

Lactate and Lactylation in Sepsis: A Comprehensive Review

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Abstract: Sepsis is a disorder of the immune response to infection or infectious factors with high morbidity and mortality in clinical settings. The lactylation of lysine residues, fueled by lactate, plays a pivotal role in its pathophysiology. In conducting a literature review on sepsis-related research, we employed a systematic approach to ensure comprehensiveness and accuracy. Initially, we conducted an extensive literature search through the PubMed database, utilizing a range of keywords including “sepsis”, “lactate”, “lactylation”, and “epigenetic modification”. The aim was to capture the most recent research related to the pathophysiological mechanisms of sepsis, metabolic disorders, and the role of lactylation. The results of the literature review revealed a close link between sepsis and metabolic dysfunction, particularly the pivotal role of lactylation in regulating immune responses and inflammatory processes. Lactate, not only an energy metabolic byproduct produced during glycolysis, affects the activity of various proteins, including those involved in immune regulation and cell signaling, through lactylation. In the context of sepsis, changes in the levels of lactylation may be closely associated with the severity and prognosis of the disease. In summary, lactylation, as an emerging type of epigenetic modification, provides a new perspective for the diagnosis and treatment of sepsis. Future research needs to further elucidate the exact mechanisms of lactylation in sepsis and explore its potential as a therapeutic target.

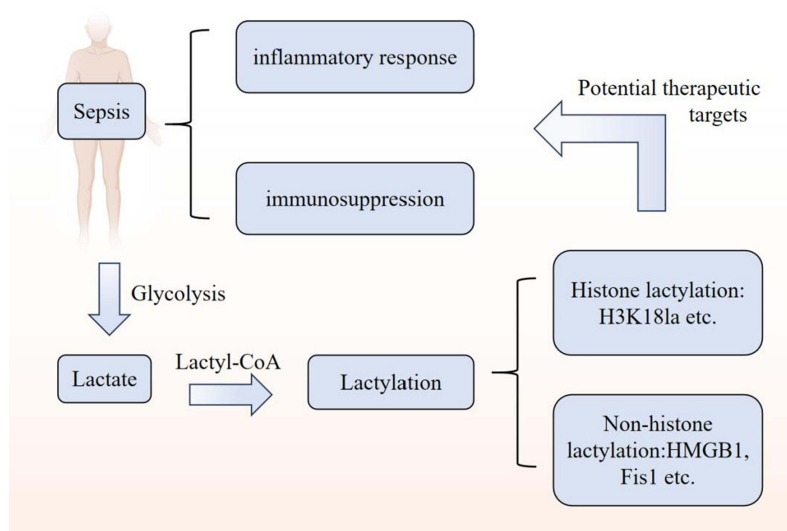
Plain Language Summary: The annual incidence and mortality rates associated with sepsis are on the rise, and to date, no medications or therapies have been proven effective in clinical practice. Glycolysis plays a pivotal role in regulating lactylation, a process derived from lactate generated by cellular glucose metabolism. In the context of sepsis, elevated lactate levels are indicative of a poor prognosis. It is imperative to delve into the mechanisms underlying lactylation alterations during sepsis to enhance our comprehension of its complex pathophysiology and to pinpoint innovative therapeutic targets for the condition.

Keywords: sepsis, lactate, lactylation, epigenetic modification

Introduction

The Third International Consensus Task Force defines sepsis as a “life-threatening organ dysfunction caused by a dysregulated host response to infection”.¹ Sepsis is a leading cause of morbidity and the leading cause of death in clinically critical patients. In 2017, an analysis of the Global Burden of Disease Survey reported approximately 48.9 million cases of sepsis worldwide, with 11.0 million deaths.² Because of the complicated pathophysiological basis of sepsis, there is still no viable treatment to increase patient survival.³ The Surviving Sepsis Campaign guidelines’ recommendations for the clinical management of sepsis are mostly all-encompassing and include the use of antibiotics to treat the underlying infection, fluid resuscitation, etc.^{4,5} Sepsis involves an initial inflammatory response followed by immune suppression, leading to increased risk of secondary infections and potential multi-organ failure, which are major contributors to its high mortality rate.⁶ Effective management of this immune dysregulation is critical for improving patient survival.

Graphical Abstract



Epigenetic alterations are intimately linked with the progression of sepsis, spanning from host-pathogen interactions to the acute inflammatory phase and subsequent immune suppression.⁷ With advancements in genomics, epigenetics has shown promise in the diagnosis and prognosis of sepsis.⁸ DNA methylation and post-translational protein modifications are two of the most prevalent types of epigenetic changes.^{9,10} Notably, lactylation has emerged as a novel form of post-translational protein modification. This process involves the accumulation of lactate from cellular metabolism altering lysine residues on histones. Specifically, lactate produced through aerobic glycolysis is implicated in modulating inflammation and immune suppression in sepsis.^{11–14}

Clinically, capillary lactate (CL) and serum lactate (SL) serve as prognostic indicators for mortality within 48 hours and 7 days, respectively.¹⁵ These markers enable emergency physicians to rapidly and accurately identify sepsis patients at a higher risk of death, facilitating appropriate prognostic assessments and aiding in the management and diagnosis of sepsis. Furthermore, lactyl-histones have been recognized as potential biomarkers for sepsis diagnosis and outcome prediction.¹⁶ Building on this foundation, we propose that lactate and its modifications as a product of glycolysis may be key factors in regulating immune function in sepsis patients.

The Pathophysiological Mechanism of Sepsis

Sepsis has a complicated pathophysiological process and pathogenesis that includes an imbalanced inflammatory response, endothelial dysfunction, mitochondrial damage, abnormal coagulation, and other pathophysiological processes that ultimately result in multiple organ failures in the body.¹⁷ The early phase of sepsis is typified by a hyper-inflammatory state, complete with a robust cytokine storm. Toll-like receptors (TLRs), a class of pattern recognition receptors, release a barrage of pro-inflammatory cytokines, chemokines, interferons, and reactive oxygen species in response to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), thereby instigating acute inflammation.¹⁸ Hotchkiss et al have posited that even patients who survive the initial inflammatory storm may continue to experience persistent immunosuppression in the later stages of sepsis, predisposing them to secondary infections and increasing their risk of mortality.¹⁹ Sepsis-induced immunosuppression (closely related to innate and adaptive immunity) is considered one of the major causes of death in patients with sepsis.⁶ During the course of sepsis, inflammatory and immunosuppressive processes may occur in tandem or sequentially. The immune system's swift elimination of pathogens can reestablish immune homeostasis in the early stages of the systemic inflammatory response. However, a failure to promptly clear pathogens can result in an imbalanced immune response, an overproduction of anti-inflammatory mediators, and the development of a compensatory anti-inflammatory response syndrome.²⁰ This leads to the

suppression of immune function and a heightened vulnerability to infections.¹ The immunosuppressive phase is marked by a decrease in CD4 lymphocytes, diminished B-lymphocyte function, reduced expression of HLA-DR on monocytes, and a dominance of anti-inflammatory Th2 and Treg responses over pro-inflammatory Th1 and T17 responses, as well as impaired neutrophil phagocytosis.²⁰ Consequently, sepsis should not be simplistically categorized as either a pro-inflammatory or an anti-inflammatory condition but rather as a dynamic interplay between inflammation and immunosuppression.

Sepsis and Metabolic Disorders

The cause of sepsis organ dysfunction is not the direct damage caused by pathogens and endotoxin, but the serious immune and metabolic dysfunction caused by host damage when facing infection.²¹ Therefore, metabolism-associated molecular patterns are thought to be strongly associated with metabolic disorders in sepsis. Systemic and organ-specific metabolic changes that disrupt normal metabolic homeostasis characterize sepsis. Sepsis leads to hypermetabolism, increased energy expenditure, and the development of insulin resistance, which is clinically characterized by hyperglycemia, hyper-lactylation, and increased proteolytic effects.²² Mitochondria are bioenergetic organelles and sepsis-induced mitochondrial damage or dysfunction is a major cause of cellular metabolic disorders, inadequate energy supply, and oxidative stress, which leads to organ cell and immune cell apoptosis and ultimately to immune disorders and multi-organ dysfunction, resulting in increased mortality in patients with sepsis.²³

During various stages of sepsis, immune cells are governed by distinct cellular metabolic pathways. Macrophages, as crucial innate immune cells, play a pivotal role in the immune response. The metabolic traits of macrophages vary with their activation state and the phase of metabolism they are in, which has different implications for their immunomodulatory functions.²⁴ Under normal physiological conditions, oxidative phosphorylation of glucose is the predominant metabolic pathway for macrophages. M1 macrophages enhance glucose uptake and aerobic glycolysis, whereas M2 macrophages increase fatty acid uptake and improve the efficiency of oxidative phosphorylation.²⁵ The inflammatory response engages multiple cell types, including pro-inflammatory cells like M1 macrophages, Th1, and Th17 lymphocytes, which produce lactate through glycolysis to propagate inflammation. Regulatory T cells and M2 macrophages contribute to immunomodulation and anti-inflammatory actions via fatty acid oxidation in the tricarboxylic acid cycle.^{16,26} Glycolysis is essential for immune cell activation but also contributes to immunosuppression in sepsis, being upregulated in hyper-inflammatory cells and downregulated in immunosuppressive cells.²⁷

With the development of sepsis, the early stage of high inflammation transits to the late stage of low inflammatory immunosuppression. At present, there is no specific stage of treatment for sepsis.^{4,15} While clinical trials have historically concentrated on the inflammatory aspect of sepsis with limited success, recent findings suggest that metabolic dysregulation is a significant factor in sepsis pathogenesis, offering new hope for treatment via metabolic intervention. Sepsis triggers a robust metabolic response, characterized by the release of high-energy metabolites such as lactate and free fatty acids.²⁸ Metabolic reprogramming and the strategic targeting of lactate, a key metabolite in this process, may present a promising therapeutic avenue for sepsis management.

Lactate and Sepsis Glycolysis and Lactate

Glycolysis is the process of decomposition of glucose into pyruvate and lactate, the main metabolic pathway of sepsis. Lactate, a glycolytic product, is generated through both aerobic and anaerobic glycolysis and serves as a vital energy source and a precursor for glucose synthesis.²⁹ In the presence of oxygen, glycolysis converts glucose into pyruvate and ATP; the pyruvate then enters mitochondria, facilitated by pyruvate dehydrogenase, to form acetylCoA. This compound subsequently joins the TCA cycle and oxidative phosphorylation for further energy production.^{30–32} Conversely, under anaerobic conditions, pyruvate is reduced to lactate with the help of NADH.³³ L-lactic dehydrogenase plays a crucial role in lactate production, catalyzing the interconversion of pyruvate and lactate in both hypoxic and aerobic states.^{34,35}

An increasing body of research indicates that lactate participates in the regulation of numerous biological and pathological processes. Hypoxia, inflammation, viral infections, and the tumor microenvironment are known to stimulate lactate production.³⁶ Recent theories regarding lactate's role include the lactate shuttle hypothesis, lactate homeostasis,

and the microenvironmental interactions of lactate in various diseases.³⁷ Lactate also engages in complex interactions with its environment; it activates the G-protein-coupled receptor 81 through monocarboxylate transporters or shuttles across different organs, cells, and cell types to generate ATP.³⁸ It fuels cell growth and development, and as a signaling molecule, it influences the functional alterations of intracellular proteins.^{36,38,39} These multifaceted roles of lactate underscore its importance in both physiological and pathological contexts, particularly in conditions such as sepsis.

Role of Lactate in Sepsis

A retrospective analysis of septic/non-septic patients revealed higher serum lactate levels in septic patients.⁴⁰ Serum lactate levels greater than 2 mmol/L are identified as septic shock.⁴¹ The interaction between blood pressure and lactate was evaluated and found to be nonsignificant ($p = 0.67$ for the interaction term).⁴² In a state of septic shock, anaerobic glycolysis caused by tissue hypoxia produces large amounts of lactate, which increases the lactate concentration and even leads to lactic acidosis.⁴³ Serum lactate levels are an important biomarker for sepsis and correlates positively with morbidity and mortality in sepsis or septic shock. Also, in animal models, lactate ≥ 1.64 mmol/L can act as a potential biomarker to identify sepsis models with cecal ligation and puncture in rats.⁴⁴ In sepsis clinical treatment, lactate levels and clearance rates are key clinical indicators linked to patient prognosis.⁴⁵ Elevated lactate reflects tissue hypoperfusion and metabolic disruption. Lactate clearance rate is a measure of hemodynamic improvement and tissue perfusion recovery, with optimized fluid resuscitation and hemodynamics potentially reducing mortality.¹⁷

Studies have shown that there are metabolic changes occur between the lactate produced by glycolysis and septic endothelial cells. Lactate can lead to vascular permeability and organ dysfunction. Inhibition of lactate production in the body or the elimination of the lactate receptor GPR81 may reduce vascular permeability and multiple organ damage and improve survival in sepsis.⁴⁶ Interestingly, studies related to immune metabolism have shown that activation of immune cells by aerobic glycolysis and the production of lactate may play an immunosuppressive role in the local environment of innate immunity and inflammation.⁴⁷ The lipopolysaccharide-induced sepsis tolerance model is considered being a mechanism of immunosuppression, and it was found that lactate levels first increased and then decreased 24 to 48 hours after induction of sepsis.^{48,49} In another study, inhibition of glycolysis via the PI3K/Akt-HIF-1 α pathway mediated the downregulation of lactate dehydrogenase resulting in immunosuppression of neutrophils during sepsis and providing a therapeutic target for improving immune function in sepsis.^{34,50}

Lactate is closely related to glycolysis, which involves a variety of enzymes and complexes that play a role in the regulation of sepsis (Table 1). The pyruvate dehydrogenase complex is a multienzyme complex of a glycolytic metabolic pathway.⁵¹ Protective mechanisms of PDHC in sepsis include regulation of lactate balance, release of inflammatory mediators, remodeling of the TCA cycle, and enhancement of lipid and energy metabolism.⁵² Activation of PDHC with dichloroacetate has been shown to mitigate sepsis-induced endothelial dysfunction by inhibiting lactate formation.⁵¹ By knocking down pyruvate kinase isoenzymes M2, hypoxia-inducible factor 1 α and glycolysis-related genes.^{53–55} Shikonin, a PKM2 inhibitor, lowered serum lactate levels and high mobility group protein 1 release in septic mice.^{44,56} Shikonin administration has also been shown to decrease HMGB1 release, lactate generation, and septic mouse mortality in Adenosine 5'-monophosphate -activated protein

Table 1 Role of Lactate and Aerobic Glycolysis in Sepsis

Molecule	Drug	Impact Pathways	Mechanism	Model	Ref
LDHA	Galloflavin	Inhibits glycolysis	PI3K/Akt-HIF-1 α	Neutrophils	[50]
PDHC	Dichloroacetate	Inhibits glycolysis	Phosphorylation of E1 α Ser293 and Ser300	HUVECs, C57 BL/6 mice	[51]
PKM2	Shikonin	Reduces lactate production	Activate HIF-1 α -dependent enzymes and HMGB1 release	Macrophages, AMPK α -deficient mice	[56]
GRP81	N/A	Inhibits pro-inflammatory cytokines	Active Yap and NF- κ B	Raw264.7, BMDM	[63]
PKM2	Lycium barbarum Polysaccharide	Inhibits glycolysis	Enhanced ubiquitination and down-regulation of PKM2	RAW264.7	[58]
LC3-II	2-Deoxy-D-glucose	Inhibits glycolysis	Lactate/SIRT3/AMPK	HK-2, C57BL/6 mice	[62]

Abbreviations: N/A, No available.

kinase -deficient mice.^{57,58} A discovery by Ding et al showed that *Lycium barbarum* polysaccharide plays a role in inhibiting LPS-induced inflammation by enhancing ubiquitination and downregulation of PKM2 by altering the glycolytic pathway and M1 differentiation in macrophages.⁵³ Lactate also exerts anti-inflammatory effects in macrophages, reducing the production of IL-6 and TNF- α and curbing NF- κ B and YAP activation.⁵⁹ Moreover, 2-deoxy-D-glucose, an aerobic glycolysis inhibitor, alleviates sepsis-induced acute kidney injury by promoting autophagy via the lactate/SIRT3/AMPK pathway.^{60–62}

Research indicates that modulating lactate production through glycolytic pathways holds promise for sepsis treatment.⁶⁴ Lactate's role extends to histone lactylation, influencing cancer, inflammation, and pulmonary fibrosis, and impacting immune regulation and homeostatic maintenance.⁶⁵ Lactate acts as a double-edged sword and can play different roles depending on the metabolic state, cell type, and pathological process. On the one hand, activated immune cells rely on the use of lactate to support their function. On the other hand, lactate that accumulates in the tissue microenvironment acts as a signaling molecule that restricts immune cell function. Recently, researchers have proposed a new line of research for lactate, namely the lactylation of lysine residues mediated by lactate as a substrate.⁶⁶

Lactylation

Discovery of Lactylation

The notion of lactylation, introduced by Professor Zhao from the University of Chicago in 2019, distinguishes between histone and non-histone lactylation. Research has predominantly concentrated on the latter, with fewer studies exploring lactylation in non-histone proteins. It is recognized that lactate, a byproduct of glycolysis, can lactylate lysine residues on histones through lactyl-coenzyme A, with L-lactate specifically promoting this modification^{39,67} (Figure 1). However, lactylation in non-histones was initially identified only in plant pathogenic fungi, and its occurrence and downstream function in other organisms are still

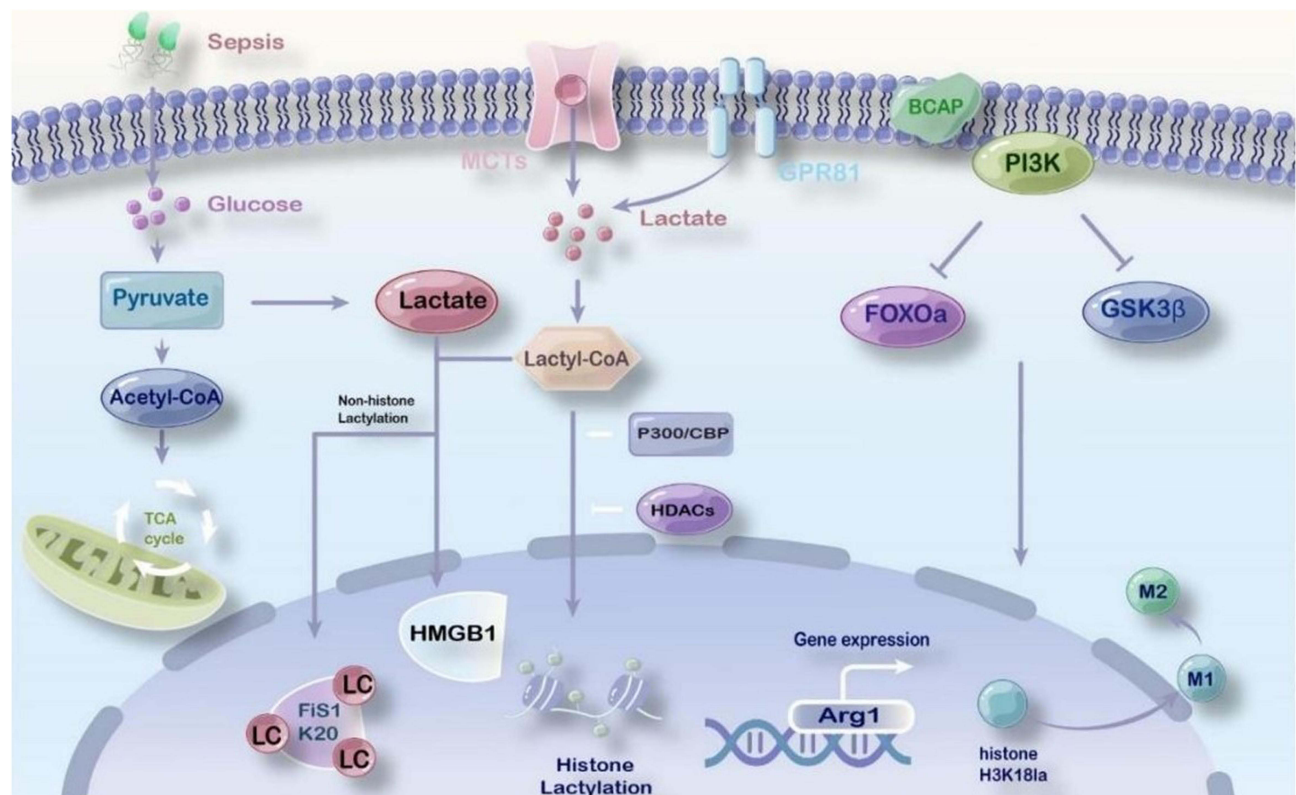


Figure 1 The role of lactylation in sepsis. Lactate shuttles through organs, cells, and cells through monocarboxylate transporter³² and G protein-coupled receptor 81.⁷¹ Under the conditions of aerobic or anoxic and bacterial stimulation, the lactate produced by glycolysis catalyzes the production of lactyl-CoA, and the lactate is transferred to histone through a writer³⁸ or an eraser⁷² and participates in the lactylation of lysine residues. PI3K-regulated B-cell adapter¹² regulates FOXO1 and GSK3 β . Reducing histone lactylation affects the expression of damage repair genes, and affects the transformation of inflammatory macrophages to repair macrophages. Lactylation of histone H3K18 promotes the expression of damage repair gene Arg1 and polarization to M2-type macrophages.

unclear.⁶⁸ Recently, Wan et al identified novel lactylation sites on both histones and non-histone proteins, utilizing fragment ions as a diagnostic marker for lactylation and employing proteomic data. Their findings provide preliminary evidence for lactylation on human non-histone proteins, such as the metabolic enzyme aldolase A, which has significant regulatory implications.⁶⁹ Lactylation is regulated by enzymes and non-enzymes. Enzymatic regulation mainly influences inflammatory homeostasis via the inflammatory pathway; non-enzymatic regulation influences the covalently modified glycolytic pathway, inhibits enzyme activity and reduces metabolites of glycolysis.⁶⁵ The study also found that glycolytic inhibitors not only inhibit the production of lactate, but also reduce lactylation. Mitochondrial inhibitors or hypoxia conditions increase production of lactate and promote lactylation, which is involved in the homeostatic regulation of M1 macrophages infected by bacteria, inflammation, cancer, and other diseases.⁷⁰ So far, the discovery of lactylation has given a new direction to the study of metabolite lactate in tumors, immunity and other fields.

Histone Lactylation Sites

In 2019, Zhang et al identified 26 histone lactylation sites in human HeLa cells and 18 in mouse macrophages using mass spectrometry, revealing the importance of this epigenetic modification in gene regulation.⁶³ Subsequent studies found histone lactylation sites in gastric cancer cells, HEK 293 cells, and the fungus *Botrytis cinerea*, underscoring its prevalence and potential roles in diverse biological contexts.^{68,73–75} H3K18la, a specific lactylation site, has been linked to the advancement of sepsis, colon cancer, and ocular melanoma by influencing the expression of genes like METTL3 and YTHDF2, which are involved in methylation and mRNA decay, respectively.^{76–78}

Non-Histone Lactylation Sites

However, due to the limitations of current methods for analyzing lactylated proteins, the substrate range of lactylated proteins, especially the substrate range of non-histones, cannot be determined. Sun et al utilized an innovative approach with an alkynyl-functionalized bioorthogonal chemical reporter, YnLac, to conduct proteomic analysis in mammalian cells. This method allowed for the identification of two previously unknown histone lactylation sites, H2AK4 and H2AK9, and the discovery of four novel lactylation sites on non-histone proteins: HMGN1, NPM1, PDCD4, and PHF3.⁷⁹ This work underscores the potential of innovative bioorthogonal chemistry tools in expanding our understanding of lactylation's role in cellular processes. Recently, Yang et al reported 9275 lactylation sites in hepatocellular carcinoma, of which 9256 were found on non-histones. And they showed that lactylation at K28 on the non-histone AK2 can lead to energy disturbances and cell deterioration in HCC.^{80,81} In summary, lactylation is an emerging post-translational modification with wide-ranging effects on both histone and non-histone proteins. The identification of lactylation sites on non-histone proteins in various cancers and the functional implications of these modifications are crucial for understanding cell metabolism and function, and they may offer new targets for therapeutic intervention.

“Writer” and “Eraser”

Protein PTMs, including lactylation, play a vital role in epigenetic regulation, with specific enzymes acting as “writers” and “erasers” to control cellular functions.^{82,83} Zhang et al found that p300 can promote lactylation, while HDAC1-3 can remove it, along with other modifications.^{16,55,73,84} Moreno Yruela et al demonstrated the roles of HDACs and SIRT1-3 in delactylation, with varying efficiency in removing different lysine marks.^{71,85,86} Sun et al identified Sirtuin1 as a potential delactylase.⁸⁷ And Dong et al discovered YiaC and CobB as regulators of lactylation in prokaryotes.⁸⁸ These studies collectively advance our understanding of the enzymatic regulation of lactylation.

Signaling Pathways Related to Lactylation

Lactate signaling and lactylation are implicated in numerous pathways and processes, linking to diseases such as cancer, inflammation, and immune-related disorders (Table 2).⁶⁴ Under hypoxia, lactate accumulation can stabilize NDRG3, influencing Raf-ERK signaling for cell growth and angiogenesis.⁸⁹ Chen et al reported that hypoxia-induced mROS inhibited HIF-1 α hydroxylation and triggered glycolytic conversion in hypoxic pulmonary artery smooth muscle cells via the upregulated HIF-1 α /PDK1&2/p-PDH-E1 α axis, thereby promoting lactate accumulation and histone lactylation.³¹ Second, lactate has been shown to be associated with tumor progression. Lactate regulates cellular metabolic processes in non-small

Table 2 Lactylation-Related Signaling Pathways

Lactylated Protein Site	Related Signaling Pathway	Cell Model	Disease	Ref
N/A	NDRG3-Raf-ERK	PLC/PRF/5, SK-HEP-1, MCF-10A, MCF-7, IMR-90, HeLa, SW480, and HEK293T	Hypoxia-induced diseases	[89]
H3K18la, H4K5la, Pan-Kla	HIF-1 α /PDK1&2/ p-PDH-E1 α	PASMCs	Pulmonary hypertension	[31]
Pan-Kla	HK-1, PKM; SDHA, IDH3G	BEAS-2B, A549, H1299	Non-small cell lung cancer	[26]
H3K18la, Pan-Kla	PDGFR β	HK-2,768-O, Caki-1, ACHNSiHa, WiDr, FaDu, HeLa, HCT116	Clear cell renal cell carcinoma	[90]
H3K9la, H3K56la	Glycolysis pathway	HCCLM3, Hep3B	Hepatocellular carcinoma	[80]
AK2-K28	Adenylate kinase 2	HCC cells	Hepatitis B virus-related hepatocellular carcinoma	[81]
H3K18la	METTL3, YTHDF2	Tumor-infiltrating myeloid cells; Ocular melanoma cells: 92.1, MUM2B, OCM1, MEL290, OMM1, CRMM1, CRMM2, CM2005	Tumor microenvironment, ocular melanoma	[76,78]
L-MOESIN	TGF- β , SMAD3	Treg	Cancer	[91]
N/A	TGF- β	MPCs, Macrophages	Lung fibrosis	[92]
H4K12la	Glycolysis/ H4K12la/PKM2	Microglia	Alzheimer's disease	[32]

Abbreviations: N/A, No available.

cell lung cancer by downregulating glycolytic enzymes and upregulating mRNA levels of TCA cycle enzymes, increasing histone lactylation, and mediating gene expression.²⁶ Von Hippel-Lindau, which is associated with metabolic reprogramming, has been reported to stimulate histone lactylation through activation of platelet-derived growth factor receptor β (PDGFR β) and promote clear cell carcinoma (ccRCC) progression.^{89,90} Tumor progression of hepatocellular carcinoma stem cells was found to be inhibited by inhibition of histone H3K9la and H3K56la modification site.⁸⁰ However, Yang et al found that lactylation at non-histone K28 promotes the proliferation and metastasis of HCC cells by inhibiting the function of adenylate kinase 2.⁸¹ In addition, Yu et al found that lactylation of histone H3K18 recognized m6A modification and promoted the expression of YTH N6-methyladenosine RNA binding protein 2, thereby accelerating tumorigenesis in ocular melanoma.⁷⁸ Similarly, Xiong et al reported that 1 METTL3-mediated RNA m6A modification induced by lactylation promoted immunosuppression of the tumor immunological microenvironment.^{2,77} Gu et al found that the tumor metabolite lactate promotes tumorigenesis by regulating MOESIN lactylation and enhancing transforming growth factor- β (TGF- β) signaling in Treg cells.⁹¹ In inflammation, lactate promotes histone lactylation and pro-fibrotic gene expression, while in Alzheimer's disease, it influences microglial function and cognitive abilities.^{92,93} These findings highlight lactate's role in epigenetic regulation and suggest that targeting lactate-related signaling could offer novel therapeutic strategies for various diseases.

Lactylation and Sepsis Inflammation and Infection

Recent data suggest metabolic dysregulation occurs in sepsis and targeting these pathways could be a therapeutic target for sepsis.²⁸ During sepsis, the host and pathogen trigger a robust anti-infection response. This leads to reduced tissue perfusion, edema induction, decreased oxygen transport between cells, increased in oxygen consumption by immune cells in inflammatory tissues and cell hypoxia. Additionally, lactate produced by aerobic glycolysis in hypoxia conditions or because of bacterial stimulation has been found to influence the activation of macrophages and the expression of specific genes, relying on certain signaling pathways.⁹⁴ Furthermore, B-cell adaptor deletion regulated by Phosphoinositide 3-kinase has been linked to defective aerobic glycolysis and reduced lactate production, affecting gene expression and the transformation of inflammatory macrophages into

reparative ones.^{71,95} Histone lactylation has been observed in both healthy individuals and critically ill patients. H3K18 has been identified as a potential biomarker for diagnosing and predicting the severity of septic shock, as it mediates inflammatory cytokine expression, promotes Arg1 overexpression, and stimulates the anti-inflammatory function of macrophages in sepsis.⁹⁶ Ma et al conducted a study using a mouse model of peritonitis infection to evaluate the impact of methylxanthoymethane on methicillin-resistant *Staphylococcus aureus* infection.⁷⁶ Their findings suggest that methylxanthoymethane promotes Arg1 expression via H3K18 lactylation to control macrophage polarization toward M2, offering potential therapeutic benefits for drug-resistant infections and sepsis.^{71,76}

Organ Dysfunction

From the perspective of pathogenesis, sepsis is associated with inflammatory disorder, disseminated intravascular coagulation, and organ dysfunction. Clinically, lactate levels and high mobility group protein-1 are frequently used as biomarkers and are associated with sepsis severity and mortality.⁷⁶ Yang et al found that lactate contributes to increased vascular permeability and worsens organ dysfunction in CLP sepsis. Vascular permeability and organ damage could be mitigated by inhibiting lactate production and depleting of the lactate receptor GPR81 in vivo.⁹⁷ Additionally, the research team also found that the extracellular lactate uptake by MCT promoted the lactylation/acetylation of HMGB1 through p300/CBP-dependent pathway and GPR81. The modified HMGB1 is translocated from the nucleus to the cytoplasm, released into the circulatory system, resulting in endothelial barrier dysfunction and promoting sepsis development.^{38,46} Therefore, inhibiting lactylated HMGB1 and exosomal release may be a therapeutic target for sepsis. The results presented in [Figure 1](#) highlight the significant role of lactylation in the occurrence and development of sepsis, expanding our understanding of lactylation's biological function. Seng et al's study reveals a novel mechanism between lactate and organ damage in sepsis, indicating that septic kidney injury will be lessened by decreased levels of non-histone mitochondrial fission protein 1 lactylation.^{72,98}

Immune Response

An innovative potential treatment for reducing inflammation involves regulating cell metabolism, leading to the repolarization of inflammatory immune cells in an anti-inflammatory manner. Strict regulation of the metabolic pathway in immune cells is crucial to maintaining immunological balance and proper functional specialization.⁹⁸ Innate immune cells play a role in modulating the immune response during sepsis. For instance, dysfunction in macrophages and dendritic cells can impair the body's ability to respond to initial infections and weaken the defense against secondary hospital-acquired infections.⁹⁹ Immune tolerance to infections is a characteristic of the immunosuppressive stage of sepsis, during which dendritic cell transition to a tolerant phenotype and promote the development of regulatory T cells to suppress the immune system.¹⁰⁰ Recent studies have shown that exogenous lactate can induce a shift in metabolism and induce innate immune cells to assume a tolerant phenotype.^{101,102} Myeloid-derived suppressor cells are immunosuppressive immune cells that play a role in suppressing the immune system during sepsis by restricting T cell activity and promoting Treg development.^{103,104} The development of MDSC and immunosuppression is triggered by an increase in glycolysis and lactate concentration. In order to regulate cell activity and maintain homeostasis, T cells monitor the concentration of extracellular lactate and initiate intracellular signal transduction.¹⁰⁵ Zhang et al discovered that LPS-activated M1 macrophages increased lactate concentration through glycolysis and promoted histone lactylation, leading to increased expression of Arg1 and other genes related to wound healing, indicating a phenotypic shift to immunosuppressive M2 macrophages.³⁴

Discussion

Sepsis is a severe systemic inflammatory syndrome usually caused by infection and characterized by metabolic reprogramming of immune cells, in particular by abnormal activation of glycolytic pathways under aerobic conditions. This metabolic reprogramming leads to increased glucose consumption, increased lactate secretion and increased inflammation levels, which in turn affects the patient's prognosis. Lactate, a metabolic byproduct of cellular glycolysis, has attracted considerable attention due to its role in the Warburg effect within the tumor microenvironment. Research has increasingly implicated lactate in the development of sepsis, where it correlates with the severity of mortality and prognosis. Although the pathophysiological mechanisms of sepsis are not fully elucidated, evidence points to epigenetic

processes that modulate the inflammatory response in sepsis, with lactate acting as a substrate for histone lactylation and influencing immune cell function. The identification of lactylation as a novel epigenetic modification has emerged as a critical area of sepsis research. Glycolysis inhibitors such as DCA (dichloroacetic acid), 2-DG and oxamate reduce lactate production by inhibiting key enzymes of the glycolytic pathway.⁶⁰ By reducing the rate of glycolysis, these inhibitors reduce intracellular lactate levels, which can mitigate the inflammatory response and tissue damage caused by sepsis. Lactylation is an epigenetic modification that involves the lactylation of lysine residues on proteins. The extent and pattern of lactylation can change during sepsis and influence the function of immune cells and the regulation of inflammatory responses. The extent of lactylation can be regulated by influencing lactylation modifying enzymes such as p300/CBP, HDACs and sirtuins (deacetylases).^{12,85} By regulating the activity of these enzymes, the balance of lactylations can be influenced, which in turn can improve the immune response and inflammatory state in sepsis patients. Further research is needed to clarify the upstream and downstream regulatory pathways of these lactylation enzymes. Employing proteomics in tandem with genomics and metabolomics to monitor proteomic alterations and the differential expression of identified proteins in sepsis may offer a comprehensive view of the pathophysiological mechanisms at play. For instance, interventions that reduce the lactylation of HMGB1 and Fisi1 have shown promise in ameliorating organ dysfunction and acute kidney injury in sepsis. Current research has predominantly focused on core histones such as H3, H4, H2A, and H2B, with a relative paucity of studies on non-histone proteins. Further investigation into additional histone lactylation sites and non-histone lactylation sites are essential for advancing our understanding in this area.

Conclusion

In summary, targeting glycolysis inhibition, modulating lactylation enzymes and discovering new histone lactylation sites and non-histone lactylation sites presents a promising therapeutic strategy to improve the prognosis of sepsis patients. These approaches have the potential to offer new perspectives and methods for the treatment of sepsis by regulating the metabolic state and inflammatory response of immune cells. However, further research and validation are required to ensure the safety and efficacy of these treatment strategies in clinical applications. In the future, these strategies may become an integral part of sepsis treatment, providing patients with a broader range of therapeutic options.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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