

Metabolism meets inflammation: lactate and lactylation in inflammatory pathogenesis

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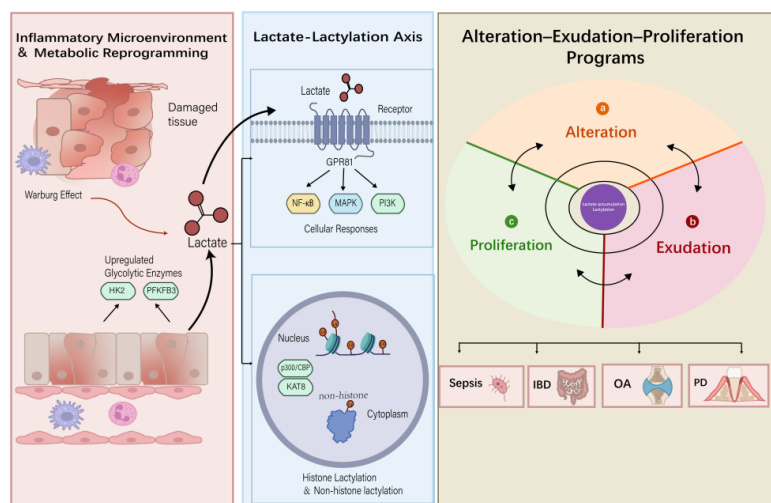
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ABSTRACT: Once regarded primarily as a glycolytic by-product, lactate is increasingly recognized as an active signaling metabolite involved in a broad spectrum of diseases. In parallel, lysine lactylation, a recently described post-translational modification, has been linked to the regulation of cellular functions, immune responses, and metabolic reprogramming. This review summarizes the metabolic mechanisms underlying lactate production and lactylation within the inflammatory microenvironment, and discusses how the lactate-lactylation axis relates to the dynamic “alteration-exudation-proliferation” trajectory of inflammation. We outline how lactate functions beyond bioenergetics to influence gene-regulatory programs and immune-cell behavior through lactylation, thereby shaping the alteration, exudation and proliferation phases of inflammation. Evidence from sepsis, inflammatory bowel disease, osteoarthritis, and periodontitis is highlighted to illustrate disease-relevant roles and to frame current knowledge gaps. These four diseases were selected as representative inflammatory or infection-related conditions because they share key pathological features, including dysregulated inflammatory responses, immune-metabolic reprogramming, lactate accumulation, and emerging evidence for the involvement of lactylation. Finally, we discuss future directions, emphasizing that integrating single-cell multi-omics with high-specificity reagents will be important for resolving the spatiotemporal features of lactylation and for advancing translational applications. A deeper understanding of lactate signaling and the lactate-lactylation axis may inform new strategies for the diagnosis and treatment of inflammation-associated diseases.

KEYWORDS: lactate, lactylation, inflammatory diseases, epigenetic modification



1 Introduction

Inflammation is a protective response to harmful stimuli, including damaged cells, pathogens, and irritants. Its primary functions are to eliminate the insult, repair injured tissue, and restore homeostasis. When tightly regulated, inflammation is beneficial, for example by providing protection against infection. In contrast, dysregulated inflammation can be detrimental and may culminate in septic shock^[1]. Classical pathology describes the basic pathological changes

of inflammation as alteration, exudation, and proliferation^[2]. Alteration refers to injury-associated degeneration or necrosis of local parenchymal or stromal cells. Exudation denotes the transvascular movement of fluid, plasma proteins, and immune cells into the interstitium, mucosal surfaces, body surfaces, or serous cavities, and is regarded as a characteristic feature of inflammation. Proliferation involves the regeneration and expansion of local tissue cells, and contributes to tissue repair, remodeling, or fibrosis. Importantly, these three pathological programs are interrelated and may coexist throughout inflammation rather than occurring as a strictly linear sequence. Their relative predominance varies according to the type, duration, and intensity of inflammation; acute or early inflammation is often dominated by alteration and exudation, whereas chronic or later inflammation is more commonly characterized by proliferative and remodeling responses.

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Defining the molecular features and regulatory mechanisms associated with these overlapping programs is essential for improving the prevention and treatment of inflammatory diseases.

Since its discovery in 1780, lactate was long regarded as a harmful metabolic by-product generated by glycolysis under hypoxic conditions^[3]. This view has been revised. Lactate serves not only as a substrate for mitochondrial oxidation and gluconeogenesis but also as a signaling metabolite that regulates diverse physiological and pathological processes through autocrine, paracrine, and endocrine mechanisms^[4]. During inflammation, tissue hypoxia and metabolic reprogramming promote pronounced lactate accumulation in the local milieu, as reported in sepsis^[5,6], pancreatitis^[7], glomerulonephritis^[8], and wound healing^[9]. By engaging lactate-responsive receptors and related pathways, lactate can modulate cytokine release, vascular permeability, and cell migration, thereby modulating inflammatory responses^[10]. Consistent with these observations, lactate levels tend to increase during active inflammatory responses, whereas lactate clearance during recovery is associated with reduced inflammatory burden, suggesting that lactate is dynamically linked to inflammatory activity and may contribute to stage-specific inflammatory regulation^[11].

Protein lactylation was first reported by Zhang et al. in 2019 as a post-translational modification in which lactate is covalently attached to lysine residues through enzymatic or non-enzymatic mechanisms^[12]. Local lactate accumulation also provides a substrate for lactylation, which can, in turn, regulate the activity, stability, or function of key proteins, including histones, thereby influencing chromatin accessibility and gene transcription. Through these effects, lactylation influences transcription of inflammation-associated genes and the activation state of immune cells. In this

manner, lactate can convert metabolic changes into gene-regulatory outputs via lactylation. Lactylation has been linked to the development of inflammatory diseases by directly altering target-protein activity or function and by regulating gene transcription, thereby contributing to cell fate decisions, immune responses, and metabolic reprogramming.

Inflammatory diseases are highly prevalent and impose substantial health burdens. Their pathogenesis is heterogeneous and complex, and they remain among the leading causes of death worldwide. A clearer understanding of the underlying molecular regulation is therefore of clinical importance. Guided by the alteration-exudation-proliferation framework, this review discusses disease-specific roles and mechanisms of lactate and lactylation in representative inflammatory disorders, including sepsis, inflammatory bowel disease (IBD), osteoarthritis (OA), and periodontitis. We also summarize current challenges and outline future directions, with the aim of providing a theoretical basis for therapies targeting the lactate-lactylation axis.

2 Lactate metabolism and the mechanistic basis of lactylation

Lactate accumulation is a prominent metabolic feature of the inflammatory microenvironment^[13]. Rather than representing a passive glycolytic by-product, lactate is generated through coordinated changes in glucose uptake, glycolytic enzyme activity, pyruvate fate, redox balance, and mitochondrial metabolism. In inflamed tissues, these processes determine the size, localization, and persistence of the lactate pool, which can subsequently participate in metabolic exchange, receptor-mediated signaling, and lactylation-dependent regulation (Fig. 1).

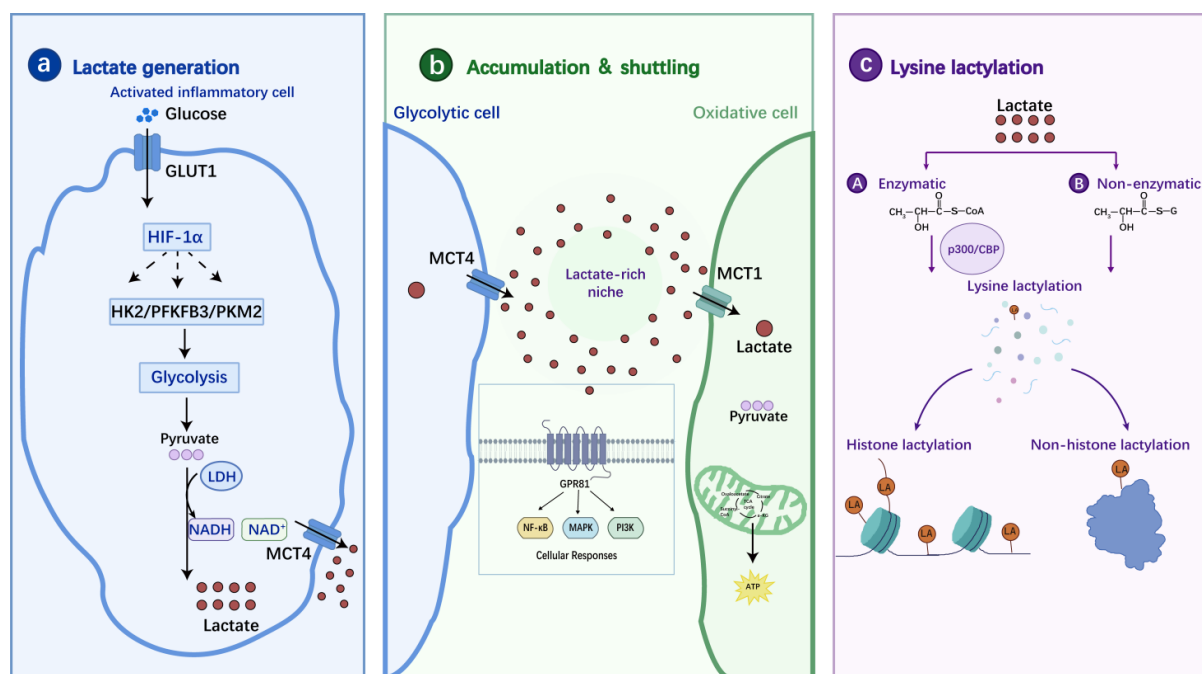


Figure 1 Lactate generation, intercellular shuttling, and lysine lactylation in the inflammatory microenvironment. (a) Activated inflammatory cells enhance GLUT1-mediated glucose uptake and HK2/PFKFB3-driven glycolysis. LDH converts pyruvate to lactate while regenerating NAD⁺, and MCT4 facilitates lactate export. (b) Extracellular lactate accumulates within the inflammatory niche, where it activates GPR81-dependent signaling through NF- κ B, MAPK, and PI3K pathways. Lactate is also shuttled from glycolytic cells to oxidative cells through MCT4 and MCT1, respectively, and can be converted back to pyruvate to support mitochondrial ATP production. (c) Lactate promotes histone and non-histone lysine lactylation through a lactyl-CoA-dependent, p300/CBP-associated enzymatic route or through non-enzymatic lactoyl transfer, thereby linking metabolic reprogramming to transcriptional and protein-level regulation.

During inflammatory activation, immune and stromal cells frequently increase glucose uptake and glycolytic flux. This process is supported by glucose transporters such as GLUT1 and GLUT3, followed by sequential glycolytic control through enzymes including hexokinase 2 (HK2), 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), phosphofructokinase-1 (PFK1), and pyruvate kinase M2 (PKM2). In myeloid cells, HIF-1 α is essential for maintaining glycolytic capacity and inflammatory function, and loss of HIF-1 α markedly impairs myeloid cell aggregation, motility, invasiveness, and bacterial killing^[14]. In macrophages, HIF-1 α and PFKFB3 couple pro-inflammatory activation to increased glycolytic flux^[15], whereas PKM2 links LPS-induced glycolytic reprogramming to HIF-1 α activity and IL-1 β expression^[16]. These regulatory nodes increase pyruvate generation and support rapid ATP production under inflammatory conditions.

The conversion of pyruvate to lactate is mainly catalyzed by lactate dehydrogenase A/B (LDHA/LDHB). This reaction regenerates NAD⁺ from NADH, thereby sustaining glycolytic flux when mitochondrial oxidation is limited or when cells require rapid glycolytic ATP production^[17]. Lactate generation is also influenced by carbon source utilization. Glutamine-derived carbon can contribute to pyruvate and lactate production through anaplerotic metabolism^[18]. Thus, inflammatory lactate accumulation reflects coordinated changes in glycolysis, redox cycling, and substrate utilization rather than a simple endpoint of glucose metabolism.

Pyruvate fate is further controlled by the balance between mitochondrial entry and cytosolic lactate production. The pyruvate dehydrogenase complex converts pyruvate to acetyl-CoA for entry into the tricarboxylic acid cycle, whereas pyruvate dehydrogenase kinase 1 (PDK1) phosphorylates and inhibits pyruvate dehydrogenase, limiting pyruvate oxidation. HIF-1 has been shown to induce PDK1 expression and thereby shift pyruvate away from mitochondrial oxidation toward glycolytic metabolism under hypoxia^[19]. HIF-1 also downregulates mitochondrial oxygen consumption by inducing PDK1, providing a mechanism by which hypoxic or inflamed cells preserve glycolytic metabolism and favor lactate accumulation^[20]. In trained innate immunity, activation of the Akt-mTOR-HIF-1 α pathway increases glucose consumption, lactate production, and the NAD⁺/NADH ratio in human monocytes, linking inflammatory memory to aerobic glycolysis^[21].

After lactate is generated, it is redistributed between cells primarily through monocarboxylate transporters, especially MCT1 and MCT4^[22]. MCT4 mainly supports lactate export from highly glycolytic cells, whereas MCT1 facilitates lactate uptake by cells with greater oxidative capacity, allowing imported lactate to be converted back to pyruvate and used for mitochondrial metabolism^[23]. Extracellular lactate may also act as a signaling ligand through receptors such as GPR81 or GPR132, while intracellular lactate can contribute to histone or non-histone lysine lactylation when appropriate donor-generating and writer systems are available. In this way, lactate production, transport, oxidation, receptor signaling, and lactylation form connected but mechanistically distinct layers of inflammatory regulation^[24].

Protein lysine lactylation (Kla) is a covalent post-translational modification in which a lactyl group is added to lysine residues through enzymatic or non-enzymatic routes^[25]. Histones were among the first substrates in which lactate-derived Kla was systematically characterized, linking inflammatory or metabolic lactate accumulation to chromatin regulation and gene transcription. Among the enzymes implicated in this process, p300

has been most directly associated with histone Kla: p300 overexpression increases histone lactylation, whereas p300 depletion reduces it^[12]. CBP is often discussed together with p300 because of their structural and functional similarity as lysine acyltransferases^[26]; however, its independent contribution to lactylation remains less clearly separated from that of p300.

The formation of an activated lactyl donor represents another regulatory layer. Lactyl-CoA provides a chemically plausible donor for enzymatic lactylation, and recent work showed that ACSS2 can generate lactyl-CoA and cooperate with KAT2A to promote histone lactylation in a tumor immune-evasion model^[27]. Other lysine acyltransferases, such as HBO1, have also been reported to catalyze histone lactylation in defined biological contexts^[28]. These findings indicate that lactylation can be coupled to specific acyl-CoA-producing enzymes and writer complexes, although the contribution of each route is likely to vary according to cell type, substrate, and pathological setting.

Removal of Kla is also regulated enzymatically. HDAC1-3 have been identified as histone lysine delactylases through biochemical screening, with cellular validation reported for HDAC1 and HDAC3^[29]. In addition, selected sirtuins have been linked to delactylation in specific settings. For example, SIRT2 has been reported to function as a histone delactylase in neuroblastoma cells^[30], while SIRT6 was recently characterized as a histone delactylase acting on H3K9la and H3K18la in vitro and in mammalian cells^[31]. These observations suggest that delactylation is shaped by enzyme isoform, substrate type, and cellular context.

Beyond writing and erasing, lactylation can also be interpreted by reader or reader-like proteins. DPF2 has been identified as an H3K14la-binding effector that links histone lactylation to transcriptional activation and cell survival^[32]. BRG1 has also been reported to bind H3K18la during early iPSC reprogramming, connecting histone lactylation with chromatin remodeling and mesenchymal-to-epithelial transition-related gene programs^[33]. These findings add a recognition layer to lactylation biology, although the spectrum of Kla readers in inflammatory tissues remains largely unresolved.

In parallel with enzymatic mechanisms, non-enzymatic lactoylation can occur through reactive intermediates generated by glycolytic side pathways. Lactoylglutathione, an intermediate of the glyoxalase system, can transfer a lactoyl group to lysine residues without requiring a writer enzyme, producing LactoylLys on glycolytic enzymes^[34]. This route is chemically distinct from enzyme-mediated histone L-lactylation and is particularly relevant under conditions of enhanced glycolytic flux or altered glyoxalase metabolism. Together, these mechanisms show that Kla is controlled by donor availability, writer and eraser activity, reader recognition, and non-enzymatic chemistry, all of which may operate differently across inflammatory microenvironments.

Functionally, histone and non-histone lactylation share the same basic feature of lysine modification but differ in their major biological consequences. Histone lactylation mainly affects chromatin organization and gene transcription, thereby linking lactate metabolism to epigenetic regulation. For example, lactate-induced H3K18 lactylation in macrophages has been reported to accumulate at promoters of inflammation-related genes and regulate their transcription^[12]. In contrast, non-histone lactylation can directly alter protein activity, stability, localization, or protein-protein interactions, thereby influencing signaling pathways, immune responses, and metabolic reprogramming.

Accordingly, the high-lactate milieu established by metabolic reprogramming and intercellular lactate shuttling can regulate gene expression and cellular function through lactylation-dependent mechanisms. This metabolism-lactylation-inflammation link provides a molecular basis for understanding lactate not merely as a metabolic by-product, but as an active modulator of inflammatory responses (Table 1).

3 Lactate signaling and protein lactylation in the alteration-exudation-proliferation framework

Classical pathology describes inflammation in terms of three interrelated pathological programs: alteration, exudation, and proliferation/repair. These programs often overlap within inflamed tissues. Alteration reflects local cellular and tissue injury; exudation involves vascular opening and the recruitment of fluid, plasma

proteins, and immune cells; and proliferation/repair encompasses resolution, regeneration, angiogenesis, and tissue remodeling. Lactate is dynamically involved in each program. It can act as an extracellular signaling metabolite through lactate-responsive receptors, as an intracellular metabolic intermediate through MCT-dependent transport and LDH-dependent lactate-pyruvate exchange, and as a source for histone or non-histone lysine lactylation. These interconnected mechanisms allow lactate to influence inflammatory initiation, amplification, and repair (Fig. 2).

3.1 Alteration phase: roles of lactylation in tissue injury and cellular dysfunction

Alteration refers to injury-associated changes in local tissues or cells, including cellular dysfunction, degeneration, and necrotic or regulated cell death. Barrier cells and parenchymal cells are commonly among the earliest affected cell populations. Their damage can release damage-associated molecular patterns

Table 1 Experimental evidence for key molecules involved in lactate metabolism and lactylation regulation.

Molecule	Functional role	Molecular/enzymatic classification	Mechanism-level evidence reported	Representative study
PFKFB3	Glycolytic rate-control enzyme	Bifunctional glycolytic enzyme	Human and murine macrophages with pro-inflammatory activation showed increased HIF-1 α and PFKFB3 expression together with enhanced glucose uptake and lactate production. Pharmacologic and molecular analyses linked PFKFB3-dependent glycolysis to inflammatory activation.	[15]
PKM2	Pyruvate-generating glycolytic enzyme	Pyruvate kinase	In LPS-activated macrophages, PKM2 underwent dimerization and nuclear translocation. Genetic and pharmacologic manipulation of PKM2 altered HIF-1 α activity, IL-1 β expression, and glycolytic reprogramming, demonstrating a mechanistic link between PKM2, inflammatory signaling, and lactate-producing metabolism.	[16]
LDHA/LDHB	Lactate dehydrogenase	Lactate dehydrogenases	The study combined metabolic measurements, LDHA-associated lactate analysis, and functional immune assays to show that enhanced LDHA-linked lactate production drives extracellular lactate accumulation and immune suppression. Although performed in a tumor-immune context, it provides direct mechanism-level evidence for enzyme-dependent lactate production and its immunologic consequences.	[35]
p300	Writer	Lysine acyltransferase	Histone K1a sites were identified by mass spectrometry. p300 overexpression increased global histone K1a, whereas p300 deletion reduced histone K1a in cells. Lactate-induced histone K1a was linked to transcriptional activation during macrophage polarization.	[12]
CBP	Writer	Lysine acyltransferase	p300 and CBP are closely related lysine acyltransferases with structural and functional similarity. However, most lactylation studies have not enzymatically separated CBP-specific activity from p300 activity.	[12],[26]
KAT2A	Writer	Lysine acyltransferase	KAT2A was linked to ACSS2-derived lactyl-CoA and histone lactylation. KAT2A perturbation affected histone K1a and downstream transcriptional programs in the same model.	[27]
HBO1	Writer	Lysine acyltransferase	HBO1 was reported to catalyze lysine lactylation and regulate H3K91a-dependent transcription. Cell-based perturbation and tumor-related functional analyses supported its role.	[28]
HDAC1-3	Eraser	Class I histone deacetylases	A biochemical screen of 18 HDACs using lactylated peptide and histone substrates identified class I HDAC1-3 as efficient lysine delactylases. HDAC1 and HDAC3 showed site-specific delactylase activity in cells.	[29]
SIRT1-3	Eraser	NAD ⁺ -dependent deacylases	The same HDAC screen showed in vitro delactylase activity for selected sirtuins, including SIRT1-3, but cellular validation was more limited than for HDAC1-3.	[29]
SIRT2	Eraser	NAD ⁺ -dependent deacylase	SIRT2 was reported to act as a histone delactylase in neuroblastoma cells. SIRT2-dependent changes in histone K1a were linked to altered proliferation and migration.	[30]
SIRT6	Eraser	NAD ⁺ -dependent deacylase	SIRT6 was characterized as a histone delactylase in vitro and in mammalian cells, with H3K91a and H3K181a identified as responsive sites.	[31]
DPF2	Reader	PHD-finger protein	DPF2 was identified as an H3K141a-binding effector. Binding and chromatin-based analyses linked DPF2-H3K141a recognition to transcriptional activation and cell survival.	[32]
ACSS2	Lactyl-CoA synthetase	Acyl-CoA synthetase	ACSS2 was reported to generate lactyl-CoA and functionally couple KAT2A to histone lactylation. ACSS2 perturbation altered histone K1a, downstream transcription, and tumor immune-evasion phenotypes.	[27]

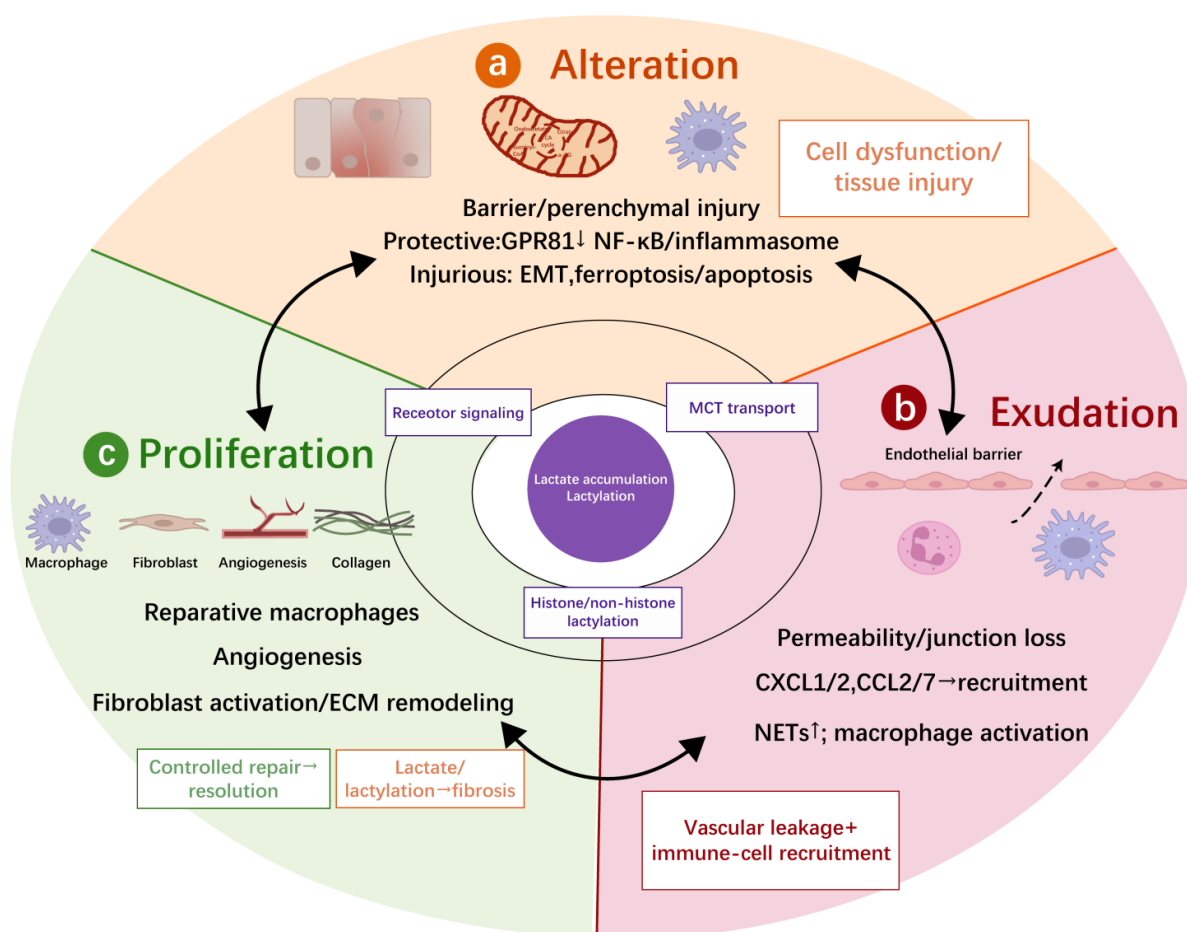


Figure 2 Lactate signaling and protein lactylation within the alteration-exudation-proliferation framework.

(DAMPs), thereby initiating or amplifying inflammatory responses.

Epithelial cells form organized barrier layers that preserve tissue compartmentalization and limit excessive exposure to luminal or environmental stimuli^[36]. During inflammation, epithelial metabolism often shifts from oxidative phosphorylation toward aerobic glycolysis^[37], accompanied by increased expression of glycolytic enzymes such as hexokinase 2 (HK2)^[38,39]. This metabolic shift increases lactate production and may reshape intracellular redox balance, mitochondrial metabolism, and stress adaptation. Extracellular lactate can also function as a signaling molecule. Lactate-GPR81 signaling has been reported to suppress NF-κB and MAPK activation, reduce pro-inflammatory mediators and MMP-9 expression, and preserve epithelial barrier function in inflammatory bowel disease^[40]. In liver and pancreatic injury models, lactate also reduces Toll-like receptor- and inflammasome-mediated inflammation through GPR81-dependent suppression of innate immune activation^[41]. These findings indicate that lactate itself can influence early epithelial and parenchymal injury through receptor-mediated and metabolic pathways.

In parallel, histone lactylation can convert lactate-enriched metabolic states into transcriptional changes in injured barrier cells. In airway epithelial cells, silica exposure induces H3K18la and increases SIX1 transcription, thereby promoting epithelial-to-mesenchymal transition (EMT)^[42]. In renal tubular epithelial cells, H3K14la enhances KLF5 expression and promotes EMT in diabetic kidney disease^[43]. These examples link lactate-associated metabolic

stress to chromatin-dependent epithelial remodeling.

Parenchymal cell death is another major component of alteration. Ferroptosis, an iron-dependent form of lipid peroxidation-driven cell death, can intensify oxidative injury and inflammatory amplification^[44]. In the heart, liver, and brain, enhanced glycolytic flux and upregulation of HK2^[45] or PFKFB3^[46], promote lactate accumulation. Lactate transport through MCTs and lactate-pyruvate conversion through LDH may affect mitochondrial metabolism and redox homeostasis, thereby influencing cellular susceptibility to injury^[47]. Protein lactylation further modifies key ferroptosis-related enzymes. In hepatocytes, KAT8 mediates PCK2 lactylation at Lys100, enhances PCK2 activity, stabilizes OXSM by inhibiting Parkin-mediated ubiquitination, and promotes hepatic ferroptosis through mitochondrial metabolic reprogramming^[48]. In myocardial ischemia-reperfusion injury, GPX4 lactylation at K218 and K228 reduces GPX4 stability, weakens anti-ferroptotic defense, and increases lipid peroxidation and tissue damage^[49]. Thus, in ferroptosis, lactate-associated metabolism and non-histone protein lactylation can converge on mitochondrial and lipid-peroxidation pathways.

Apoptosis may also be shaped by lactate exchange and lactylation of regulatory proteins. Astrocytes produce lactate in response to neuronal activity, export it through MCTs, and support neuronal metabolism after uptake by neurons^[50]. In cerebral ischemia, MeCP2 lactylation at K210/K249, regulated by HDAC3 and p300, suppresses transcription of cell-death-related genes such as Pdc4

and Pla2g6, thereby reducing neuronal apoptosis^[51]. Taken together, during alteration, lactate may either support adaptive stress responses or contribute to tissue injury depending on its concentration, cellular localization, receptor engagement, and the modified protein targets.

3.2 Exudative phase: lactylation regulates immune responses and immune-cell recruitment

Exudation is characterized by the movement of fluid, plasma proteins, and immune cells from local vessels into tissue spaces, mucosal surfaces, body surfaces, or serous cavities. This process requires endothelial barrier opening, leukocyte adhesion and transmigration, and chemokine-guided immune-cell recruitment. Lactate accumulates rapidly in this environment because endothelial cells and recruited immune cells rely heavily on glycolysis.

Endothelial cells contribute to immunity and help maintain tissue fluid balance and vascular tone^[53]. During the exudative phase, inflammatory mediators disrupt the expression, localization, and stability of tight junction and adherens junction proteins, weakening intercellular contacts and increasing endothelial permeability^[53,54]. Unlike many other cell types, endothelial cells rely predominantly on glycolysis for energy^[55]. Inflammation further enhances endothelial glycolysis by upregulating HK2, PKM2, and PFKFB3^[56]. Lactate directly affects endothelial barrier function. It activates the ERK-calpain1/2 axis, promoting VE-cadherin proteolysis and endocytosis and increasing vascular permeability^[57]. Lactate also suppresses HSPA12B through HCAR1/GPR81-dependent signaling, leading to disruption of Claudin-5 and ZO-1^[58]. At the chromatin level, lactate-driven H3K18la promotes SNAI1 transcription and endothelial-to-mesenchymal transition (EndoMT), further weakening endothelial barrier integrity^[59]. Thus, vascular leakage can be driven by both lactate receptor-associated signaling and histone lactylation-dependent endothelial transcriptional remodeling.

Endothelial junctional opening creates routes for leukocyte adhesion, crawling, and transmigration^[60]. In parallel, endothelial cells express adhesion molecules such as ICAM-1, VCAM-1, and PECAM-1, and produce chemokines including CXCLs and CCLs to guide leukocyte recruitment^[61]. Neutrophils are among the earliest immune cells mobilized during exudation^[62]. Hypoxia, endotoxin, and bacterial stimulation enhance neutrophil glycolysis and lactate release^[63]. Lactate released by inflammatory bone marrow neutrophils activates endothelial GPR81 signaling, increases local vascular permeability, and promotes CXCL1/2 release, thereby accelerating neutrophil mobilization and migration^[10]. Lactate can also induce CCL2 and CCL7 through GPR81, promoting granulocyte recruitment to inflammatory lesions^[64]. Once neutrophils enter inflamed tissues, lactylation can regulate their effector programs. HMGB1 lactylation increases circulating neutrophil extracellular trap (NET) levels and aggravates inflammation-induced organ injury^[65]. In parallel, H3K18la enhances MICU3 transcription in neutrophils, promotes mitochondrial calcium uptake, and contributes to NET formation and organ damage^[66]. These two examples represent different regulatory modes: HMGB1 lactylation modifies a non-histone inflammatory mediator, whereas H3K18la regulates a transcriptional program.

Macrophages are recruited after early neutrophil infiltration and

participate in pathogen clearance^[67], cytokine production^[68], and inflammatory amplification^[69]. The effects of lactate on macrophages vary with tissue context and inflammatory state. Lactate can suppress macrophage pro-inflammatory responses through GPR81-mediated inhibition of YAP and NF- κ B activation^[70]. It can also inhibit LPS-induced pro-inflammatory activation and metabolic reprogramming in murine macrophages through GPR81-independent mechanisms. Conversely, in other inflammatory settings, lactate stabilizes HIF-1 α and activates NF- κ B signaling, favoring pro-inflammatory polarization^[71]. Histone lactylation adds another layer to macrophage regulation: H3K18la activates glycolytic gene transcription and supports M1-like activation^[72]. In liver ischemia-reperfusion injury, inhibition of glycolysis reduces HMGB1 lactylation and secretion from hepatocytes, thereby suppressing macrophage chemotaxis and activation^[73]. These findings show that macrophage responses during exudation are shaped by lactate signaling, lactate-dependent metabolic rewiring, histone lactylation, and non-histone lactylation.

3.3 Proliferative phase: lactylation mediates tissue repair, angiogenesis, and fibrosis

The proliferation/repair program includes resolution of inflammation, clearance of apoptotic cells, granulation tissue formation, angiogenesis, fibroblast activation, and extracellular matrix remodeling. Properly regulated, these processes restore tissue integrity. When persistent or excessive, they may drive pathological fibrosis. Lactate participates in this program both as a repair-associated metabolic signal and as a substrate source for lactylation-dependent remodeling.

Resolution begins with termination of neutrophil-driven inflammation and clearance of apoptotic cells^[74]. Macrophage efferocytosis activates TGF- β /Smad and PI3K-Akt signaling, increases anti-inflammatory mediators, and promotes reparative macrophage phenotypes^[75-77]. Lactate generated during efferocytosis signals through GPR132, stabilizes Myc, and promotes proliferation of reparative macrophages, thereby supporting tissue repair^[78]. Lactate transport also shapes repair programs. Knockdown of MCT4 in macrophages reduces lactate efflux, increases intracellular lactate availability and H3K18la, and activates anti-inflammatory and TCA cycle-related gene programs, promoting lesion repair^[79]. In addition, MeCP2 K271 lactylation promotes reparative macrophage polarization and plaque stabilization [80]. During pancreatic inflammation, enhanced macrophage glycolysis promotes tissue repair by facilitating lactylation and inhibiting JAK2-STAT1 signaling^[81]. Through these pathways, lactate metabolism and lactylation help coordinate the shift from inflammatory activation toward repair.

Angiogenesis supplies oxygen and nutrients to healing tissues^[82] and supports granulation tissue formation^[83]. Lactate itself has pro-angiogenic activity. Endothelial MCT1-mediated lactate uptake can activate HIF-1-dependent signaling and support tumor angiogenesis^[84], and lactate administration has been reported to stimulate angiogenesis and accelerate wound repair in experimental models^[85]. Lactylation-dependent mechanisms further connect lactate-rich environments to pro-angiogenic transcription. HIF-1 α lactylation under normoxia increases KIAA1199 transcription and enhances VEGFA signaling^[86]. Under hypoxia, YY1 lactylation at K183 increases FGF2 transcription and promotes angiogenesis^[87]. Histone lactylation also promotes endothelial cell-cycle progression

and tip-cell formation^[88]. VEGF stimulation increases H3K9la in endothelial cells and augments angiogenesis^[89], while histone lactylation can promote GP73 expression and STAT3 activation^[90]. These findings indicate that angiogenesis is supported by lactate-dependent endothelial metabolism and by lactylation-dependent regulation of transcription factors and chromatin.

Fibroblasts are central regulators of tissue repair and fibrosis^[91]. During normal repair, activated fibroblasts produce extracellular matrix and respond to TGF- β /Smad signaling^[92], whereas PPAR γ activation restrains fibroblast-to-myofibroblast transition and excessive matrix synthesis^[93]. Lactate can regulate fibroblast behavior through receptor-mediated pathways. Lactate-GPR81 signaling suppresses NF- κ B activation and IL-6 production, and lactate can increase hepatocyte growth factor expression, favoring a reparative fibroblast phenotype^[94]. Sustained lactate accumulation, however, can promote fibrotic remodeling through histone lactylation. p300- or KAT8-associated histone lactylation activates profibrotic gene promoters and increases COL1A1/Col1a1 transcription^[95]. Myofibroblast-derived extracellular lactate can enter fibroblasts through MCT1, increase H3K18la, promote Ythdf1 transcription, and facilitate fibroblast-to-myofibroblast transition^[96]. In lung fibroblasts, GLP-1R activation suppresses NLRP3 inflammasome activation and attenuates p300-mediated histone lactylation, thereby limiting fibroblast activation and lung fibrosis in mice^[97]. Overall, lactate can support repair-associated signaling under controlled conditions, whereas sustained lactate accumulation and lactylation-dependent transcriptional activation may shift tissue remodeling toward fibrosis.

Lactate accumulation links metabolic reprogramming to the three overlapping pathological programs of inflammation through receptor signaling, MCT-dependent transport, and histone or non-histone lysine lactylation. During alteration, lactate may protect barrier and parenchymal cells by suppressing NF- κ B and inflammasome activation through GPR81, but may also promote cellular dysfunction, EMT, ferroptosis, or apoptosis depending on the cellular context and lactylated targets. During exudation, lactate and lactylation regulate endothelial junction integrity, vascular permeability, chemokine-mediated leukocyte recruitment, NET formation, and macrophage activation. During proliferation and repair, they promote reparative macrophage responses, angiogenesis, fibroblast activation, and ECM remodeling. Controlled responses favor inflammation resolution and tissue restoration, whereas persistent lactate accumulation and lactylation may drive pathological fibrosis.

4 Lactate and lactylation in inflammatory diseases

The roles of lactate and lactate-driven lactylation in inflammatory diseases have attracted increasing attention. Although their regulatory logic shares common features, the underlying mechanisms also exhibit disease-specific patterns. Here, we focus on four representative disorders—sepsis, IBD, OA, and periodontitis—which correspond to acute systemic inflammation, chronic mucosal inflammation, and localized degenerative inflammation, respectively (Fig. 3).

4.1 Sepsis

Sepsis is an acute systemic inflammatory response triggered by infection and characterized by dysregulated host immunity leading

to organ dysfunction^[98]. Elevated lactate is an important biomarker in sepsis and is positively associated with sepsis-related mortality^[99]. Unlike localized inflammatory diseases, sepsis does not usually follow a clearly separable alteration-exudation-proliferation sequence. Instead, it represents an acute systemic inflammatory syndrome in which tissue injury, vascular leakage, immune-cell activation, metabolic stress, and defective repair may occur simultaneously or reinforce one another. Therefore, sepsis is discussed here as a representative disease in which alteration-, exudation-, and repair/remodeling-related programs are highly overlapping rather than strictly sequential^[98].

In the alteration-related program of sepsis, lactate and lactylation are closely associated with acute cellular injury and organ dysfunction, particularly in sepsis-associated acute lung injury (ALI). Lipopolysaccharide (LPS) treatment of human pulmonary alveolar epithelial cells (HPAEPICs) increases apoptosis, inflammation, and oxidative stress^[80]. Notably, inhibition of aerobic glycolysis reduces apoptosis in LPS-exposed alveolar epithelial cells, suggesting that LPS may promote apoptotic injury through lactate-dependent mechanisms^[100]. LPS can also suppress MCT1 expression in mouse alveolar epithelial cells, thereby impairing lactate transport, inducing lactate accumulation, and ultimately facilitating EMT and epithelial barrier injury^[101]. In parallel, elevated lactate during sepsis can promote histone lactylation, including H3K14la and H3K18la. H3K14la or H3K18la may regulate ferroptosis-related pathways, such as TFRC/SLC40A1 promoter activation or the METTL3-m6A-ACSL4 axis, thereby inducing mitochondrial ROS overproduction, lipid peroxidation, ferroptosis, and aggravation of lung injury^[81,102]. Thus, in sepsis, alteration-related injury is not limited to direct pathogen-induced damage but also involves lactate-dependent metabolic stress and lactylation-associated cell death programs.

The exudation-related program in sepsis overlaps with the above injury process and is characterized by vascular barrier disruption, immune-cell recruitment, and systemic inflammatory amplification^[103]. Lactate directly impairs endothelial junctional integrity through GPR81-associated signaling and ERK-calpain activation, leading to VE-cadherin disruption, increased vascular permeability, and aggravated organ dysfunction^[57]. In addition to these receptor-mediated effects, macrophages can take up extracellular lactate through MCTs and promote HMGB1 lactylation and acetylation through a p300/CBP-dependent mechanism. Lactylated HMGB1 is subsequently released via exosomes and contributes to endothelial permeability and inflammatory propagation^[104]. Moreover, loss of macrophage Spns2 enhances glycolysis and intracellular lactate production, increases ROS generation, and strengthens pro-inflammatory responses, driving lethal hyperinflammation in early sepsis^[105]. These findings indicate that lactate functions both as an active signaling/metabolic mediator and as a substrate for lactylation-dependent inflammatory amplification in sepsis.

The repair/remodeling-related program in sepsis is also not temporally isolated from acute injury. In patients who survive the initial insult, persistent inflammation, immunosuppression, catabolism, and unresolved organ injury may coexist and contribute to chronic critical illness or post-sepsis complications^[106]. Persistent lactate accumulation may interfere with orderly tissue repair and contribute to maladaptive remodeling, although this area remains less well defined than the role of lactate in acute vascular leakage and organ injury. Sustained inflammation can activate

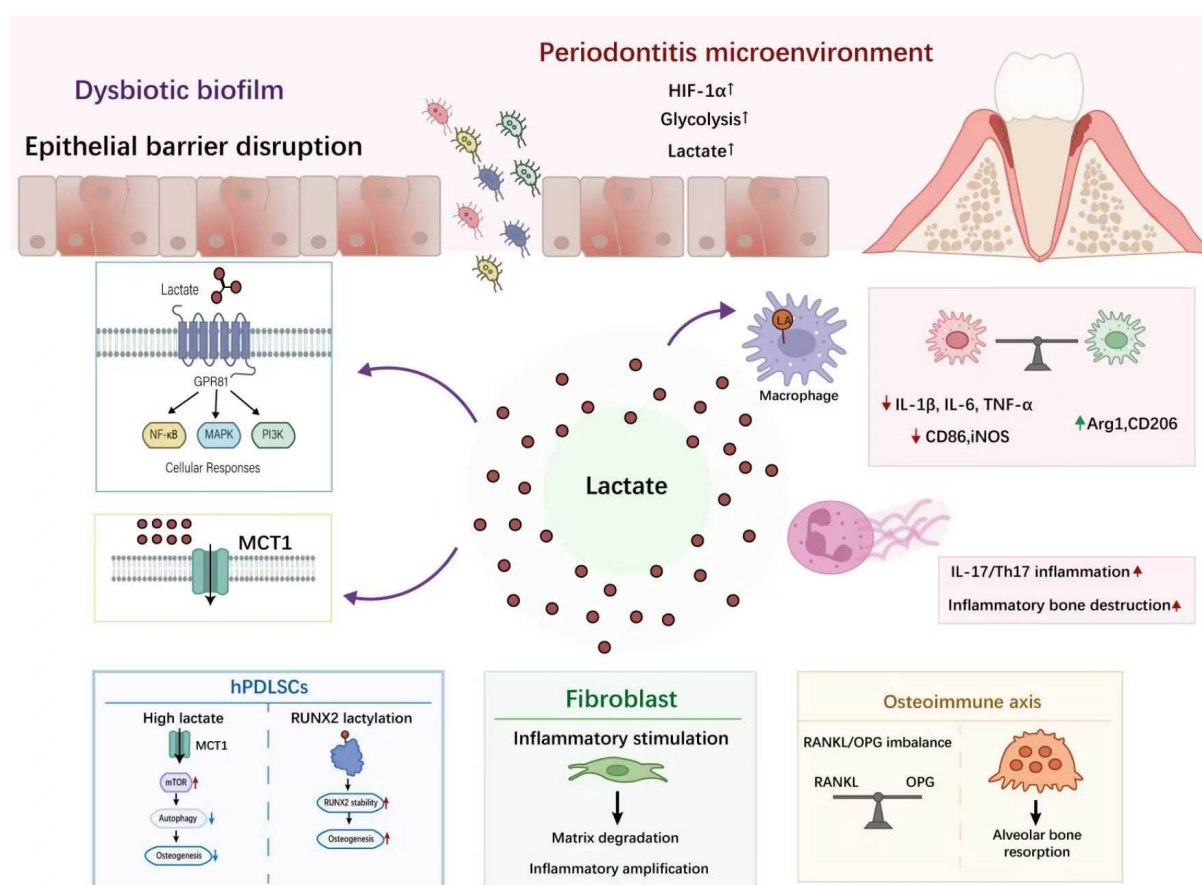


Figure 3 Lactate-lactylation signaling in the periodontitis microenvironment. Dysbiotic biofilms and epithelial barrier disruption promote hypoxia-associated glycolysis and lactate accumulation in periodontal lesions.

fibroblast-related repair pathways, including YAP/TAZ signaling and extracellular matrix synthesis, which may ultimately promote organ fibrosis. In the lung, fibroblast accumulation and deposition of collagen and other extracellular matrix components can drive post-injury fibrotic remodeling. Although lactate and lactylation have been linked to fibrosis in the lung, liver, and kidney, direct evidence for lactate- or lactylation-dependent mechanisms in sepsis-associated fibrosis remains limited. Therefore, in sepsis, the lactate-lactylation axis should be viewed as participating in overlapping injury, exudative, immune-amplifying, and repair/remodeling programs.

4.2 Inflammatory bowel disease

Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, is a chronic relapsing inflammatory disorder of the gastrointestinal tract^[107]. In this disease context, lactate-related regulation is most relevant to mucosal barrier integrity, epithelial repair, immune-cell activity, and intestinal fibrosis. Patients with IBD exhibit perturbations in lactate metabolism^[108], but the functional consequences of lactate appear to depend on its source, concentration, receptor engagement, cellular uptake, and disease stage.

At the epithelial surface, lactate may support mucosal protection and repair. Exogenous lactate has been reported to inhibit TNF- α -induced MMP-9 expression through GPR81 signaling, suppress NF- κ B activation, and prevent tight-junction disruption, thereby preserving intestinal epithelial barrier function^[40]. L-lactate can also promote intestinal epithelial cell migration by supporting

mitochondrial ATP production, contributing to wound closure and attenuation of colitis^[109]. These findings highlight a disease-specific protective role of lactate in IBD: appropriate lactate signaling and metabolism may strengthen epithelial restitution rather than simply aggravating inflammation.

The immune microenvironment of IBD provides another setting in which lactate metabolism and lactylation intersect. Gegen Qinlian decoction was reported to attenuate ulcerative colitis by regulating macrophage histone lactylation and reducing pro-inflammatory M1-like activation^[110]. In Crohn's disease, lactate metabolic disturbances have also been associated with lactylation-related hub genes whose expression correlates with immune-cell infiltration in intestinal tissues^[111]. These data suggest that lactylation may participate in shaping intestinal immune activity, although much of the current evidence is based on animal models, macrophage-centered experiments, or transcriptomic associations rather than site-specific lactylome mapping in human intestinal lesions.

A particularly important disease-specific consequence in IBD is intestinal fibrosis. Fibrosis can lead to bowel wall thickening, strictures, obstruction, and limited response to anti-inflammatory therapy, especially in Crohn's disease^[112]. In this setting, lactate accumulation has been linked to epithelial remodeling through histone lactylation. Downregulation of glucagon receptor and glucagon-like peptide-1 receptor signaling can increase lactate accumulation, and excess lactate induces H3K9la in intestinal epithelial cells, promoting EMT-like remodeling, extracellular matrix deposition, intestinal wall fibrosis, and stricture formation^[109].

Thus, in IBD, lactate may support epithelial restitution under controlled conditions, whereas persistent lactate accumulation and H3K9la-associated transcriptional remodeling may favor maladaptive fibrotic repair.

4.3 Osteoarthritis

Osteoarthritis (OA) is a whole-joint disease involving cartilage, synovium, subchondral bone, ligaments, and periarticular tissues rather than cartilage alone^[113]. In this setting, lactate accumulation within the joint cavity and lacylation-related regulation are most relevant to chondrocyte stress, cartilage matrix loss, synovial inflammation, and limited repair capacity.

In articular cartilage, lactate acts as both a metabolic signal and a contributor to chondrocyte injury. OA chondrocytes show metabolic alterations, including enhanced glycolysis, mitochondrial dysfunction, oxidative stress, and disturbed extracellular matrix metabolism^[114]. Lactate activates GPR81-dependent PI3K/Akt signaling and increases NOX4-mediated ROS production, thereby promoting chondrocyte damage^[115]. This represents a lactate receptor-mediated effect rather than a lacylation-dependent mechanism. In contrast, UDP-glucose dehydrogenase lacylation represents a non-histone lacylation event in chondrocytes. UGDH lacylation suppresses glycosaminoglycan synthesis and alters its nucleocytoplasmic distribution, leading to MAPK activation, extracellular matrix degradation, and OA progression^[116]. These findings distinguish lactate-driven chondrocyte stress from direct protein lacylation of a cartilage matrix-regulating enzyme.

Synovial tissue provides a second OA-specific compartment affected by lactate-related regulation. Fibroblast-like synoviocytes are active contributors to OA synovitis, inflammatory mediator production, and matrix-degrading enzyme release^[117]. In synovial tissue, lactate upregulates ARG2 through the mTOR/S6K1 pathway and induces senescence of fibroblast-like synoviocytes^[118]. Senescent synoviocytes can reinforce a chronic inflammatory and catabolic joint environment through a senescence-associated secretory phenotype. Bioinformatic analyses further indicate that lacylation-related gene expression correlates with immune-cell infiltration in OA joint tissues^[119], suggesting that lacylation may contribute to the inflammatory landscape of OA, although direct site-specific lacylation evidence in synovial cell subsets remains limited.

The reparative phase of OA differs from classical wound healing because articular cartilage has poor intrinsic regenerative capacity. Persistent lactate-associated metabolic stress may therefore hinder functional matrix restoration and contribute to chronic joint remodeling. Characteristic structural outcomes, such as subchondral sclerosis and osteophyte formation, reflect maladaptive whole-joint repair rather than effective tissue regeneration^[120]. At present, evidence for lactate- or lacylation-dependent regulation of OA repair remains less developed than evidence for chondrocyte injury and synovial inflammation. Future studies defining lactate transport, GPR81 signaling, and site-specific lacylation in chondrocytes, fibroblast-like synoviocytes, and subchondral bone cells may help clarify whether this axis can be therapeutically targeted to slow OA progression.

4.4 Periodontitis

Periodontitis is a chronic biofilm-associated inflammatory disease characterized by dysregulated host immune responses, periodontal connective tissue destruction, and alveolar bone loss^[121]. Unlike many systemic inflammatory conditions, periodontitis develops

within a highly specialized oral niche composed of gingival epithelium, periodontal ligament, cementum, alveolar bone, fibroblasts, immune infiltrates, and a dysbiotic subgingival biofilm. This tissue architecture makes periodontitis a useful disease context for examining how lactate metabolism and lacylation influence local barrier injury, osteoimmune regulation, periodontal regeneration, and bone resorption. Single-cell studies of human periodontitis tissues have revealed substantial heterogeneity among immune cells, epithelial cells, fibroblasts, osteoblast-lineage cells, and osteoclast-related populations, indicating that metabolic and epigenetic regulation in periodontal lesions is likely to be strongly cell-type specific^[122].

In periodontal lesions, dysbiotic microbial stimulation and epithelial barrier disruption promote local metabolic remodeling. Increased lactate content and elevated lysine lacylation levels have been observed in periodontitis tissues, suggesting that lactate accumulation and protein lacylation coexist in the periodontal inflammatory microenvironment^[123]. Lactate may act on periodontal cells through several mechanistically distinct routes. As an extracellular signal, it may activate G protein-dependent pathways; as a transported metabolite, it may enter cells through monocarboxylate transporters and alter intracellular metabolism; and as a substrate source, it may support histone or non-histone lacylation. In human periodontal ligament stem cells (hPDLSCs), high lactate suppresses alkaline phosphatase activity and osteogenic protein expression through Gα-dependent signaling and inhibits mineralized nodule formation through the MCT1-mTOR-autophagy pathway^[124]. These findings link lactate accumulation to impaired osteogenic potential of periodontal progenitor cells, a process directly relevant to periodontal regeneration.

The immune component of periodontitis further connects lactate-related metabolism to local tissue destruction. Neutrophil extracellular traps (NETs) have been identified as early drivers of pathogenic IL-17/Th17 inflammation and inflammatory bone destruction in periodontitis^[125]. Although NET-associated lacylation has been described in other inflammatory settings, direct evidence for NET-related lacylation events in periodontal tissues remains limited. In macrophages, lacylation may influence the inflammatory balance within periodontal lesions. In a rat periodontitis model, both lactate content and global lacylation levels increased in periodontal tissues; inhibition of the lacylation writer p300 in RAW264.7 macrophages reduced lacylation but increased IL-1β, IL-6, TNF-α, CD86, and iNOS, while decreasing Arg1 and CD206^[123]. These observations suggest that macrophage lacylation may restrain excessive M1-like activation and support immune balancing in experimental periodontitis. However, most available evidence is still derived from animal tissues, macrophage cell models, or lacylation-related transcriptomic signatures rather than cell-resolved lacylome mapping in human periodontal lesions^[126].

Alveolar bone loss is the defining hard-tissue consequence of periodontitis. Osteoimmune studies have established that inflammatory RANKL production and RANKL/OPG imbalance drive osteoclast differentiation and periodontal bone resorption^[127]. Recent single-cell analyses further suggest that periodontal ligament fibroblasts and other stromal populations contribute to osteoclastogenic signaling, including inflammatory factors and RANKL expression, thereby linking soft-tissue inflammation to bone destruction^[128]. At present, the connection between lactate/ lacylation and this osteoclastogenic axis remains largely indirect.

Lactate accumulation may influence the osteoimmune environment by altering macrophage activation, fibroblast behavior, and hPDLSC osteogenic capacity, but direct evidence showing site-specific lactylation in osteoclasts, osteoblast-lineage cells, or periodontal ligament fibroblast subsets during alveolar bone resorption is still scarce.

The regenerative side of periodontal disease also appears to be influenced by lactate-related mechanisms. Periodontal repair requires coordinated activity of hPDLSCs, gingival and periodontal ligament fibroblasts, endothelial cells, immune cells, and bone-forming cells. Gingival fibroblasts and periodontal ligament fibroblasts maintain extracellular matrix homeostasis, but inflammatory stimulation can shift these cells toward matrix degradation and inflammatory amplification^[129]. Sustained lactate exposure may compromise hPDLSC osteogenic differentiation through MCT1-mTOR-dependent inhibition of autophagy^[124]. In contrast, selected lactylation events may support osteogenic programs. Restoration of lysine lactylation by proanthocyanidins rescues LPS-inhibited osteogenesis of PDLSCs by activating the Wnt/ β -catenin pathway and increasing RUNX2 expression^[130]. RUNX2 lactylation has also been reported to stabilize RUNX2 and promote osteogenic differentiation of hPDLSCs^[131]. These findings indicate that lactate accumulation and target-specific lactylation may have different consequences in periodontal regeneration: excessive extracellular or intracellular lactate may impair progenitor-cell osteogenesis, whereas non-histone lactylation of osteogenic regulators such as RUNX2 may help maintain osteogenic transcriptional programs under selected conditions.

Overall, periodontitis highlights the need to interpret the lactate-lactylation axis within a tissue-specific oral framework. Existing data support associations among lactate accumulation, global lactylation, macrophage polarization, hPDLSC osteogenesis, and periodontal inflammatory activity, but several key questions remain unresolved. The spatial distribution of lactate and K_{la} across gingival epithelium, periodontal ligament, immune infiltrates, and the alveolar bone interface has not been systematically mapped. The relative contribution of GPR81-mediated signaling, MCT-dependent metabolic effects, histone lactylation, and non-histone lactylation remains unclear in human periodontal tissues. Future studies combining spatial metabolomics, single-cell or spatial transcriptomics, and site-specific lactylome profiling may clarify whether targeting lactate transport, lactate signaling, or specific lactylation events can improve periodontal regeneration and limit inflammatory alveolar bone loss.

Lactate regulates local cells through GPR81-mediated signaling, MCT1-dependent transport, and protein lactylation. In macrophages, lactylation may restrain pro-inflammatory polarization and support immune balance, whereas neutrophil-associated IL-17/Th17 responses contribute to inflammatory bone destruction. In hPDLSCs, excessive lactate impairs osteogenesis through the MCT1-mTOR-autophagy pathway, while RUNX2 lactylation stabilizes RUNX2 and promotes osteogenic differentiation. Lactate-related mechanisms also influence fibroblast-mediated matrix degradation and the RANKL/OPG osteoimmune axis, thereby linking metabolic remodeling to periodontal inflammation, impaired regeneration, and alveolar bone resorption.

5 Conclusions and perspectives

Research on lactate and lactate-driven lactylation in inflammatory

diseases is rapidly expanding. Current evidence indicates that lactate is not merely a metabolic product but also a signaling molecule capable of influencing immune-cell activation, differentiation, and functional states throughout inflammation. In parallel, lactylation—recently described as a post-translational modification—is emerging as a potentially important regulatory layer, particularly in controlling expression of inflammation-related genes and in shaping immunometabolic reprogramming.

Nevertheless, lactylation research remains relatively limited, and functional heterogeneity across cell types and disease models has not been fully delineated. Future studies may prioritize the following directions:

(1) Next-generation mass spectrometry and lactylation-specific antibodies can enable proteome-wide identification of lactylation sites and may support spatiotemporal tracking in cells or tissues. For example, combining mass spectrometry with anti-lactylation antibodies could map tissue- or immune-cell-specific “lactylomes” and delineate temporal dynamics across disease states.

(2) Conventional proteomics has limited capacity to capture lactylation features across distinct cell subsets within the immune microenvironment. Single-cell proteomics could enable comparisons of protein lactylation across cell subtypes (e.g., T-cell subsets), clarify how lactylation regulates immune polarization through epigenetic programs and metabolic enzymes, and track lactylation kinetics during macrophage transitions from M1 to M2. When integrated with pseudotime analysis, these approaches may help interrogate links between lactylation and functional phenotypes. Methodological advances in modified-peptide enrichment efficiency and computational pipelines will be required and may reveal actionable targets for precision immunometabolic interventions.

(3) Lactylation studies have largely relied on mass spectrometry or Western blotting and often provide limited information on tissue spatial organization and cellular heterogeneity. Multiplex imaging technologies can quantify dozens to hundreds of proteins, metabolites, or epigenetic markers in a single tissue section while preserving spatial context, thereby enabling assessment of lactylation patterns and functional impacts within heterogeneous tissues.

(4) Nanobodies, owing to their small size, strong tissue penetration, and high epitope-binding performance, may serve as tools to interrogate dynamic lactylation regulation. Developing lactylation-specific nanobodies with high affinity could help overcome detection limitations for low-abundance lactylation, and engineering strategies may enhance specificity under pathological conditions, creating opportunities for drug development in immunometabolism.

Blood lactate remains the most readily implementable metabolic indicator in clinical practice, yet its ability to discriminate among diseases is limited. A more promising next step is to develop a panel of lactylation-related biomarkers. First, site-specific histone lysine lactylation can be quantitatively measured in peripheral blood immune cells as an objective pharmacodynamic readout to evaluate whether an intervention is exerting its intended effect. Second, a lactylome map can be established using mass spectrometry and integrated with transcriptomic data and inflammatory phenotypes to identify candidate biomarkers that are more closely linked to barrier dysfunction, immunosuppression, or fibrosis. Together, these approaches may provide information that more directly reflects organ-injury processes in systemic inflammation, thereby

supporting efficacy prediction and assessment of relapse risk.

Abbreviations

Arg1	arginase 1
ATP	adenosine triphosphate
CBP	CREB-binding protein
CCL2/7	C-C motif chemokine ligands 2 and 7
CD	cluster of differentiation
CoA	coenzyme A
CXCL1/2	C-X-C motif chemokine ligands 1 and 2
ECM	extracellular matrix
EMT	epithelial-to-mesenchymal transition
GLUT1	glucose transporter 1
GPR81	G protein-coupled receptor 81
HIF-1 α	hypoxia-inducible factor 1 alpha
HK2	hexokinase 2
hPDLSCs	human periodontal ligament stem cells
IL	interleukin
iNOS	inducible nitric oxide synthase
LA	lactyl group
LDH	lactate dehydrogenase
MAPK	mitogen-activated protein kinase
MCT	monocarboxylate transporter
MCT1/4	monocarboxylate transporter 1 and 4
mTOR	mechanistic target of rapamycin
NAD ⁺ /NADH	oxidized/reduced nicotinamide adenine dinucleotide
NETs	neutrophil extracellular traps
NF- κ B	nuclear factor kappa B
OPG	osteoprotegerin
p300	E1A-binding protein p300
PFKFB3	6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3
PI3K	phosphoinositide 3-kinase
RANKL	receptor activator of nuclear factor kappa B ligand
RUNX2	runt-related transcription factor 2
TCA	tricarboxylic acid
Th17	T helper 17
TNF- α	tumor necrosis factor alpha

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Data available statement

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Author contributions

H.X., F.F. and Q.W. formulated the topic. H.X. and Z.Y. drafted the manuscript. F.F., Q.W. and G.R. supervised the manuscript and critically revised the manuscript. All authors gave final approval and

agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

Ethics approval and consent

N/A

Consent for publication

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Conflicts of interest

The authors declare no conflict of interest.

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