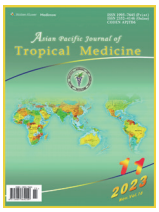

Review Article

Asian Pacific Journal of Tropical Medicine

apjtm.org

doi: 10.4103/1995-7645.388388

Impact Factor: 3.1

Glycolysis and acute lung injury: A review

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ABSTRACT

Acute lung injury is featured as diffuse pulmonary edema and persistent hypoxemia caused by lung or systemic injury. It is believed that these pathological changes are associated with damage to the alveolar epithelium and vascular endothelium, recruitment of inflammatory cells, and inflammatory factor storms. In recent years, the metabolic reprogramming of lung parenchymal cells and immune cells, particularly alterations in glycolysis, has been found to occur in acute lung injury. Inhibition of glycolysis can reduce the severity of acute lung injury. Thus, this review focuses on the interconnection between acute lung injury and glycolysis and the mechanisms of interaction, which may bring hope for the treatment of acute lung injury.

KEYWORDS: Acute lung injury; Glycolysis; Hypoxia-inducible factor 1; Endothelium; Macrophages

1. Introduction

Acute lung injury (ALI) is one of the most common complications of sepsis and generally refers to non-cardiogenic pulmonary edema caused by damage to pulmonary capillary endothelial cells and alveolar epithelial cells during severe infection and shock. The main clinical manifestations are progressive hypoxemia and dyspnea. There are approximately 3 million people diagnosed with ALI worldwide each year, and the mortality rate reaches 35%-46%[1]. The research on the treatment of ALI is focused on regulating the release of inflammatory factors, reducing damage to the pulmonary vascular endothelium and alveolar epithelium. To the best of our knowledge, there is still no effective pharmacological treatment for this disease, despite decades of scientific and clinical research. Treatment consists mainly of pulmonary protective ventilation and conservative fluid management strategies. However, metabolic reprogramming provides a novel strategy for treating acute lung injury.

The discovery of metabolic reprogramming was originally proposed by Otto Warburg in his studies of tumor cells in the 1920s, where he noted that even under adequate oxygenation conditions, cancer cells exhibited increased glucose uptake and lactate production[2]. This phenomenon, which is known as the Warburg effect, provides enough energy for rapidly proliferating cancer cells to promote cell division[2,3]. In recent years, an increasing number of studies have shown that glycolysis plays a crucial role in the development and progression of several pulmonary inflammatory diseases. Hu *et al.*[4] found that glycolytic metabolism, which is enhanced in a pulmonary fibrosis model, promoted the synthesis of collagen Ⅰ in pulmonary fibroblasts and accelerated the progression of pulmonary fibrosis. Similarly, several studies have shown that in acute lung injury models, enhanced glycolysis promotes M1 macrophage polarization, increases vascular endothelial cell adhesion, and promotes NLRP3 inflammasome formation; however, inhibition of key glycolytic enzymes with drugs or gene knockout can reduce the severity of

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How to cite this article: Yi Y, Chen J, Li N, Huang Y, Peng JC, Liu XR. Glycolysis and acute lung injury: A review. Asian Pac J Trop Med 2023; 16(11): 490-497.

Article history: Received 21 May 2023 Revision 9 October 2023
Accepted 31 October 2023 Available online 8 November 2023

lung injury and improve survival rate[5,6]. A further study showed that COVID-19 patients had increased levels of monocyte glycolysis, which promoted viral replication and cytokine release, exacerbated lung inflammation, and increased COVID-19-related mortality[7]. He further demonstrated that enhanced glycolytic metabolism exacerbates the severity of acute lung injury and increases the incidence of adverse events. This review aims to explore the relationship between ALI and glycolytic metabolism, as well as potential drugs that exert therapeutic effects by inhibiting glycolysis, to provide a theoretical basis for experimental studies and new drug development in acute lung injury.

2. Factors that enhance glycolysis in ALI

Controlling glycolysis is crucial in attenuating acute lung injury, as has been demonstrated in several studies, and the clarification of the upstream mechanisms regulating glycolysis is an important step that should be followed. Several common factors, such as tissue and cell hypoxia, a shortage of energy and the dual effects of increased inflammatory factors and enhanced oxidative stress, lead to elevated glycolytic metabolism, which is similarly manifested in acute lung injury.

2.1. Hypoxia

Hypoxia is the primary reason for glycolysis and the predominant symptom of acute lung injury. Hypoxia inducible factor-1 (HIF-1), an oxygen-dependent transcription factor, is widely expressed in hypoxic tissues and it plays an important role in maintaining the balance of the oxygen supply and regulating inflammation *in vivo*. Under normal tissue oxygenation, the half-life of HIF-1α is short, and the oxygen-dependent structural domain of this gene is easily hydroxylated by prolyl hydroxylase (PHD), resulting in its rapid degradation. However, in hypoxic conditions, substances such as reactive oxygen species (ROS) and lactic acid inhibit PHD, reducing the degradation of HIF-1α and stabilizing its expression[8]. HIF-1α acts as a transcription factor that binds to the hypoxia response element and can regulate the expression of several downstream target protein, including glycolysis-related enzymes, such as pyruvate kinase M2 (PKM2), hexokinase (HK), pyruvate dehydrogenase kinase, lactate dehydrogenase, and glucose transporter (GLUT), shifting cellular metabolism from mitochondrial oxidative phosphorylation to glycolysis to maintain adenosine triphosphate (ATP) levels[8–10]. A few studies have confirmed that lipopolysaccharide (LPS) stimulation of macrophages promotes the expression of GLUT1, HK2, and 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase (PFKFB3) and enhances glycolysis; however, inhibiting HIF-1α expression reduces the level of glycolysis[11,12]. A number of scholars have found that dimethyloxallyl glycine, which is an inhibitor of PHD, can increase the expression of HIF-1α and boost glycolysis in alveolar epithelial cells[13,14]. In addition, transcriptomic analysis of neutrophils from patients with acute lung injury in sepsis revealed that glycolysis genes and genes related to the HIF-1α pathway were significantly upregulated in ALI patients compared to normal subjects[15]. HIF-1α can also regulate the release of proinflammatory factors, angiogenesis and cell proliferation[9,16], which indirectly promote glycolysis and aggravate acute lung injury. These evidence suggest that HIF-1α expression not only regulates the level of cellular metabolism, especially glycolysis, but also stimulates the release of inflammatory factors, amplifies the inflammatory response and exacerbates lung injury.

2.2. Energy requirements

To maintain normal immune cell functions and the natural potential for tissue repair, increased glycolytic metabolism is necessary as a source of energy during ALI. Although glycolytic ATP production is significantly lower than that produced by oxidative phosphorylation, it can provide energy rapidly to meet the needs of metabolic and immune responses. In this process, adenosine 5'-monophosphate-activated protein kinase (AMPK) is one of the most important signaling molecules that maintains cellular energy metabolism. A reduction in ATP levels *in vivo* and the stimulation of hepatic kinase B1 can activate the AMPK pathway, promoting mitochondria-dependent catabolism and inhibiting the anabolic process[15,16]. However, in oncological diseases, it has been proposed that by suppressing glycolysis in tumor cells, AMPK can inhibit their growth and proliferation, as acting as a negative regulator of tumor cells[17,18]. This effect may be related to the inhibition of mammalian target of rapamycin (mTOR) by AMPK. Previous studies have suggested that mTOR is a major regulator of cell growth and metabolism. mTOR has two subtypes (mTORC1 and mTORC2) that are closely related to glucose metabolism[20]. mTORC1 can be activated by the phosphatidylinositol3-kinase (PI3K)/AKT pathway to promote glycolysis, as well as protein and lipid synthesis, while mTORC2 can be activated by AKT to promote GLUT expression and increase glucose uptake[21]. In the field of oncology and immunity, a large number of studies have demonstrated that activation of the mTOR pathway promotes glycolysis and maintains cellular function and stability[22,23]. It has also been demonstrated in a chronic lung injury model that LPS enhances glycolysis in lung fibroblasts *via* the PI3K-AKT-mTOR pathway[4]. In addition, mTOR has been described as an important regulator of HIF-1α activity, but the exact mechanism is not yet known. Thus, it can be

inferred that inhibiting mTOR *via* AMPK stimulation may be the key to negatively regulating glycolysis. However, it is interesting to note that in ALI, although the levels of mTOR and AMPK expression are increased due to inflammatory activation and a lack of energy, respectively, the inhibition of glycolysis by AMPK has not beenobserved. The possible reasons for this phenomenon are listed as following: 1) glycolysis is also regulated by other factors, such as hypoxia and inflammatory factor stimulation; and 2) due to energy shortage, the intensity of the increase in AMPK expression is not sufficient to inhibit glycolysis through the regulation of mTOR. Of course, these hypotheses need to be verified by further experiments.

2.3. Proinflammatory factors

Stimulation of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns induces the production of large amounts of proinflammatory factors by cells in the lung, and the contribution of these inflammatory factors promotes changes in cellular metabolism. Among them, granulocyte-macrophage colony-stimulating factor (GM-CSF) may be an important inflammatory factor that enhances glycolytic metabolism. In response to LPS stimulation, GM-CSF enhances macrophage glycolysis and promotes M1 macrophage polarization by upregulating the expression of macrophage c-myc (proliferation-associated gene) and GLUT1[24]. According to another study, GM-CSF may significantly enhance glycolysis *in vitro via* PFKFB3, which belongs to the phosphofructokinase-1 variable activator family and is the second rate-limiting enzyme of glycolysis[25]. *In vitro* enhancement of macrophage glycolysis with GM-CSF is also gaining widespread acceptance as a method[26]. Meng *et al.*[26] found that pretreatment with GM-CSF could completely reverse the anti-inflammatory effect of dexmedetomidine by inhibiting macrophage glycolysis *in vitro*. It has also been discovered that the NLRP3 (NOD-, LRR-, and pyrin-domain containing protein 3) inflammasome promotes macrophage glycolysis by upregulating the expression of PFKFB3 and exacerbating the LPS-induced inflammatory response[27].

2.4. ROS

Oxidative stress is also an important factor that contributes to ALI. The production of large amounts of ROS affects the activation of cells in the lung and the release of inflammatory mediators. It also disrupts the structure of the alveolar-vascular endothelial cell barrier, leading to a reduction in barrier stability and thereby affecting gas exchange, which ultimately leads to metabolic disorders. Under physiological conditions, the scavenging of ROS depends on the effectiveness of antioxidant substances *in vivo*, which maintain a dynamic balance. Oxidase 4 (NOX4) is an essential source of cellular hydrogen peroxide and ROS[28]. Yuan *et al.*[29] found that LPS enhanced macrophage glycolysis in an acute lung injury model; however, this metabolic alteration was attenuated in NOX4-knockout macrophages. It has been suggested that enhanced oxidative stress increases glucose uptake by endothelial cells and enhances glycolysis while increasing the levels of reduced coenzyme Ⅱ (NADPH) and growth-stimulating hormone through the pentose phosphate pathway, which can play a role in scavenging ROS[30]. Large amounts of ROS can also promote the stability of the HIF-1α protein, regulating changes in glycolytic metabolism through HIF-1α[9]. These results showed that the increase in ROS levels may be one of the driving factors of glycolysis.

3. Role of glycolysis in acute lung injury

In addition to the enhancement of glycolysis to meet the energy needs of organs, the intermediates derived from this process are also essential for cell proliferation and for exerting immune effects. First, glycolysis provides the fuel for the pentose phosphate pathway, which produces biosynthetic precursors of nucleotides and amino acids that facilitate cell growth and cytokine secretion, and the NADPH produced by the pentose phosphate pathway is oxidized by oxidase, which can be used for growth-stimulating hormone biosynthesis and protects cells from oxidative stress[31–33]. Moreover, the actions of key glycolytic enzymes can promote the recruitment of neutrophils to the site of injury to phagocytose and kill pathogens[34], support the differentiation of macrophages to the proinflammatory phenotype, assist the synthesis of NLRP3 inflammasomes, and defend against pathogen invasion[5,35,36]. Glycolysis can also promote proliferation and repair in alveolar epithelial cells[37], enhance the adhesion of pulmonary vascular endothelial cells to inflammatory cells and promote angiogenesis[38]. However, excessive or prolonged activation of glycolysis can exacerbate cell and tissue damage.

3.1. Neutrophil activation

Neutrophils are the most abundant leukocytes in the circulation. These cells can reach the infected area early and perform different cellular functions, including chemotaxis, phagocytosis, degranulation, ROS production, and the formation of neutrophil extracellular trap networks (NETs), which require an adequate energy supply[39,40]. Although a certain number of functional mitochondria are found in mature neutrophils, glycolysis remains the main metabolic pathway for neutrophil-mediated pathogen clearance[41]. Several scholars have claimed that the formation of NETs is almost entirely dependent on glycolysis for energy and is associated with

increased expression of GLUT1 on neutrophil membranes in response to PMA stimulation[42]. In contrast, glycolysis-induced extracellular acidosis inhibits neutrophil functions such as bacterial killing, migration, and the release of NETs[43]. This finding suggests that glycolysis and the activities of neutrophils have a connection that is both mutually reinforcing and reciprocally restricting to one another. The chemokine receptor CXCR2 plays an important role in the migration of neutrophils from the circulation to the site of infection. Tan *et al.*[39] found that inhibiting glycolysis reversed the sepsis-induced decrease in CXCR2 expression on the surface of neutrophils, promoted neutrophil migration and improved bacterial clearance in the focal area. A clinically relevant study showed that genes encoding glycolytic enzymes (HK2 and PKM2) and the HIF-1α pathway were significantly upregulated in neutrophils of septic patients compared to healthy subjects and neutrophil chemotaxis and phagocytosis were significantly enhanced in the patients too. In contrast, inhibiting glycolysis decreases neutrophil immune functions during sepsis[13]. It has been shown that LPS stimulation enhances neutrophil glycolysis, thereby promoting the immune actions of neutrophils. However, sustained stimulation leads to the suppression of cellular function. This may be related to the fact that prolonged stimulation leads to the accumulation of lactate and triggers different degrees of suppression in immune cells.

3.2. M1 macrophage polarization

Macrophages are the first line of defense that the host has against the invasion of pathogens, and these cells play an important role in maintaining tissue homeostasis and tissue regeneration. It is a common practice to classify macrophages according to one of two phenotypes: the traditionally activated M1 type and the alternatively activated M2 type. M1 macrophages are induced by PAMPs, such as bacterial lipopolysaccharide and interferon γ, producing a wide range of cytokines including tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6 and inducible nitric oxide synthase, to aggravate inflammation. M2-type macrophages, which are also known as anti-inflammatory macrophages, are induced by IL-4 and IL-13 and primarily express IL-1β, IL-10, and Arg-1, which have anti-inflammatory effects and promote angiogenesis and tissue repair[5,44]. Glycolysis is a critical factor affecting the functions of macrophages after tissue injury and infection by driving macrophages towards the M1 subtype and plays an essential role in macrophage migration[45–47].

Glycolysis is the main metabolic pathway of M1-type macrophages. Inhibiting glycolysis suppresses macrophage phagocytosis, reduces the activation of inflammatory vesicles, and reduces the secretion of proinflammatory cytokines[5]. One of the most important regulators of inflammatory responses mediated by macrophages is boosted by HIF-1α. HIF-1α not only directly regulates the expression of glucose-related metabolic enzymes to enhance glycolytic metabolism but also indirectly controls the expression of microRNAs that regulate glycolytic metabolism[48,49]. PKM2 is one of the rate-limiting enzymes of glycolysis, converting phosphoenolpyruvate to pyruvate, and is mainly expressed in cancer cells and activated immune cells[15]. PAMPs such as LPS enhance PKM2 expression and promote M1-type polarization in macrophages *via* the TLR-NF-κB and AKT-mTOR pathways[50]. In turn, activating PKM2 reduces lactate production and inflammatory factor release, promotes macrophage polarization toward the M2 type, decreases IL-1β and induces IL-10 production, thereby protecting mice from lethal endotoxemia and sepsis[51]. Xie *et al.*[35] found that PKM2 could selectively promote NLRP3 inflammatory vesicle activation and IL-1β production in macrophages by activating eukaryotic translation initiation factor 2α phosphorylation.

3.3. Endothelial cell function

Endothelial cells are arranged in a single layer throughout the vascular system. In addition to its role as a selective permeability barrier, endothelial cell has metabolic and synthetic functions and can regulates immune responses. Its cellular structural and functional integrity is also important in maintaining vascular barrier and circulatory function. Even though endothelial cells are often in a richly oxygenated environment, glycolysis produces up to 85% of the total cellular ATP and is the main metabolic pathway in endothelial cells[52]. The reasons for this phenomenon may be as follows: first, glycolysis minimizes ROS production, avoids oxidative stress-induced apoptosis, and produces ATP faster than oxidative phosphorylation, which makes glycolysis essential for proliferation and angiogenesis; second, glycolysis saves oxygen consumption and facilitates oxygen diffusion to perivascular cells.

Angiogenesis is regulated not only by perivascular growth factors but also by glycolysis. Among the numerous glycolytic regulatory proteins, PFKFB3 is mainly expressed in vascular endothelial cells and acts as an allosteric activator of phosphofructokinase-1 by controlling the synthesis of fructose-2,6-bisphosphate (F-2, 6-P2)[53]. Furthermore, among the PFKFB isozymes, the kinase activity of PFKFB3 is approximately 700-fold higher than that of phosphatase, making it an effective glycolytic activator and improve the efficiency of glycolysis[54].

In neoplastic diseases, blocking or knocking down PFKFB3 in endothelial cells reduces pathological angiogenesis. Cao *et al.*[38] examined pulmonary cells from patients with pulmonary hypertension and found that glycolysis mediated by PFKFB3 promoted the production of growth factors and proinflammatory factors in pulmonary vascular endothelial cells and facilitated

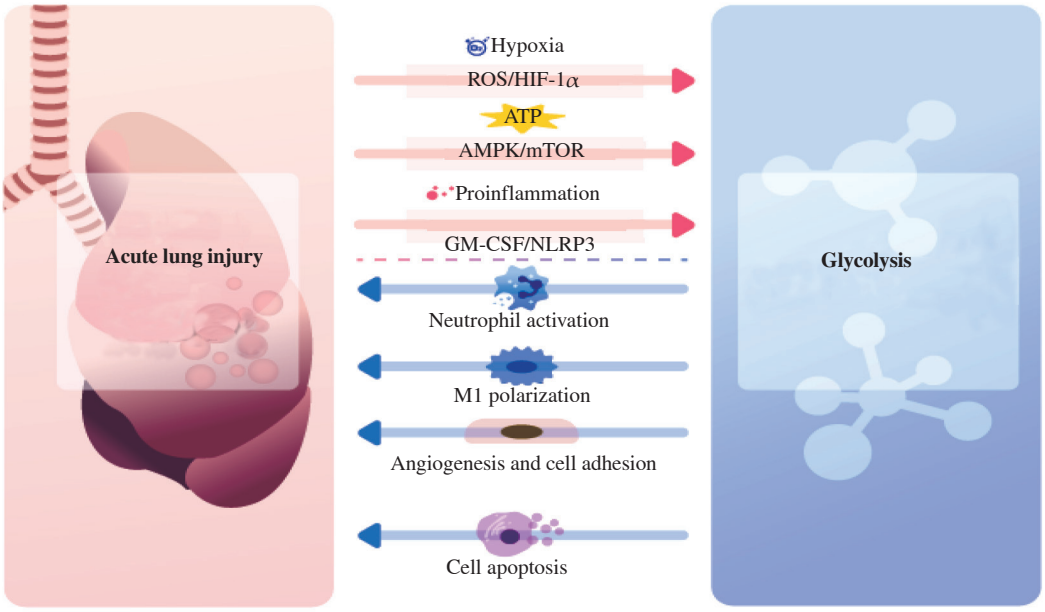

Figure 1. The overview of relationship of acute lung injury and glycolysis.

the proliferation of pulmonary artery smooth muscle cells and fibroblasts, thus accelerating the progression of pulmonary hypertension. When glycolysis levels increase or lactate accumulates, it will lead to a decrease in intracellular pH. It has been reported that increased VEGF promoter activity under such low pH conditions leads to the upregulation of VEGF expression and affects angiogenesis[16,55].

Recent studies have revealed that PFKFB3 not only promotes angiogenesis but also plays an important role in the regulation of inflammatory responses[56,57]. Recruitment of inflammatory cells into the lung or other organs requires the expression of adhesion molecules in endothelial cells, including intercellular adhesion molecule, vascular cell adhesion molecule, P-selectin and E-selectin. These adhesion factors promote the adhesion and migration of inflammatory cells and increase vascular permeability, leading to the development of pulmonary edema. Activation of glycolysis was found in the lung endothelial cells of septic mice, and specific knockdown of PFKFB3 reduced the permeability of mouse lung endothelial cells and improved the survival rate[58]. Zhang *et al.*[53] examined a TNF-α-induced endothelial cell inflammation model and found that inhibiting PFKFB3 expression reduced the release of proinflammatory factors such as MCP-1, IL-8, intercellular adhesion molecule, and GM-CSF and decreased the adhesion and migration of monocytes on endothelial cells, which was possibly related to PFKFB3-mediated promotion of NF-κB activation. Transcriptomic analysis of pulmonary artery endothelial cells revealed that TNF-α and LPS promoted metabolic reprogramming. Among the three glucose metabolism pathways, oxidative phosphorylation and the pentose phosphate pathway mainly play inhibitory roles in inflammation, while PFKFB3-mediated glycolysis had the proinflammatory effect. Inhibiting the pentose phosphate pathway and oxidative phosphorylation promote glycolytic metabolism, thereby exacerbating the inflammatory response[59-61]. This evidence suggests that PFKFB3-mediated enhancement of glycolysis in pulmonary vascular endothelial cells is critical to pulmonary vascular leakage and the massive recruitment of inflammatory factors. PFKFB3 may be a potential therapeutic target for regulating inflammation in vascular endothelial cells.

3.4. Apoptosis in alveolar epithelial cells

Damage and apoptosis in the alveolar epithelium are also important factors in the development of ALI. Gong *et al.* found that stimulation with LPS induces apoptosis and inflammatory factor release in the alveolar epithelium; however, pretreatment with the glycolysis inhibitor 3PO inhibits the increases in ROS and apoptosis in epithelial cells[54]. In contrast, Tojo *et al.*[37] found that pretreating alveolar epithelial cells with an inhibitor of PHD (dimethyloxallyl glycine) reduced apoptosis in alveolar epithelial cells by promoting HIF-1α-dependent glycolytic metabolism but did not attenuate the LPS-induced inflammatory response. This may be related to the expression of HIF-1α-promoting cell growth factors and the duration of inflammatory stimulation (Figure 1).

4. Conclusions

In summary, glycolysis involves in the pathologic progress

in acute and chronic inflammatory diseases, which is essential for inflammatory cells to resist pathogen invasion and maintain functional homeostasis. However, the continued activation of glycolysis leads to excessive activation of inflammatory cells, which inhibits inflammatory cell function and ultimately aggravates tissue injury. In this review, we summarized the triggers of enhanced glycolysis in acute lung injury, including hypoxia, energy requirements, and oxidative stress and outlined the effects of enhanced glycolysis on acute lung injury through the performance of different cells after metabolic changes. By summarizing the research progress on glycolysis in acute lung injury, we provide a theoretical basis for the treatment of acute lung injury. It is proposed that the future research directions of ALI might be blocking the triggers that induce the enhancement of glycolysis in acute lung injury, regulating the expression of key enzymes of glycolysis, and breaking the synergistic promotional relationship between glycolysis and ALI.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Acknowledgements

We thank Yong Chen from Riblab Workshop for the assistance in making the figure.

Funding

This study was supported by National Natural Science Foundation of China (No. 81960351) and High-level Talent Fund of Hainan Province (No. 822RC835).

Authors' contributions

YY contributed in drafting the manuscript and revising the draft; JC contributed in the conception of the work and conducting the study; NL and YH contributed in organizing thoughts for the study and gathering information for the study; JCP contributed in translated and revised the draft; XRL contributed in offering opinions for the draft, approval of the final version of the draft, and agreed for all aspects of the work. All authors read and approved the final version of the manuscript.

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