crucial component of the vascular remodeling process. LDHA plays a significant role in this context by facilitating glycolysis and lactate production, thereby supplying the necessary energy and metabolic intermediates. The restoration of mitochondrial function has been shown to normalize hypoxia-induced oxidative stress and mitigate the inflammatory response in murine models by decreasing excessive lactate accumulation and correcting abnormal glycolytic activity [20]. Furthermore, the overexpression of LDHA has been confirmed in human vascular smooth muscle cell lines, promoting a transition to a synthetic phenotype. Conversely, the knockdown of LDHA results in reduced proliferation and lactate production in human coronary artery smooth muscle cells (HACSMCs) [19].

3. Mechanisms of LDHA Regulation of Metabolic Reprogramming in Vascular Smooth Muscle

Energy metabolism serves as a crucial regulator of cellular function and is significantly altered when tissues and cells experience pathological changes. Under normal physiological conditions, cells are efficiently supplied with adenosine triphosphate (ATP) through glycolysis and oxidative phosphorylation. One molecule of glucose can yield a net production of 36 ATP molecules, which provide the necessary energy for various cellular activities. In hypoxic conditions, cells are unable to utilize oxidative phosphorylation effectively for ATP production; instead, they resort to aerobic glycolysis facilitated by M2-type pyruvate kinase (PKM2) and LDHA, resulting in a net production of only 2 ATP molecules. Concurrently, LDHA sustains aerobic glycolysis by regenerating NAD^+ from NADH. Although aerobic glycolysis is less efficient, it occurs at a rate that is approximately 100 times faster than oxidative phosphorylation, thereby meeting the short-term energy demands of the cell in the absence of adequate oxygen, albeit at the cost of increased glucose consumption and lactate production. Notably, certain cell types, including activated immune cells, tumor cells, and infected cells, adopt an aerobic glycolytic pathway to convert glucose to lactate even under normoxic conditions. This metabolic shift signifies a change in cellular function and signaling pathways and is commonly referred to as the Warburg effect [21].

Acute injury leads to an insufficient supply of oxygen to lung tissue, prompting VSMCs to depend primarily on LDHA-mediated glycolysis for energy production, rather than on mitochondrial oxidative phosphorylation. This metabolic reprogramming represents a crucial adaptive mechanism for VSMCs to manage oxidative stress and inflammation. In conditions of hypoxia, hypoxia-inducible factor 1 alpha ($\text{HIF1}\alpha$) exhibits sensitivity to fluctuations in oxygen levels and serves as the active subunit of the HIF. Under hypoxic conditions, $\text{HIF-1}\alpha$ becomes more stable and, upon translocating to the nucleus, it dimerizes with the oxygen-independent $\text{HIF-1}\beta/\text{ARNT}$ to initiate the expression of downstream target genes. However, the lactate-mediated response to sustained hypoxia appears to be functionally independent of $\text{HIF-1}\alpha$, as it involves the NDRG family member 3 (NDRG3) [22]. Similar to $\text{HIF1}\alpha$, NDRG3 undergoes degradation in a prolyl hydroxylase domain 2 (PHD2)/von Hippel-Lindau (VHL)-dependent manner under normoxic conditions. However, during prolonged hypoxia, NDRG3 is protected from degradation through its binding to lactate. The resultant increase in NDRG3 levels, independent of $\text{HIF1}\alpha$, activates the RAF-ERK signaling pathway, which regulates hypoxia-related pathophysiological responses, including inflammation and angiogenesis. Furthermore, both pharmacological and genetic inhibition of LDHA restricts NDRG3 protein accumulation in a dose-dependent manner. Lactate is capa-

ble of reversing these effects without influencing $\text{HIF1}\alpha$ protein levels. Recent studies have identified endogenous branched-chain α -keto acids (BCKAs) as newly discovered inhibitors of PHD2, which aerobically activate $\text{HIF1}\alpha$ signaling in normal VSMCs. This process involves a positive feedback loop in which BCKAs stimulate $\text{HIF1}\alpha$, leading to increased expression of LDHA. The resultant production of lactate is anticipated to lower cellular pH, thereby enhancing the production of L-2-hydroxyglutarate (L2HG), which subsequently inhibits PHD2 activity. This inhibition further amplifies $\text{HIF1}\alpha$ activity under aerobic conditions. $\text{HIF1}\alpha$ plays a unique and complex role in regulating VSMC function across various vascular beds. Specifically, BCKAs inhibit PHD2 activity, activate $\text{HIF1}\alpha$ signaling, enhance glycolytic activity, and facilitate the transition of pulmonary arterial smooth muscle cells (PASMCs) to a synthetic phenotype. Collectively, these mechanisms contribute to vascular dysfunction, including the development of pulmonary arterial hypertension (PAH) [23,24].

Research has demonstrated that the supplementation of lactate in growth medium enhances the synthetic phenotype of VSMCs derived from human induced pluripotent stem cells [25]. Furthermore, lactate promotes the polarization of alternatively activated macrophages exhibiting an anti-inflammatory (M2-like) phenotype. These macrophages play a crucial role in angiogenesis and tissue remodeling, as well as stimulating the release of vascular endothelial growth factor from endothelial cells, thereby facilitating wound healing and tumor-associated angiogenesis [26–29].

4. Effect of LDHA-Regulated Metabolic Reprogramming of Vascular Smooth Muscle on the Inflammatory Response to ALI

4.1 Pathophysiologic Processes of the Inflammatory Response to ALI

The etiology of ALI/ARDS has not been fully defined, and its pathogenesis encompassing a range of direct and indirect risk factors. It is widely acknowledged that uncontrolled inflammation, either localized within the lungs or systemic, constitutes the primary mechanism underlying ALI/ARDS. The principal contributors to this inflammatory response include biological, chemical, and physical factors. ① Biological stimuli, such as bacteria or viruses that invade the lungs, induce inflammation through their proliferation within the host, the production of toxins, and their antigenic properties. Pathogen-associated molecular patterns (PAMPs), including LPS, unmethylated CpG DNA, and RNA derived from pathogens, interact with various surface and intracellular pattern recognition receptors (PRRs) present on immune cells. These receptors encompass Toll-like receptors, nucleotide oligomerization domain-like receptors (NLRs), and C-type lectins (which recognize end products of late glycosylation). The engagement of these PRRs activates the expression and secretion of inflamma-

tory mediators, such as interleukin-1 (IL-1), tumor necrosis factor (TNF), and reactive oxygen species. ② Chemical or physical stimuli, such as lung tissue damage resulting from the inhalation of noxious gases, radiation, and contusion, lead to the production of damage-associated molecular patterns (DAMPs). These include heat shock proteins (HSP), high mobility group protein B1 (HMGB-1), uric acid, and extracellular ATP. In ALI, the hypoxic and inflammatory microenvironment of the lung significantly upregulates the expression in lung VSMC through the activation of signaling pathways, including HIF-1 α . This localized upregulation facilitates the rapid production of ATP via enhanced glycolysis, commonly referred to as the while simultaneously generating lactate to maintain NAD⁺ regeneration, thereby supporting cell survival and function. Concurrently, DAMPs bind to receptors such as the receptor for advanced glycation end products (RAGE), triggering receptor expressed on myeloid cells (TREM), and various ion channels. This interaction prompts immune cells to clear dead cells, activate pro-inflammatory pathways, and result in the secretion of pro-inflammatory factors and other mediators. An overreaction of the immune system to foreign invasions can lead to the synthesis and secretion of excessive cytokines, culminating in a cytokine storm. This phenomenon results in the attack of normal cells, ultimately triggering a systemic inflammatory response, organ failure, and potentially death.

4.2 Direct Effects of LDHA on the Inflammatory Response

During glycolysis, NADH engages with the Rossmann folding domain of LDHA, and through the catalytic activity of LDHA and the thermodynamic stabilization of free radical intermediates, electrons are transferred from NADH to oxygen-containing compounds at an accelerated rate. This process leads to the production of increased levels of oxygen radicals, which may contribute to oxidative damage and cytotoxicity, as well as to the promotion of inflammatory responses [10]. It also promotes T-cell effector function by increasing acetylation and transcription of IFNG, thus highlighting the key role of LDH in inflammation [17]. The application of (S)-N-Hydroxy-3-(4-methoxybenzylsulfonyl)-2,2-dimethylchroman-4-carboxamide (FX11), an inhibitor of LDHA, in chondrocytes resulted in a significant reduction in the expression of the inflammatory factors IL-6 and matrix metalloproteinase-13 (MMP13). Although I κ B- ζ functions as an inhibitor of NF- κ B, but the modulation of NF- κ B by IL-1 β was not impeded by the administration of the LDHA inhibitor. This phenomenon can be attributed to the dual mode of transcriptional regulation governing I κ B- ζ . Specifically, IL-1 β influences the mRNA transcription of Nfkbiz (which encodes the I κ B- ζ protein) through the I κ B kinase 2 (IKK2) pathway, while LDHA is involved in the post-translational stabilization of I κ B- ζ . Notably, FX11 does not impact the transcription of the Nfkbiz gene; rather, it enhances the production of the encoded protein, which

subsequently contributes to the inhibition of inflammatory responses [18]. The analysis of single-cell transcriptome sequencing conducted on the retina and lymph nodes of mice with autoimmune uveitis revealed that the inhibition of LDHA could restore the imbalance between effector T cells (Teff) and regulatory T cells (Treg) during inflammatory conditions. In the context of acute inflammation, the application of specific LDHA inhibitors significantly diminished the population of neutrophils and reactive oxygen species (ROS)-producing neutrophils in the bloodstream, while also effectively suppressed LPS-induced NF- κ B activation of NF- κ B in lung epithelial cells. These findings suggest a potential role for LDHA in the pathophysiology of sepsis-associated ARDS. Post-translational modifications such as phosphorylation, enhance the enzymatic activity of LDHA and facilitate energy metabolism in VSMC, further exacerbating the inflammatory response [30]. LDHA promotes the expression of inflammatory factors by destabilizing the I κ B- ζ protein. Furthermore, it directly activates immune cells, which in turn triggers inflammatory responses. Preliminary evidence indicates that the signaling pathway linked to LDHA is significantly involved in enhancing the inflammatory response (Fig. 1).

4.3 LDHA Indirectly Influences the Inflammatory Response Through Lactate Production

Under normoxia, LDHA is a key enzyme associated with aerobic glycolysis that contributes to lactate production in cancer cells [31,32], tumor cells convert 69–80% of glucose into lactate; while under hypoxia, the conversion efficiency reaches 90%. Lactate, the end product of glycolysis, was once considered a metabolic waste product, but current research suggests that lactate has a variety of important biological functions. Lactate serves a crucial physiological function by facilitating the exchange between lactate-producing and lactate-consuming cells within the body. It has been identified as an amplifier of inflammation, with its accumulation exacerbating the inflammatory response. Elevated levels of LDH activity can impair immune cell functionality, while high concentrations of lactate may diminish the efficacy of effector T cells and promote the production of interleukin-17 (IL-17) by Cluster of Differentiation 4 (CD4⁺) T cells through the PKM2/STAT3 signaling pathway [33]; Inhibition of LDHA activity in macrophages downregulates the expression of pro-inflammatory cytokines, inducible nitric oxide synthase (iNOS), and other anti-inflammatory effects [34]. During ALI, hyperlactatemia arises as a consequence of the upregulation of anaerobic glycolysis, which is activated by an inadequate supply of oxygen. Anaerobic glycolysis refers to the metabolic conversion of glucose to lactate, a process regulated by various rate-limiting glycolytic enzymes, including LDHA. A recent study has demonstrated that the inhibition of the glycolytic pathway using the inhibitor PFKFB3, specifically 3-(3-pyridyl)-1-(4-pyridyl)-

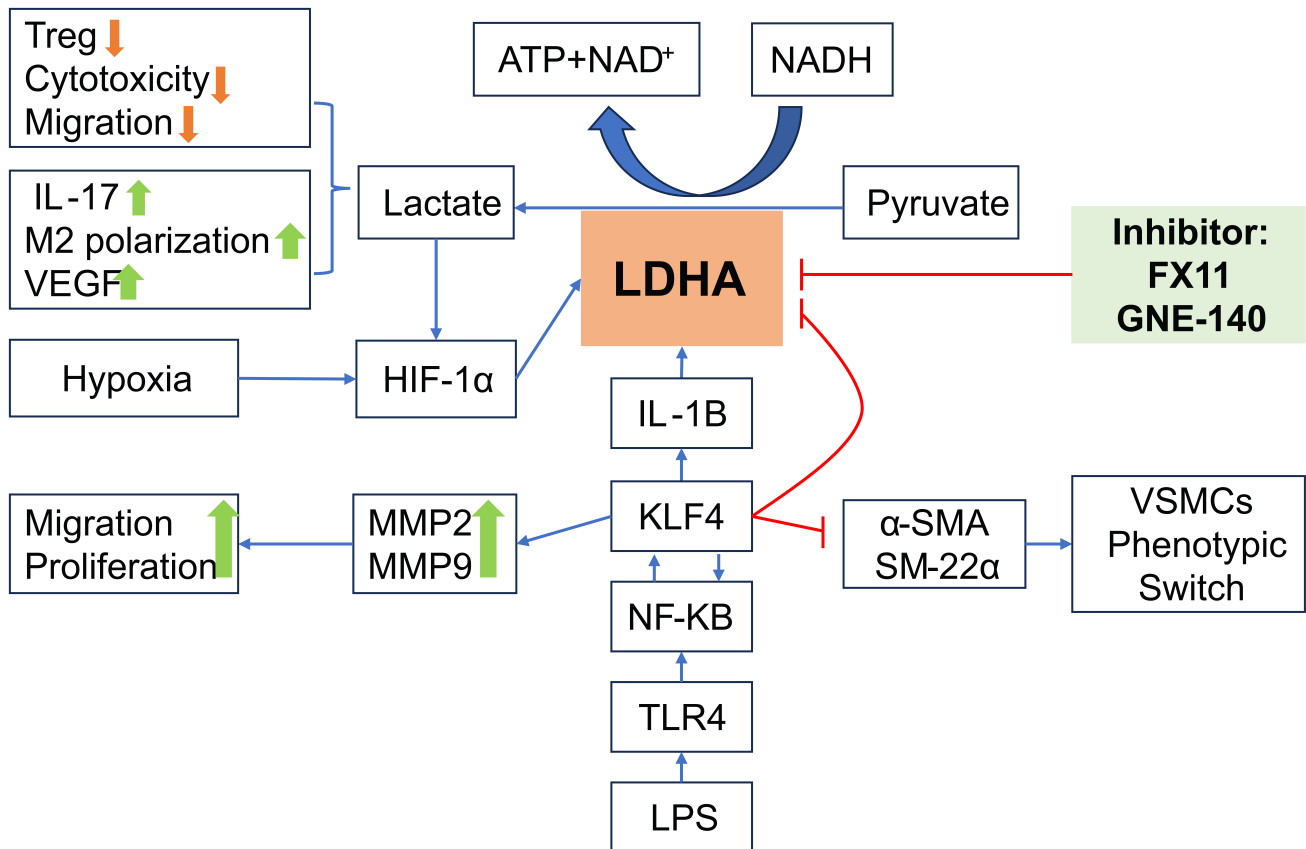


Fig. 1. LDHA affects the inflammatory response in acute lung injury by modulating metabolic reprogramming in vascular smooth muscle. ATP, adenosine triphosphate; NAD^+ , Nicotinamide Adenine Dinucleotide (oxidized form); HIF-1 α , hypoxia-inducible factor-1 alpha; KLF4, Kruppel-like factor 4; NF-KB, Nuclear Factor Kappa-light-chain-enhancer of Activated B cells; TLR4, Toll-like Receptor 4; LPS, lipopolysaccharides; α -SMA, alpha-smooth muscle actin; SM-22 α , Smooth Muscle Protein 22-Alpha; GNE-140, dihydropyrimidine derivative 14; VSMCs, vascular smooth muscle cells.

2-propen-1-one (3PO), results in reduced glucose uptake and inhibits the flux of glycolysis to lactate. This intervention effectively obstructs the energy source for VSMCs and has been identified as a promising strategy for preventing sepsis-associated ALI [9] (Table 1, Ref. [10,17,18,31–39]).

5. Therapeutic Strategies Targeting LDHA-Regulated Metabolic Reprogramming in Vascular Smooth Muscle and Future Research Directions and Challenges

The etiology of ALI is multifaceted, resulting in damage to alveolar epithelial cells and vascular endothelial cells. This condition triggers an inflammatory response and induces persistent hypoxemia, ultimately leading to the development of ARDS, and the high mortality associated with ALI has garnered significant attention within the medical community. LDHA is a crucial metabolic enzyme that regulates hypoxemia during the progression of ALI. It induces alterations in the energy metabolism of VSMCs and provides energy for cellular proliferation and differentiation through aerobic glycolysis. Additionally,

LDHA promotes the repair of damaged tissues, vasoconstriction, endothelial-mesenchymal transition, cell proliferation, and migration, while also generating reactive oxygen species that further exacerbate inflammatory responses. LDHA serves not only as an enzyme involved in energy metabolism but also as a protein factor that regulates various biological processes. It is recognized as an important biomarker and potential therapeutic target for ALI, ARDS, tumor development, and poor prognosis. Consequently, comprehensive research into the pro-inflammatory and metabolic functions of LDHA, along with the identification of novel genes that synergistically interact with LDHA, will significantly enhance the foundational theoretical understanding of ALI pathogenesis.

Numerous studies have substantiated the efficacy of various LDHA inhibitors in models of lung injury and tumors. FX11, a competitive inhibitor of NADH, has been shown to reduce bacterial load and inhibit necrotic lesions in the lungs of tuberculosis-infected mice by impeding glycolysis [40]. Furthermore, its nanocarrier formulation (FX11@TPEG-WS₂) targets mitochondria and enhances antitumor efficacy when used in conjunction with acoustic

Table 1. LDHA affects inflammation in both direct and indirect ways.

Modes of action	Mechanisms	Concrete content	Reference
Direct effect	• NADH-LDHA interaction	• During glycolysis, it promotes electron transfer, increases oxygen radical production, and enhances oxidative killing and inflammatory responses.	[10,35]
	• T-cell effector function promotion	• Increased acetylation and transcription of interferon- γ (IFNG) to enhance T-cell effector function; inhibition of LDHA to rescue effector T-cell (Teff)/regulatory T-cell (Treg) imbalance under inflammation.	[17,36]
	• Inflammatory factor regulation	• The LDHA inhibitor FX11 significantly inhibited IL-6 and MMP13 expression, increased I κ B- ζ protein production, and suppressed inflammation; it inhibited I κ B- ζ protein stability, enhanced inflammatory factor expression, and exacerbated inflammation.	[18,37]
	• Immunocytosis	• Direct activation of immune cells promotes their inflammatory response; macrophages produce LDHA-containing exocysts that promote glycolysis and inhibit macrophage infiltration, reducing inflammation.	[38]
Indirect effect	• Lactic acid production and effects	• Promotes massive conversion of glucose to lactate, and lactate accumulation amplifies the inflammatory response.	[31,32]
	• Suppression of immune cell function	• Increased LDH activity suppresses immune cell function, and high concentrations of lactate decrease effector T cell activity and promote IL-17 production by CD4 ⁺ T cells.	[33,39]
	• Anti-inflammatory effect	• Inhibition of LDHA activity down-regulates pro-inflammatory factors and iNOS expression and exerts anti-inflammatory effects.	[34,37]

NADH, nicotinamide adenine dinucleotide; LDHA, lactate dehydrogenase A; FX11, (S)-N-Hydroxy-3-(4-methoxybenzylsulfonyl)-2,2-dimethylchroman-4-carboxamide; IL-6, interleukin-6; MMP13, matrix metalloproteinase-13; I κ B- ζ , Inhibitor of kappa B zeta; CD4⁺, Cluster of Differentiation 4; iNOS, inducible nitric oxide synthase.

kinetic therapy [41]. In combination with metformin, FX11 activates the AMPK α axis, thereby inducing apoptosis in pancreatic cancer cells [42]. Dihydropyrimidine derivative 14 (GNE-140) demonstrated significant inhibitory activity against human lactate dehydrogenase A (hLDHA) within the low micromolar range (IC₅₀ = 0.48 μ M) [43]. It effectively blocked glycolysis-dependent histone lactylation (H3K18la) in a model of PM2.5-induced pulmonary fibrosis, down-regulated the TGF- β /Smad2/3 (Mothers Against Decapentaplegic Homolog 2/3) and VEGFA (Vascular Endothelial Growth Factor A)/ERK signaling pathways, and mitigated inflammation and fibrosis [44]. Additionally, N-hydroxyindole derivatives (NHI-Glc-2), in conjunction with PDK1 (3-Phosphoinositide-Dependent Protein Kinase-1) inhibitors, facilitate metabolic reprogramming of lung adenocarcinoma from glycolysis to oxidative phosphorylation by targeting critical nodes of glycolysis, thereby synergistically inhibiting the AKT (AKT Serine/Threonine Kinase)/mTOR and RAS (Rat Sarcoma virus oncogene homolog)/ERK pathways [45]. Furthermore, oxaloacetate, a competitor at the pyruvate site, enhances CD8⁺ T-cell infiltration in a non-small cell lung cancer (NSCLC) model [43]. Cotton-phenol derivatives exhibit non-selective inhibition of LDH and reduce collagen deposition in bleomycin-induced lung fibrosis [43]. Natural products such as curcumin and gallic acid

(EGCG) have emerged as promising drug candidates showing efficacy as LDHA inhibitors and in overcoming EGFR-TKI resistance, especially in cancer therapy [46]. Despite the demonstrated efficacy of these compounds in preclinical models, no LDHA inhibitors have progressed to clinical trials. This limitation is primarily attributed to issues related to target selectivity, pharmacokinetic deficiencies, and toxicity risks. Therefore, structural optimization strategies, such as the nanocarrierization of FX11 [41], along with combination therapy approaches, are essential to enhance the translational potential of these compounds.

The comprehensive investigation of the LDHA regulatory network is crucial for addressing the challenges associated with clinical translation. Clarifying the role of LDHA in modulating endothelial inflammation and permeability via the lactate-NF- κ B/STAT3 axis [47], in conjunction with spatial metabolomics, is expected to significantly enhance our understanding of endothelial-vascular smooth muscle interactions in ALI. Moreover, examining the interaction between LDHA and cyclic GMP-AMP synthase (cGAS)-STING, particularly the mechanism by which FX11 induces cGAS to bolster anti-tumor immunity, as well as its association with the human tumor suppressor FLCN (Folliculin), will provide valuable insights into the regulation of glycolysis and mitochondrial metabolic transitions [43,48]. This exploration aims to elucidate the

mechanisms underlying the interplay between metabolism and immunity. We propose the development of humanized lung-like organoids and the application of a single-cell multi-omics platform to investigate the cell-specific effects of LDHA on macrophage polarization, epithelial-mesenchymal transition (EMT), and T-cell depletion [44, 49]. Inhibition of LDHA has been demonstrated to modulate the reactive oxygen species (ROS)/AMP-activated protein kinase (AMPK)/mechanistic target of rapamycin (mTOR) and HIF-1 α signaling networks, thereby facilitating the formulation of synergistic strategies in conjunction with immunotherapeutics, such as anti-PD-1 (Programmed Cell Death Protein 1) agents, or epigenetic drugs, including histone deacetylase (HDAC) inhibitors [42,43, 45,49]. Furthermore, we aim to optimize these combinations by designing dual-targeted inhibitors that concurrently target LDHA and pyruvate kinase M2 (PKM2) to mitigate metabolic compensation [46]. Additionally, we will develop lung-targeted smart delivery systems, such as glutathione-responsive vesicles [50], and identify synthetic lethal targets through CRISPR screening. This research presents a novel framework for metabolic-immune interventions in the context of lung diseases.

6. Conclusions

ALI represents a critical inflammatory disorder characterized by elevated mortality rates, primarily resulting from dysregulated metabolism in VSMCs and sustained inflammatory responses. This review aims to clarify the significant function of LDHA in the metabolic reprogramming of VSMCs and the enhancement of inflammatory processes during ALI. In the context of hypoxia and inflammation, LDHA expression is increased through the HIF-1 α signaling pathway, thereby facilitating the Warburg effect. This metabolic alteration not only supports ATP generation but also intensifies inflammation through two distinct mechanisms. Firstly, LDHA directly contributes to oxidative stress via the interaction between NADH and LDHA, activates NF- κ B/STAT3 signaling pathways, and destabilizes I κ B- ζ , which leads to an increased release of pro-inflammatory cytokines such as IL-6 and TNF- α . Secondly, lactate produced by LDHA indirectly exacerbates inflammation by inhibiting immune cell functionality, promoting IL-17 secretion in CD4⁺ T cells, and driving macrophage polarization towards pro-inflammatory phenotypes. Experimental approaches to inhibit LDHA, such as the use of FX11, have demonstrated a reduction in lung edema, neutrophil infiltration, and lactate levels, underscoring its potential as a therapeutic target. Additionally, post-translational modifications of LDHA, including crotonylation and ubiquitination, further influence VSMC proliferation, migration, and vascular remodeling. Despite encouraging results from preclinical studies, the translation of LDHA inhibitors into clinical practice faces challenges related to selectivity and toxicity. Future investigations

should prioritize the optimization of LDHA-targeted therapies through the use of nanocarrier delivery systems, dual-target inhibitors (e.g., LDHA/PKM2), and combinatorial approach has with immunotherapies. Furthermore, employing multi-omics strategies to investigate LDHA's role in metabolic-immune interactions and vascular-endothelial dynamics will enhance our comprehension of ALI pathogenesis and facilitate the development of innovative interventions to address this life-threatening condition.

Author Contributions

DL and XLF contributed equally to the study design, data analysis, literature search, and preparation of the initial draft of the manuscript. LXX was responsible for the study conception and supervision, while LXX and SLD were involved in the design, editing, and revision of the manuscript. All authors have approved the final version of the manuscript and have participated sufficiently in the work, thereby agreeing to be accountable for all aspects of the research.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received funding from China NSFC Key Grant (82341119).

Conflict of Interest

The authors declare no conflict of interest.

References

- [1] Li D, Yang L, Wang W, Song C, Xiong R, Pan S, *et al.* Eriocitrin attenuates sepsis-induced acute lung injury in mice by regulating MKP1/MAPK pathway mediated-glycolysis. *International Immunopharmacology*. 2023; 118: 110021. <https://doi.org/10.1016/j.intimp.2023.110021>.
- [2] Price DR, Garcia JGN. A Razor's Edge: Vascular Responses to Acute Inflammatory Lung Injury/Acute Respiratory Distress Syndrome. *Annual Review of Physiology*. 2024; 86: 505–529. <https://doi.org/10.1146/annurev-physiol-042222-030731>.
- [3] Kovacic JC, Dimmeler S, Harvey RP, Finkel T, Aikawa E, Krenning G, *et al.* Endothelial to Mesenchymal Transition in Cardiovascular Disease: JACC State-of-the-Art Review. *Journal of the American College of Cardiology*. 2019; 73: 190–209. <https://doi.org/10.1016/j.jacc.2018.09.089>.
- [4] Dunham-Snary KJ, Wu D, Sykes EA, Thakrar A, Parlow LRG, Mewburn JD, *et al.* Hypoxic Pulmonary Vasoconstriction: From Molecular Mechanisms to Medicine. *Chest*. 2017; 151: 181–192. <https://doi.org/10.1016/j.chest.2016.09.001>.
- [5] Zhu JJ, Liu YF, Zhang YP, Zhao CR, Yao WJ, Li YS, *et al.* VAMP3 and SNAP23 mediate the disturbed flow-induced endothelial microRNA secretion and smooth muscle hyperplasia. *Proceedings of the National Academy of Sciences of the United States of America*. 2013; 110: 1030–1035. <https://doi.org/10.1073/pnas.1210300110>.

- States of America. 2017; 114: 8271–8276. <https://doi.org/10.1073/pnas.1700561114>.
- [6] Cao G, Xuan X, Hu J, Zhang R, Jin H, Dong H. How vascular smooth muscle cell phenotype switching contributes to vascular disease. *Cell Communication and Signaling: CCS*. 2022; 20: 180. <https://doi.org/10.1186/s12964-022-00993-2>.
 - [7] Flicek P, Ahmed I, Amode MR, Barrell D, Beal K, Brent S, *et al.* Ensembl 2013. *Nucleic Acids Research*. 2013; 41: D48–D55. <https://doi.org/10.1093/nar/gks1236>.
 - [8] Urbańska K, Orzechowski A. Unappreciated Role of LDHA and LDHB to Control Apoptosis and Autophagy in Tumor Cells. *International Journal of Molecular Sciences*. 2019; 20: 2085. <https://doi.org/10.3390/ijms20092085>.
 - [9] Zhou Y, Chen C, Li Q, Sheng H, Guo X, Mao E. NORAD modulates miR-30c-5p-LDHA to protect lung endothelial cells damage. *Open Medicine (Warsaw, Poland)*. 2022; 17: 676–688. <https://doi.org/10.1515/med-2022-0446>.
 - [10] Feng Y, Xiong Y, Qiao T, Li X, Jia L, Han Y. Lactate dehydrogenase A: A key player in carcinogenesis and potential target in cancer therapy. *Cancer Medicine*. 2018; 7: 6124–6136. <https://doi.org/10.1002/cam4.1820>.
 - [11] Augoff K, Hryniewicz-Jankowska A, Tabola R. Lactate dehydrogenase 5: an old friend and a new hope in the war on cancer. *Cancer Letters*. 2015; 358: 1–7. <https://doi.org/10.1016/j.canlet.2014.12.035>.
 - [12] Claps G, Faouzi S, Quidville V, Chehade F, Shen S, Vagner S, *et al.* The multiple roles of LDH in cancer. *Nature Reviews. Clinical Oncology*. 2022; 19: 749–762. <https://doi.org/10.1038/s41571-022-00686-2>.
 - [13] Cui J, Shi M, Xie D, Wei D, Jia Z, Zheng S, *et al.* FOXM1 promotes the warburg effect and pancreatic cancer progression via transactivation of LDHA expression. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*. 2014; 20: 2595–2606. <https://doi.org/10.1158/1078-0432.CCR-13-2407>.
 - [14] Shi M, Cui J, Du J, Wei D, Jia Z, Zhang J, *et al.* A novel KLF4/LDHA signaling pathway regulates aerobic glycolysis in and progression of pancreatic cancer. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*. 2014; 20: 4370–4380. <https://doi.org/10.1158/1078-0432.CCR-14-0186>.
 - [15] Brooks GA. The Science and Translation of Lactate Shuttle Theory. *Cell Metabolism*. 2018; 27: 757–785. <https://doi.org/10.1016/j.cmet.2018.03.008>.
 - [16] Cao SH, Chen ZH, Ma RY, Yue L, Jiang HM, Dong LH. Dynamics and Functional Interplay of Nonhistone Lysine Crotonylome and Ubiquitylome in Vascular Smooth Muscle Cell Phenotypic Remodeling. *Frontiers in Cardiovascular Medicine*. 2022; 9: 783739. <https://doi.org/10.3389/fcvm.2022.783739>.
 - [17] Kim JH, Bae KH, Byun JK, Lee S, Kim JG, Lee IK, *et al.* Lactate dehydrogenase-A is indispensable for vascular smooth muscle cell proliferation and migration. *Biochemical and Biophysical Research Communications*. 2017; 492: 41–47. <https://doi.org/10.1016/j.bbrc.2017.08.041>.
 - [18] Arra M, Swarnkar G, Ke K, Otero JE, Ying J, Duan X, *et al.* LDHA-mediated ROS generation in chondrocytes is a potential therapeutic target for osteoarthritis. *Nature Communications*. 2020; 11: 3427. <https://doi.org/10.1038/s41467-020-17242-0>.
 - [19] Wu X, Ye J, Cai W, Yang X, Zou Q, Lin J, *et al.* LDHA mediated degradation of extracellular matrix is a potential target for the treatment of aortic dissection. *Pharmacological Research*. 2022; 176: 106051. <https://doi.org/10.1016/j.phrs.2021.106051>.
 - [20] Lu X, Zhang J, Liu H, Ma W, Yu L, Tan X, *et al.* Cannabidiol attenuates pulmonary arterial hypertension by improving vascular smooth muscle cells mitochondrial function. *Theranostics*. 2021; 11: 5267–5278. <https://doi.org/10.7150/thno.55571>.
 - [21] Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science (New York, N.Y.)*. 2009; 324: 1029–1033. <https://doi.org/10.1126/science.1160809>.
 - [22] Lee DC, Sohn HA, Park ZY, Oh S, Kang YK, Lee KM, *et al.* A lactate-induced response to hypoxia. *Cell*. 2015; 161: 595–609. <https://doi.org/10.1016/j.cell.2015.03.011>.
 - [23] Xiao W, Shrimali N, Vigder N, Oldham WM, Clish CB, He H, *et al.* Branched-chain α -ketoacids aerobically activate HIF1 α signalling in vascular cells. *Nature Metabolism*. 2024; 6: 2138–2156. <https://doi.org/10.1038/s42255-024-01150-4>.
 - [24] Zhang C, Sun Y, Guo Y, Xu J, Zhao H. JMJD1C promotes smooth muscle cell proliferation by activating glycolysis in pulmonary arterial hypertension. *Cell Death Discovery*. 2023; 9: 98. <https://doi.org/10.1038/s41420-023-01390-5>.
 - [25] Yang L, Gao L, Nickel T, Yang J, Zhou J, Gilbertsen A, *et al.* Lactate Promotes Synthetic Phenotype in Vascular Smooth Muscle Cells. *Circulation Research*. 2017; 121: 1251–1262. <https://doi.org/10.1161/CIRCRESAHA.117.311819>.
 - [26] Walenta S, Mueller-Klieser WF. Lactate: mirror and motor of tumor malignancy. *Seminars in Radiation Oncology*. 2004; 14: 267–274. <https://doi.org/10.1016/j.semradonc.2004.04.004>.
 - [27] Végran F, Boidot R, Michiels C, Sonveaux P, Feron O. Lactate influx through the endothelial cell monocarboxylate transporter MCT1 supports an NF- κ B/IL-8 pathway that drives tumor angiogenesis. *Cancer Research*. 2011; 71: 2550–2560. <https://doi.org/10.1158/0008-5472.CAN-10-2828>.
 - [28] Trabold O, Wagner S, Wicke C, Scheuenstuhl H, Hussain MZ, Rosen N, *et al.* Lactate and oxygen constitute a fundamental regulatory mechanism in wound healing. *Wound Repair and Regeneration: Official Publication of the Wound Healing Society [and] the European Tissue Repair Society*. 2003; 11: 504–509. <https://doi.org/10.1046/j.1524-475x.2003.11621.x>.
 - [29] Beckert S, Farrahi F, Aslam RS, Scheuenstuhl H, Königsrainer A, Hussain MZ, *et al.* Lactate stimulates endothelial cell migration. *Wound Repair and Regeneration: Official Publication of the Wound Healing Society [and] the European Tissue Repair Society*. 2006; 14: 321–324. <https://doi.org/10.1111/j.1743-6109.2006.00127.x>.
 - [30] Gong F, Li R, Zheng X, Chen W, Zheng Y, Yang Z, *et al.* OLFM4 Regulates Lung Epithelial Cell Function in Sepsis-Associated ARDS/ALI via LDHA-Mediated NF- κ B Signaling. *Journal of Inflammation Research*. 2021; 14: 7035–7051. <https://doi.org/10.2147/JIR.S335915>.
 - [31] DeBerardinis RJ, Thompson CB. Cellular metabolism and disease: what do metabolic outliers teach us? *Cell*. 2012; 148: 1132–1144. <https://doi.org/10.1016/j.cell.2012.02.032>.
 - [32] Zhang W, Wang G, Xu ZG, Tu H, Hu F, Dai J, *et al.* Lactate Is a Natural Suppressor of RLR Signaling by Targeting MAVS. *Cell*. 2019; 178: 176–189.e15. <https://doi.org/10.1016/j.cell.2019.05.003>.
 - [33] Pucino V, Certo M, Bulusu V, Cucchi D, Goldmann K, Pontarini E, *et al.* Lactate Buildup at the Site of Chronic Inflammation Promotes Disease by Inducing CD4⁺ T Cell Metabolic Rewiring. *Cell Metabolism*. 2019; 30: 1055–1074.e8. <https://doi.org/10.1016/j.cmet.2019.10.004>.
 - [34] Certo M, Tsai CH, Pucino V, Ho PC, Mauro C. Lactate modulation of immune responses in inflammatory versus tumour microenvironments. *Nature Reviews. Immunology*. 2021; 21: 151–161. <https://doi.org/10.1038/s41577-020-0406-2>.
 - [35] Wu H, Wang Y, Ying M, Jin C, Li J, Hu X. Lactate dehydrogenases amplify reactive oxygen species in cancer cells in response to oxidative stimuli. *Signal Transduction and Targeted Therapy*. 2021; 6: 242. <https://doi.org/10.1038/s41392-021-00595-3>.
 - [36] Peng M, Yin N, Chhangawala S, Xu K, Leslie CS, Li MO. Aerobic glycolysis promotes T helper 1 cell differentiation through

- an epigenetic mechanism. *Science* (New York, N.Y.). 2016; 354: 481–484. <https://doi.org/10.1126/science.aaf6284>.
- [37] Song YJ, Kim A, Kim GT, Yu HY, Lee ES, Park MJ, *et al.* Inhibition of lactate dehydrogenase A suppresses inflammatory response in RAW 264.7 macrophages. *Molecular Medicine Reports*. 2019; 19: 629–637. <https://doi.org/10.3892/mmr.2018.9678>.
- [38] Kaushik DK, Bhattacharya A, Mirzaei R, Rawji KS, Ahn Y, Rho JM, *et al.* Enhanced glycolytic metabolism supports transmigration of brain-infiltrating macrophages in multiple sclerosis. *The Journal of Clinical Investigation*. 2019; 129: 3277–3292. <https://doi.org/10.1172/JCI124012>.
- [39] Haas R, Smith J, Rocher-Ros V, Nadkarni S, Montero-Melendez T, D'Acquisto F, *et al.* Lactate Regulates Metabolic and Pro-inflammatory Circuits in Control of T Cell Migration and Effector Functions. *PLoS Biology*. 2015; 13: e1002202. <https://doi.org/10.1371/journal.pbio.1002202>.
- [40] Krishnamoorthy G, Kaiser P, Abu Abed U, Weiner J, 3rd, Moura-Alves P, Brinkmann V, *et al.* FX11 limits *Mycobacterium tuberculosis* growth and potentiates bactericidal activity of isoniazid through host-directed activity. *Disease Models & Mechanisms*. 2020; 13: dmm041954. <https://doi.org/10.1242/dmm.041954>.
- [41] Truong Hoang Q, Huynh KA, Nguyen Cao TG, Kang JH, Dang XN, Ravichandran V, *et al.* Piezocatalytic 2D WS₂ Nanosheets for Ultrasound-Triggered and Mitochondria-Targeted Piezodynamic Cancer Therapy Synergized with Energy Metabolism-Targeted Chemotherapy. *Advanced Materials* (Deerfield Beach, Fla.). 2023; 35: e2300437. <https://doi.org/10.1002/adma.202300437>.
- [42] Bayindir-Bilgic M, Duman E, Turgut D, Kadikoylu AN, Ekimci-Gurcan N, Ozbey U, *et al.* Investigation of the synergistic effect of metformin and FX11 on PANC-1 cell lines. *Biological Research*. 2025; 58: 15. <https://doi.org/10.1186/s40659-025-00592-8>.
- [43] Sharma D, Singh M, Rani R. Role of LDH in tumor glycolysis: Regulation of LDHA by small molecules for cancer therapeutics. *Seminars in Cancer Biology*. 2022; 87: 184–195. <https://doi.org/10.1016/j.semcancer.2022.11.007>.
- [44] Li J, Zeng G, Zhang Z, Wang Y, Shao M, Li C, *et al.* Urban airborne PM_{2.5} induces pulmonary fibrosis through triggering glycolysis and subsequent modification of histone lactylation in macrophages. *Ecotoxicology and Environmental Safety*. 2024; 273: 116162. <https://doi.org/10.1016/j.ecoenv.2024.116162>.
- [45] Zhou Y, Guo Y, Ran M, Shan W, Granchi C, Giovannetti E, *et al.* Combined inhibition of pyruvate dehydrogenase kinase 1 and lactate dehydrogenase a induces metabolic and signaling reprogramming and enhances lung adenocarcinoma cell killing. *Cancer Letters*. 2023; 577: 216425. <https://doi.org/10.1016/j.canlet.2023.216425>.
- [46] Park W, Han JH, Wei S, Yang ES, Cheon SY, Bae SJ, *et al.* Natural Product-Based Glycolysis Inhibitors as a Therapeutic Strategy for Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor-Resistant Non-Small Cell Lung Cancer. *International Journal of Molecular Sciences*. 2024; 25: 807. <https://doi.org/10.3390/ijms25020807>.
- [47] Li K, Romero M, Cañardo M, Garcia D, Diaz A, Blomberg BB, *et al.* B cells from old mice induce the generation of inflammatory T cells through metabolic pathways. *Mechanisms of Ageing and Development*. 2023; 209: 111742. <https://doi.org/10.1016/j.mad.2022.111742>.
- [48] Rao K, Zhang X, Luo Y, Xia Q, Jin Y, He J. Lactylation orchestrates ubiquitin-independent degradation of cGAS and promotes tumor growth. *Cell Reports*. 2025; 44: 115441. <https://doi.org/10.1016/j.celrep.2025.115441>.
- [49] Mi Y, Tang M, Wu Q, Wang Y, Liu Q, Zhu P, *et al.* NMAAP1 regulated macrophage polarization into M1 type through glycolysis stimulated with BCG. *International Immunopharmacology*. 2024; 126: 111257. <https://doi.org/10.1016/j.intimp.2023.111257>.
- [50] Nguyen Cao TG, Truong Hoang Q, Kang JH, Kang SJ, Ravichandran V, Rhee WJ, *et al.* Bioreducible exosomes encapsulating glycolysis inhibitors potentiate mitochondria-targeted sonodynamic cancer therapy via cancer-targeted drug release and cellular energy depletion. *Biomaterials*. 2023; 301: 122242. <https://doi.org/10.1016/j.biomaterials.2023.122242>.