Lactylation in the regulation of macrophage polarization: Mechanisms pathophysiological significance (Review)

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Received June 3, 2026; Accepted September 9, 2026

DOI: 10.3892/mmr.2026.14063

Abstract. Macrophage polarization is regulated by metabolic reprogramming epigenetic modifications. The discovery of histone lysine lactylation has revealed that lactate is not merely a glycolytic end product but also an important metabolic signal linking cellular metabolic status to gene expression programs. Lactylation modulates both histones (such as H3K18la) non-histone proteins (such as nuclear factor-κB p65 hypoxia-inducible factor-1α), thereby influencing macrophage polarization through transcriptional regulation signal transduction. Its functions are highly context-dependent. In the tumor microenvironment, it predominantly promotes M2-type immunosuppression; in certain neuroinflammatory conditions, it may be associated with M1-like phenotypes; in metabolic diseases, it may exacerbate pro-inflammatory damage. This modification involves extensive crosstalk with acetylation, methylation, other epigenetic modifications, constituting a complex regulatory network. However, current research faces critical bottlenecks: The intracellular source metabolic flux of lactyl-CoA remain unclear; the substrate specificity physiological relevance of candidate writers, such as E1A-binding protein p300 CREB-binding protein, erasers, such as sirtuin 2, remain controversial; a bona fide reader domain that specifically recognizes lactylated lysine has not been identified; *in vivo* causal evidence remains limited. Future efforts should integrate multiomics technologies, genetic manipulation tools, precision delivery systems to decipher the spatiotemporal regulatory networks of lactylation, thereby facilitating the identification of new therapeutic targets strategies for inflammatory, neoplastic, metabolic diseases.

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Abbreviations: AD, Alzheimer's disease; CBP, CREB-binding protein; FAO, fatty acid oxidation; HATs, histone acetyltransferases; KMTs, histone lysine methyltransferases; KDMs, Histone lysine demethylases; LSD1, lysine-specific demethylase 1; METTL14, methyltransferase-like 14; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NLRP3, NLR family pyrin domain-containing 3; OXPHOS, oxidative phosphorylation; PDGF, platelet-derived growth factor; PDHA1, pyruvate dehydrogenase alpha 1; PDK1, 3-phosphoinositide-dependent protein kinase 1; PFK, phosphofructokinase; PKM2, pyruvate kinase M2; PPARγ, peroxisome proliferator-activated receptor-gamma; PRKN, parkin RBR E3 ubiquitin protein ligase; ROS, reactive oxygen species; SAKI, septic acute kidney injury; SLIT2, slit guidance ligand 2; TAMs, Tumor-associated macrophages

Key words: lactylation modification, macrophage, polarization, metabolic reprogramming, epigenetic

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1. Introduction

Macrophages are key effector cells for host defense, tissue repair and maintenance of homeostasis and are widely

distributed across various tissues and organs. Their high phenotypic plasticity and functional diversity enable them to sensitively perceive changes in microenvironmental signals and mount adaptive responses, executing diverse biological functions ranging from pathogen clearance to matrix remodeling. Traditionally, based on *in vitro* stimulation models, macrophages have been classified into two extreme phenotypes: Classically activated (M1) and alternatively activated (M2), corresponding to pro-inflammatory bactericidal and anti-inflammatory reparative functions, respectively (1). However, with the development of single-cell sequencing and spatial transcriptomics technologies, current research has fully revealed that macrophages actually exist within a continuous, dynamic, and highly heterogeneous phenotypic spectrum. Their polarization is not a simple binary switch but is subject to integrated regulation by cytokine signaling pathways (such as nuclear factor-κB (NF-κB) and STAT1/6), metabolic reprogramming (dynamic switching between glycolysis and oxidative phosphorylation), transcription factor networks [such as IRF4/5, hypoxia-inducible factor-1α (HIF-1α), and PPARγ] and tissue-specific microenvironmental signals (2). Imbalances in this multidimensional regulatory network are closely associated with the development and progression of various major human diseases including chronic inflammation, fibrosis, tumor progression and metabolic disorders. Therefore, an in-depth elucidation of the molecular regulatory mechanisms governing macrophage polarization is of great significance for understanding disease pathology and developing novel therapeutic strategies.

In this process, the function of metabolites as signaling molecules has been widely recognized: Tricarboxylic acid (TCA) cycle intermediates such as succinate and itaconate can regulate inflammatory responses by stabilizing HIF-1α or modifying KEAP1 (3,4). However, lactate has long been regarded as glycolytic 'metabolic waste'. Zhang *et al* (5) discovered that lactate could suppress innate immune signaling by directly binding to the MAVS protein and Zhang *et al* (6) first reported the existence of histone lysine lactylation (Kla) as a novel epigenetic modification. The latter revealed that lactate could directly regulate gene expression through covalent modification of histone lysine residues, tightly coupling the cellular metabolic status with the epigenetic landscape. Compared with other acylations (such as acetylation, succinylation and crotonylation), lactylation is linked to a substrate, lactate, which is generated at the terminal stage of glycolysis. Its donor lactyl-CoA is highly dependent on cellular glycolytic flux and lactate concentration, enabling lactylation to more directly and sensitively reflect intracellular metabolic fluctuations and serve as a 'metabolic sensor' connecting metabolic status gene expression (6).

In macrophages, lactylation participates in the regulation of polarization through dual mechanisms. Histone lactylation (such as H3K18la) regulates transcriptional activation or repression of M1/M2-related genes by remodeling chromatin accessibility conformation. Meanwhile, non-histone lactylation [such as NF-κB p65, HIF-1α and pyruvate kinase M2 (PKM2)] rapidly modulates the intensity and duration of inflammatory signals and the direction of metabolic flux by directly affecting the activity, stability, subcellular localization, or protein-protein interactions of signal transduction proteins (5,6). This 'transcriptional-signal transduction' synergistic regulatory mode distinguishes lactylation from modifications such as histone acetylation that regulate gene expression through changes in chromatin states, providing a more direct, efficient and spatiotemporally specific molecular foundation for the metabolic regulation of macrophage functional plasticity. Subsequent studies demonstrated that lactylation plays a critical role in various pathophysiological processes, including aberrant macrophage polarization in the tumor microenvironment, inflammatory disease progression, tissue injury repair, immunometabolic disorders (2,3,5-7).

The present review systematically explored the mechanisms pathophysiological significance of lactylation in the regulation of macrophage polarization. The present review first outlined the basic concepts of macrophage polarization and its metabolic foundation and then details the discovery, chemical nature, regulatory mechanisms (writers, erasers and readers) of lactylation and its major targets in macrophages. It next analyzed the molecular mechanisms by which lactylation regulates macrophage polarization through histone non-histone pathways, with particular emphasis on its crosstalk with acetylation, methylation and other modifications, discussed the differential roles of this regulatory network across various pathological conditions, including inflammation, tumors, metabolic diseases, neurodegenerative disorders and infectious diseases. Finally, the present review summarized current research limitations, focusing on critical bottlenecks including causal relationship establishment, substrate source elucidation, regulatory enzyme identification, synergistic network delineation and clinical translation feasibility, while proposing future research directions. By comprehensively surveying research advances in this emerging field, the present review aimed to provide a new theoretical framework for understanding the functional regulation of macrophages and offer references for the development of therapeutic strategies for related diseases.

2. Basic concepts and metabolic regulation of macrophage polarization

Phenotypic diversity and functional characteristics of macrophage polarization. Macrophages are innate immune cells that originate from bone marrow hematopoietic stem cells and colonize various tissues during embryonic development to form tissue-resident macrophages or differentiate from blood monocytes. Macrophages possess high plasticity and heterogeneity, enabling them to adjust their phenotype and function in response to changes in microenvironmental signals, a process termed macrophage polarization (1). Traditionally, for convenience, macrophage polarization has been simplified into two major phenotypes: Classically activated (M1) and alternatively activated (M2) (2). These two polarized phenotypes not only differ markedly in function but also exhibit distinct transcriptional regulatory networks and metabolic reprogramming features, together forming the foundation of macrophage functional diversity. To illustrate this complex process, Fig. 1 systematically depicts the metabolic pathway characteristics, key regulatory factors, and functional outputs of M1 and M2 macrophages.

M1 macrophages are typically induced by pro-inflammatory stimuli such as lipopolysaccharide (LPS), interferon-γ

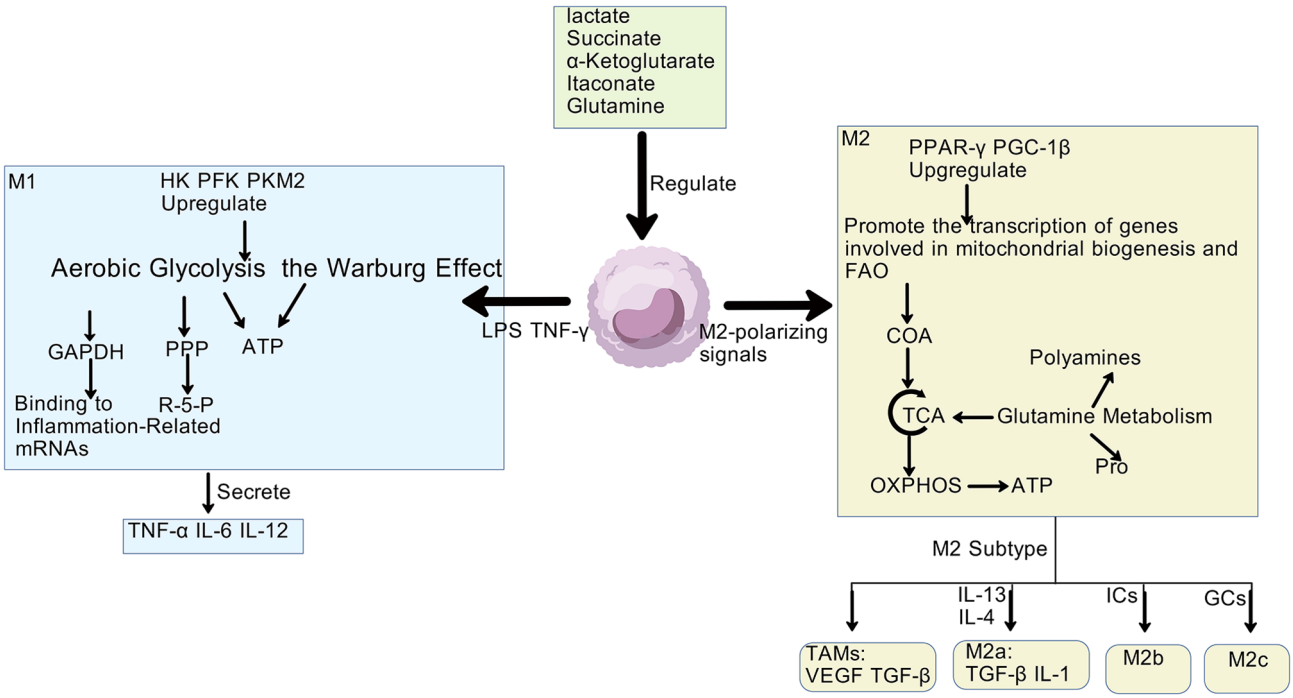


Figure 1. Metabolic reprogramming and functional outputs of M1 and M2 macrophages. Schematic illustration of the distinct metabolic pathways and functional characteristics of classically activated (M1) and alternatively activated (M2) macrophages. M1 macrophages rely heavily on aerobic glycolysis (the Warburg effect) and the PPP, producing high levels of lactate and pro-inflammatory cytokines *(TNF-α, IL-6, IL-12)*. By contrast, M2 macrophages exhibit enhanced FAO and an intact TCA cycle, supporting anti-inflammatory functions and tissue repair. The accumulation of metabolic intermediates, such as lactate, acts as a critical link between metabolic status and epigenetic regulation, driving the divergent M2 subtypes (TAMs, M2a, M2b, M2c) in different pathological contexts. The figures were created with BioGDP (biogdp.com). PPP, pentose phosphate pathway; FAO, fatty acid oxidation; TCA, tricarboxylic acid. HK, hexokinase; PFK, phosphofructokinase; PKM2, pyruvate kinase M2; R-5-P, ribose-5-phosphate; LPS, lipopolysaccharide; TNF, tumor necrosis factor; PGC-1β, peroxisome proliferator-activated receptor gamma coactivator 1-beta; OXPHOS, oxidative phosphorylation; IC, immune complexes; GCs, glucocorticoids; TAMs, tumor-associated macrophages; VEGF, vascular endothelial growth factor; TGF-β, transforming growth factor-beta; IL-1, interleukin-1.

(IFN-γ), or tumor necrosis factor-α (TNF-α) (as shown on the left side of Fig. 1). Their transcriptional program is dominated by transcription factors including NF-κB, STAT1 and IRF5, with high expression of pro-inflammatory cytokines such as TNF-α, interleukin (IL)-6, IL-1β and IL-12, as well as inducible nitric oxide synthase and reactive oxygen species (ROS)-producing enzymes, conferring potent antibacterial, antiviral and antitumor activities (8). M1 macrophages play critical roles in early acute infections and antitumor immune responses; however, their sustained activation can lead to tissue damage and chronic inflammation. Conversely, M2 macrophages are primarily induced by Th2-type cytokines such as IL-4 and IL-13 or immunoregulatory factors including IL-10, transforming growth factor (TGF)-β, and glucocorticoids (as shown on the right side of Fig. 1). Their transcriptional program is regulated by STAT6, PPARγ, KLF4 and IRF4, with high expression of markers including arginase-1 (ARG1), CD206, CD163, IL-10 and TGF-β, participating in anti-inflammatory responses, tissue repair, angiogenesis, matrix remodeling and parasite clearance (8). M2 macrophages play important roles in wound healing, late-stage fibrosis and tumor-associated immunosuppression.

Moreover, the M1/M2 dichotomy is merely a simplified *in vitro* model; *in vivo*, macrophages actually exhibit more complex mixed phenotypes and dynamic transitional states. For example, in atherosclerotic plaques, obese adipose tissue, or the tumor microenvironment, macrophages often simultaneously express both M1 and M2 markers, or display unique disease-specific phenotypes (such as *TREM2*+ lipid-associated macrophages, *CXCL10*+ interferon-responsive macrophages). This phenotypic diversity forms the basis for macrophages to adapt to complex microenvironments and execute refined functional regulation, underpinned by profound metabolic reprogramming and epigenetic remodeling.

Metabolic reprogramming in macrophage polarization. Macrophage polarization is closely linked to profound metabolic reprogramming, which supports and drives the acquisition of different functional phenotypes; the two processes are closely interconnected and can form positive feedback loops. M1 macrophages rely primarily on aerobic glycolysis (the Warburg effect) to rapidly generate ATP and support biosynthesis, even in the presence of sufficient oxygen. Their metabolic features include increased glucose uptake (upregulation of *GLUT1* expression), elevated lactate production and interruption of the TCA cycle at two critical nodes: First, inhibition of isocitrate dehydrogenase activity leads to citrate accumulation and its transport to the cytosol for fatty acid synthesis; second, altered succinate dehydrogenase activity results in succinate accumulation. This glycolytic switch is essential for the rapid production of pro-inflammatory cytokines and antimicrobial effector molecules, as glycolytic intermediates can serve as biosynthetic precursors and rapid ATP generation can occur independently of the mitochondrial respiratory chain (9,10). Expression levels of key glycolytic enzymes including hexokinase 2, phosphofructokinase-1 and

PKM2 are upregulated in M1 macrophages. In M1 macrophages, PKM2 predominantly exists as a low-activity dimer, leading to accumulation of upstream glycolytic intermediates; simultaneously, a fraction of PKM2 translocates to the nucleus, where it functions as a transcriptional coactivator and interacts with HIF-1α to promote IL-1β and other inflammatory gene transcription, thereby directly coupling metabolic status with inflammatory gene expression (11,12).

By contrast, M2 macrophages are characterized by enhanced fatty acid oxidation (FAO) and intact oxidative phosphorylation (OXPHOS), supporting the sustained energy supply required for their long-term tissue repair and homeostatic maintenance functions. In M2 macrophages, the TCA cycle runs intact and glutamine metabolism is enhanced, providing carbon sources for the cycle. The metabolic switch from glycolysis to OXPHOS is coordinated by AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor γ (PPARγ), which promote mitochondrial biogenesis, FAO-related gene expression and oxidative metabolic enzyme activities (13,14). Furthermore, M2 macrophages exhibit elevated glutaminolysis and aspartate-arginine cycle activity to support polyamine synthesis and collagen production, meeting tissue repair demands.

The metabolic differences between M1 and M2 macrophages are not merely concomitant phenomena of polarization but actively participate in and reinforce the phenotypic state as core driving forces. For example, the accumulation of certain TCA cycle intermediates in M1 macrophages has clear signaling functions: Succinate accumulation inhibits prolyl hydroxylase (PHD) activity, thereby stabilizing HIF-1α, which further promotes glycolytic gene and *IL-1β* expression; itaconate accumulation inhibits *SDH* activity and alkylates KEAP1 to release Nrf2, while also inhibiting histone demethylases to regulate inflammatory gene expression through epigenetic mechanisms (3). Similarly, increased lactate production in M1 macrophages is not merely a glycolytic byproduct but functions as a signaling molecule that can influence macrophage itself and neighboring cell functions through autocrine and paracrine mechanisms; a theme explored in subsequent sections. This intricate interplay between metabolism and function emphasizes a core concept: metabolic reprogramming is an intrinsic driving factor and functional execution foundation for macrophage polarization, not merely an energy supply adaptation.

Integration of metabolism and epigenetic regulation. The convergence of metabolic and epigenetic pathways is an important area of research in macrophage biology. Metabolic intermediates serve as essential substrates, cofactors, or inhibitors of epigenetic enzymes, thereby directly coupling cellular metabolic status with the regulation of gene expression programs, forming what is termed the 'metabolic-epigenetic axis'. Key examples include acetyl-CoA, which serves as a substrate for histone acetyltransferases (HATs) and fluctuates with glucose, fatty acid and amino acid metabolic states, thereby directly affecting histone acetylation levels and gene transcriptional activity; S-adenosylmethionine, which serves as a methyl donor for histone and DNA methyltransferases, with one-carbon metabolic flux determining global methylation levels; α-ketoglutarate, which serves as an essential cofactor for Jumonji domain-containing histone demethylases (KDMs) and TET DNA demethylases, with its ratio to succinate/2-HG influencing demethylase activity; and the recently identified lactyl-CoA, which serves as the donor for histone and non-histone lactylation and directly couples glycolytic flux with protein modification (3,15). The availability of these metabolites fluctuates dynamically with changes in nutrient supply, oxygen tension, inflammatory signals and cellular activation states. This enables macrophages to rapidly, precisely and reversibly regulate their transcriptional output according to microenvironmental demands, thereby optimizing the coordination between metabolic status and immune function.

Among these metabolic-epigenetic intersections, lactylation is associated with glycolysis; the major metabolic pathway in activated M1 macrophages. The discovery that lactate can directly influence gene expression through epigenetic remodeling has fundamentally transformed our understanding of lactate biology, converting it from a metabolic waste into a key signaling molecule at the interface of metabolism and gene regulation.

3. Biological basis of lactylation

Discovery and chemical nature of lactylation. Lactylation refers to the covalent attachment of a lactyl group ($CH_3CH(OH)CO$-) to the ε-amino group of protein lysine residues via amide bond formation and represents a type of post-translational modification. This modification was first reported in 2019 Zhang *et al* (6). Using high-resolution mass spectrometry and pan-lactylation antibodies, the aforementioned study identified Kla in bacteria-infected macrophages and found that this modification was markedly enriched in the promoter regions of anti-inflammatory and repair-related genes during the late stage of infection, suggesting its involvement in the temporal transition of macrophages from a pro-inflammatory to a reparative state. This landmark discovery challenged the long-held view that lactate is merely a glycolytic waste product, revealing an entirely new paradigm in which lactate acts as a signaling molecule that regulates gene expression and cellular functions through protein modification (6).

Chemically, lysine lactylation occurs via the transfer of a lactyl group from lactyl-CoA to lysine residues by acyltransferases. However, studies have also revealed that some lactylation events can occur through non-enzymatic pathways. For instance, the glyoxalase II substrate SLG can directly mediate D-lactylation of lysine, suggesting that the mechanisms of lactylation may be more diverse than previously recognized (16). Moreover, the lactyl group differs from the acetyl group in that it contains a chiral hydroxyl group (-OH), which affects its steric hindrance, hydrogen-bonding capacity and charge distribution relative to other acyl groups (12). This structural difference may enable lactylation to be recognized by specific reader proteins or influence higher-order chromatin structures. Furthermore, the stoichiometry and kinetic features of lactylation may differ from those of other acylations. As lactate is a glycolytic end product, its intracellular concentration can fluctuate markedly within minutes in response to metabolic status (from millimolar to tens of millimolar levels), potentially enabling lactylation to respond rapidly to changes in metabolic status under specific physiological and

pathological conditions and to serve as a 'real-time metabolic sensor' linking cellular metabolism and gene expression (12). By contrast, acetyl-CoA concentrations are relatively stable, and acetylation may reflect the long-term nutritional status rather than transient changes in metabolism.

The discovery of lactylation has benefited from advances in proteomics technologies, particularly high-resolution mass spectrometry, specific pan-lactylation antibodies and site-specific antibodies (6). Initial studies identified lactylation at 28 histone lysine sites in macrophages via mass spectrometry and found that these modifications increased in a time-dependent manner following bacterial infection, peaking at the late stage of infection (6). Subsequent studies have further identified widespread lactylation on non-histone proteins, indicating that this is a ubiquitous protein post-translational modification whose functions extend far beyond chromatin regulation (11,13). For example, lactylation has been identified on glycolytic enzymes including *PKM2*, phosphoglycerate kinase 1 (*PGK1*), and aldolase A *(ALDOA)* in tumor cells and these modifications can regulate enzymatic activity, subcellular localization and protein stability, thereby feedback-regulating glycolytic flux (11,13). In macrophages, in addition to histones, lactylation has been identified on various key signaling molecules and transcription factors including nuclear factor κB (NF-κB p65), signal transducer and activator of transcription 6 (STAT6), hypoxia-inducible factor-1α (HIF-1α) and NLR family pyrin domain-containing 3 (NLRP3) inflammasome components (12,14). These modifications directly affect DNA-binding capacity, transcriptional activity, protein stability, or complex assembly, thereby participating in macrophage polarization, inflammatory responses and metabolic regulation. Among these, NF-κB p65 K310 lactylation has attracted particular attention due to its important role in inflammatory negative feedback regulation, and its specific mechanisms will be detailed in *Effects of non-histone lactylation on macrophage signal transduction*.

Regulatory mechanisms of lactylation: Writers, erasers and readers. Similar to other post-translational modifications, the dynamic balance of lactylation is regulated by three functional classes of enzymes or protein complexes: 'writers' (lactyltransferases), 'erasers' (delactylases) and 'readers' (recognition proteins) (13,14). However, compared with the more extensively studied acetylation, the identification and functional characterization of lactylation regulatory factors remain at an early stage. A number of key regulatory factors have yet to be definitively identified or validated, which represents a core bottleneck constraining the development of the field.

Regarding lactylation 'writers', one of the most critical unresolved questions is the intracellular source and metabolic flux of lactyl-CoA. Unlike acetyl-CoA, which can be generated from glycolytic pyruvate and through FAO, amino acid catabolism and ketone body metabolism, the biosynthetic pathway for lactyl-CoA remains unclear. Theoretically, it can be generated from lactate by acyl-CoA synthetase family members, indirectly produced through the methylglyoxal pathway, or even generated through the direct reduction of pyruvate. However, no study has directly quantified the physiological concentration of lactyl-CoA in mammalian cells nor has a definitive, specific lactyl-CoA synthetase been identified (3). This fundamental knowledge gap directly limits a reliable assessment of the physiological relevance of candidate 'writers' such as E1A-binding protein p300 (p300) and CREB-binding protein (CBP), because if substrate concentrations are low, even if enzymes possess *in vitro* activity, they may lack physiological significance *in vivo*. Current research primarily focuses on whether HATs exhibit histone lactyltransferase (HLT) activity. Early studies reported that classic HATs, such as p300/CBP, could catalyze K1a *in vitro*, with the catalytic efficiency dependent on lactate or lactyl-CoA concentrations (3,17). However, the *in vitro* catalytic efficiency of p300/CBP for lactylation is far lower than that for acetylation (10- to 50-fold lower, depending on the substrate and reaction conditions) and physiological intracellular lactyl-CoA concentrations may be far lower than those of acetyl-CoA. Therefore, whether p300/CBP assumes a major lactyltransferase function under physiological conditions or functions only under extremely high lactate concentrations (such as in the tumor microenvironment) remains to be confirmed (3,12). Recent studies have shown that alanyl-tRNA synthetase 1 (AARS1) possesses lactyltransferase activity and catalyzes p53 lactylation, suggesting the possible existence of dedicated non-HAT lactyltransferases (3). However, this finding requires independent validation and the substrate specificity and physiological relevance of AARS1-mediated lactylation in macrophages remain unexplored. A recent study reported that in macrophages, the B cell PI3K adaptor protein could promote p300 lactylation, enhancing its HAT/HLT activity and thereby increasing overall histone lactylation levels (18). However, in hippocampal microglia from type 2 diabetes mellitus mice, although CBP and p300 protein levels were markedly elevated, inhibition of p300 with specific inhibitors left lactylation levels essentially unchanged, suggesting that p300 may not be a critical regulator of lactylation in this context (18,19). These apparently divergent findings highlight the complexity of lactylation regulation, suggesting that cells may employ context-dependent and substrate-specific mechanisms to control lactylation levels of different substrates, rather than relying on a single 'writer'. Future studies should prioritize the identification of bona fide and specific lactyltransferases using chemical proteomics, activity-based probe screening, and genetic approaches.

For lactylation 'erasers', initial studies found that members of the histone deacetylase family, such as SIRT1, SIRT2 and SIRT3 (class III HDACs or sirtuins), possess delactylase activity (20). Among these, SIRT2 was found to specifically remove lactylation at histone H4K8, regulating macrophage chemotactic function; and in acute kidney injury, SIRT3 downregulation mediates excessive acetylation and inactivation of pyruvate dehydrogenase E1α subunit (PDHA1), leading to excessive lactate production and exacerbation of disease progression, suggesting that erasers may influence lactylation levels through indirect regulation of metabolic flux (19,21). In addition, class IIa HDACs such as HDAC4 and HDAC5 have also been reported to participate in the removal of non-histone lactylation (19). Glyoxalase 2 *(GLO2)* knockout leads to accumulation of its substrate L-glutathionylglyoxal, which in turn drives increased histone lactylation through non-enzymatic mechanisms and enhances macrophage inflammatory signaling,

Table I. Summary of molecular mechanisms underlying lactylation-mediated macrophage polarization.

Category	Key regulatory proteins	Lactylation substrates	Core molecular function	Macrophage polarization outcome	(Refs.)
Lactylation writers (catalytic enzymes)	p300/CBP, BCAP	H3K18, NF-κB p65, HIF-1α	Catalyze lysine lactylation on histones and transcription factors; remodel chromatin and transcription programs	Suppress M1 pro-inflammatory polarization; Promote M2/TAMs polarization	(6,10,12, 17,18)
Lactylation erasers (demodification enzymes)	SIRT1/2, HDAC4/5	Global lactylated lysine residues	Erase lactylation marks reversibly; maintain dynamic balance of cellular lactylation level	Reverse M2 polarization; Restore M1 inflammatory response	(19-21,42)
Lactylation Readers (recognition proteins)	PU.1, PPARγ	Lactylated H3K18 (H3K18la)	Specifically bind H3K18la; activate M2-related transcriptional programs	Dominantly drive M2/TAMs polarization; inhibit M1 cytokine secretion	(18,21,23)

BCAP, B cell PI3K adaptor protein; CBP, CREB-binding protein; HDAC, histone deacetylase; HIF-1α, hypoxia-inducible factor-1α; NF-κB, nuclear factor-κB; PPARγ, peroxisome proliferator-activated receptor γ; PU.1, purine-rich box 1; SIRT, sirtuin; TAMs, tumor-associated macrophages; H3K18la, histone H3 lysine 18 lactylation.

suggesting that delactylase regulation is not limited to direct de-modification but may also indirectly affect lactylation levels through the availability of metabolic substrates (22). A key question that has not been systematically addressed is the substrate preference of these enzymes between lactylation and acetylation. Most current evidence comes from overexpression systems or *in vitro* substrate screening and quantitative kinetic parameters (such as K_m, k_cat) for endogenous lactylation substrates are largely missing. Whether SIRT2's specific removal of H4K8la reflects the enzyme's intrinsic substrate preference or is determined by local chromatin environment, auxiliary factors, or substrate accessibility remains unclear. Furthermore, whether SIRT3 downregulation-induced PDHA1 hyperacetylation indirectly affects lactylation dynamics and the physiological relevance of class IIa HDACs in non-histone delactylation, require further investigation. These findings suggest that lactylation and acetylation may share some 'erasers', implying that cells may coordinate the dynamic balance between different acylations by regulating the activity, subcellular localization, or substrate specificity of these enzymes. However, whether dedicated 'erasers' exist that specifically remove lactylation without affecting acetylation remains an unresolved question and a prerequisite for developing specific intervention tools.

Regarding lactylation 'readers', current research is relatively limited and controversial. The known readers of acetylation are primarily bromodomain-containing proteins (such as BRD4), which can specifically recognize acetylated lysine (12). However, whether lactylated lysine is recognized by these bromodomain proteins, or whether dedicated structural domains exist for specific recognition of lactylation, remains unclear. In macrophages, lactylated histone H3K18 is recognized by the transcription factor PU.1, promoting M2-related gene expression (18,21). In addition, in tumor-associated macrophages, lactylated histone H3K18 can recruit the nuclear receptor PPARγ, further enhancing M2-type gene transcription (18,23). Notably, although PU.1 and PPARγ have been observed to preferentially bind to lactylation-enriched chromatin regions, defining them as 'lactylation readers' requires considerable caution. To date, no study has demonstrated through direct *in vitro* binding assays (such as surface plasmon resonance SPR, isothermal titration calorimetry ITC, or fluorescence polarization) that a particular domain of PU.1 or PPARγ can directly and specifically recognize lactylated lysine residues with affinity sufficient to mediate binding at physiological concentrations. The observed chromatin co-localization phenomena cannot exclude alternative explanations: Lactylation may indirectly increase transcription factor accessibility to adjacent DNA sequences by altering local chromatin conformation or nucleosome stability; or the chromatin binding of PU.1/PPARγ may itself be regulated by other co-factors (such as coactivators or mediator complexes) rather than directly dependent on histone H3K18la. Therefore, the present review referred to PU.1 and PPARγ as 'candidate lactylation-binding proteins' or 'putative recognition factors', emphasizing that their roles in lactylation downstream functions require more direct biochemical evidence for confirmation. This field urgently requires the identification of genuine dedicated structural domains with lactylated lysine recognition capability through direct *in vitro* binding experiments, structural biology analysis and mutant functional validation, distinguishing them from transcription factors whose binding is indirectly enhanced through altered chromatin conformation. In the absence of such conclusive evidence, categorizing them as formal 'readers' may be premature and detrimental to the rigorous development of the field (24). The major regulatory machineries, writers, erasers and readers, orchestrating lactylation-mediated macrophage polarization

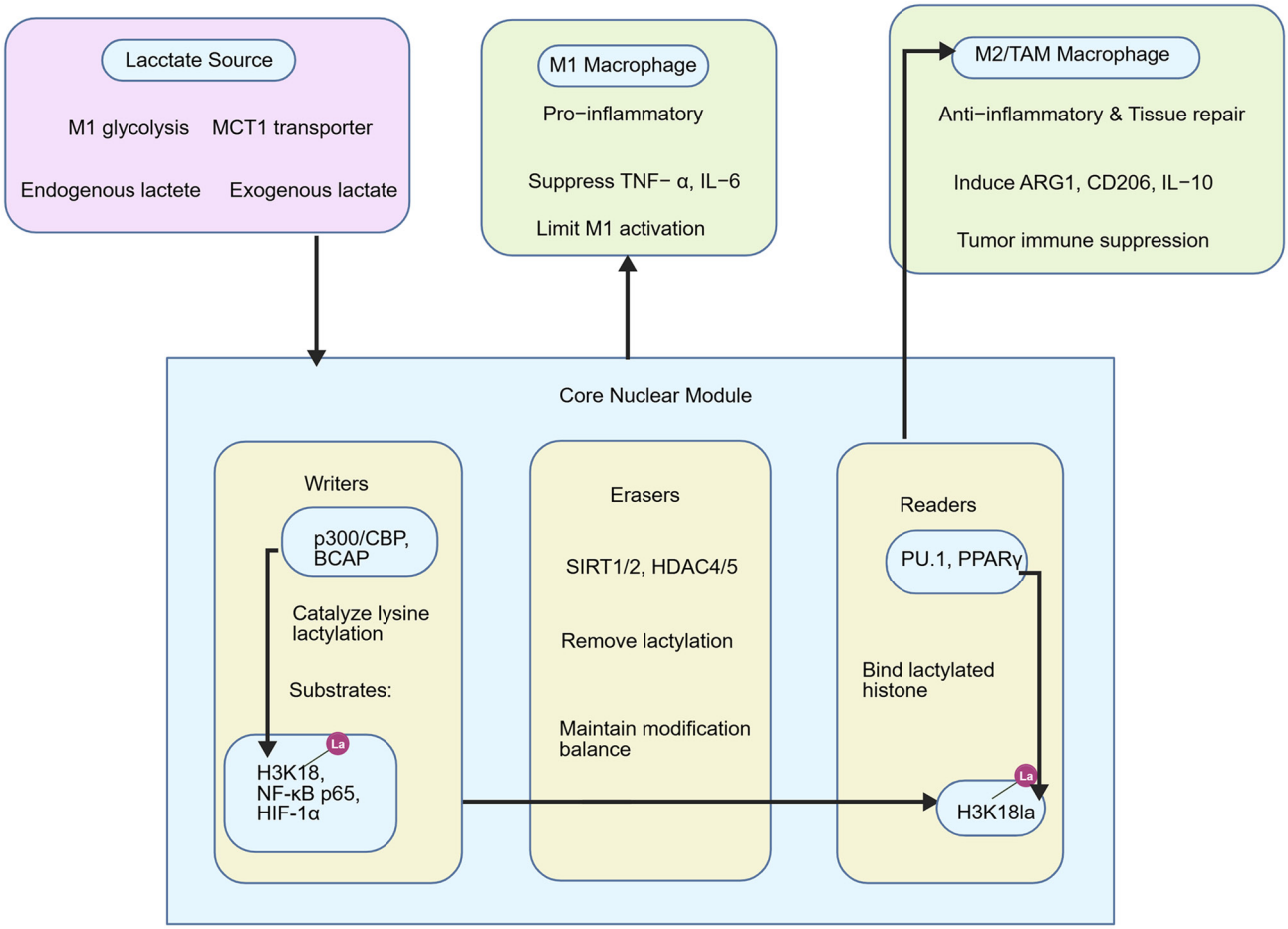


Figure 2. The core nuclear module regulating lactylation dynamics in macrophages. Schematic representation of the writers, erasers, and readers governing lysine lactylation. The modification is dynamically regulated by 'writers' (lactyltransferases, such as p300/CBP and BCAP) that catalyze lysine lactylation, and 'erasers' (delactylases, such as SIRT1/2 and HDAC4/5) that remove lactyl groups to maintain modification balance. The biological functions are executed by potential 'readers' (e.g., PU.1, PPARγ) that recognize and bind to lactylated histones (such as H3K18la). This nuclear module integrates lactate signals (derived from endogenous glycolysis or exogenous MCT1 uptake) to suppress M1 activation or promote M2/TAM polarization, thereby mediating pro-inflammatory suppression and tumor immune evasion. The figures were created with BioGDP (biogdp.com). CBP, CREB-binding protein; HDAC, histone deacetylase; PPAR, peroxisome proliferator-activated receptor; TAM, tumor-associated macrophage; MCT1, monocarboxylate transporter 1; TNF, tumor necrosis factor; ARG1, arginase 1; p300/CBP, E1A-binding protein p300/CREB-binding protein; BCAP, B cell adaptor for phosphoinositide 3-kinase; SIRT1/2, sirtuin 1/2; HDAC4/5, histone deacetylase 4/5; PU.1, purine-rich box 1; H3K18la, histone H3 lysine 18 lactylation; HIF-1α, hypoxia-inducible factor 1; la, lactylation.

are summarized in Table I. The coordinated regulation of lactylation by writers, erasers and readers is illustrated in Fig. 2.

4. Molecular mechanisms of lactylation in regulating macrophage polarization

Lactate sources and regulation of intracellular lactate levels in macrophages. This section focuses on the dynamic changes in lactate concentration and their determinants, whereas the generation pathways, enzymatic features, and detection status of lactyl-CoA as a direct donor of lactylation are detailed in *Regulatory mechanisms of lactylation: Writers, erasers and readers*. Before systematically elaborating on the molecular mechanisms by which lactylation regulates macrophage polarization, the fundamental premise that macrophage polarization is governed by a highly complex regulatory network involving the integration of cytokine signaling pathways, metabolic reprogramming, transcription factor networks and tissue-specific microenvironmental signals should first be clarified (12,14,23). Intracellular lactate levels are a key determinant of the extent of lactylation. Lactate homeostasis within cells is determined by three processes: production (glycolytic pathway), transmembrane transport [monocarboxylate transporter (MCT) family-mediated uptake and efflux] and metabolic consumption (oxidation or gluconeogenesis). Among these, lactate dehydrogenase (LDH) is the core regulatory enzyme in the production process; LDHA primarily catalyzes the conversion of pyruvate to lactate, whereas LDHB catalyzes the oxidation of lactate to pyruvate. MCTs are responsible for the bidirectional transmembrane lactate flux, with MCT1 being a high-affinity uptake transporter and MCT4 being a low-affinity efflux transporter. The detailed biochemical characteristics of these enzymes and transporters are discussed in *Regulatory mechanisms of lactylation: Writers, erasers and readers*; this section focuses on their dynamic changes in macrophage polarization and their concentration effects.

Macrophage polarization status determines distinctly different dynamic features of the lactate pool. M1 macrophages, due to markedly enhanced aerobic glycolysis (the Warburg

effect), exhibit upregulated LDHA expression and suppressed LDHB, resulting in greatly increased net lactate production, with intracellular lactate 1-3 mM in the resting state, rapidly rising to 10-30 mM following LPS/IFN-γ stimulation (6,10). By contrast, M2 macrophages, characterized by FAO and oxidative phosphorylation as their primary energy-supplying pathways, possess higher LDHB activity and can oxidize lactate taken up from the microenvironment to pyruvate for entry into the TCA cycle for energy production; consequently, their intracellular lactate concentrations are maintained at relatively low levels (1-3 mM) (10,25). In the tumor microenvironment, tumor cells produce large amounts of lactate through the Warburg effect and efflux it via MCT4, elevating local lactate concentrations to as high as 40 mM; macrophages then take up this exogenous lactate through MCT1, causing passive elevation of intracellular lactate levels (up to 15-25 mM), a key reason for markedly enhanced lactylation in tumor-associated macrophages (TAMs) (10,25).

Notably, intracellular lactate levels in macrophages are not passively determined by metabolic status but are self-regulated through a 'lactylation-metabolic enzyme' feedback loop. Histone or non-histone lactylation can alter the expression levels or activities of key metabolic enzymes (such as *PKM2, LDHA,* and *PDK1*), thereby feedback-regulating glycolytic flux and lactate production rates (10). In the late phase of M1 polarization, accumulated lactate upregulates pyruvate dehydrogenase kinase 1 *(PDK1)* expression through modifications such as histone H3K18la, redirecting metabolic flux from glycolysis back toward oxidative phosphorylation, thereby reducing lactate production rates and forming negative feedback restriction (10). This 'self-limiting' property ensures timely termination of lactylation signals, preventing pathological consequences of excessive modification (6,10).

Regulation of macrophage polarization-related gene transcription by histone lactylation. The lactylation effects described below should be considered within the phenotypic framework established by canonical polarization signals (such as LPS/IFN-γ or IL-4/IL-13), with lactylation primarily playing modulating, amplifying, or stabilizing roles. Histone lactylation is an epigenetic regulatory mechanism that plays a critical role in macrophage polarization by regulating the transcription of specific genes. Histone H3K18 lactylation (H3K18la) was markedly increased during the late stages of bacterial infection in macrophages and this modification was specifically enriched in the promoter regions of anti-inflammatory and repair-related genes (such as *Arg1*, *Cd206*, and *Il10*), promoting their transcriptional activation (6). This discovery revealed that lactylation plays a key role in the temporal transition of macrophages from the M1 pro-inflammatory state to the M2 reparative state. Further studies have shown that H3K18la neutralizes positive histone charges, weakens nucleosome-DNA interactions, and alters higher-order chromatin structures, thereby increasing the accessibility of transcription factors and RNA polymerase II to promoters and promoting the expression of M2 marker genes (6). For example, in tumor-associated macrophages (TAMs), H3K18la is associated with the recruitment of transcription factors PU.1 and PPARγ, which cooperatively activate *ARG1* and *CD206* transcription, promoting M2 polarization and formation of an immunosuppressive microenvironment (18,26,27). However, the expression and activity of PU.1 and PPARγ themselves are also regulated by canonical M2 polarization signals such as IL-4/STAT6; lactylation may fine-tune, enhance, or maintain their downstream transcriptional output in response to these canonical signaling pathway activations, rather than independently serving as the primary driver of the M2 polarization program. As aforementioned, PU.1 and PPARγ are currently considered only candidate binding proteins, and their direct reader roles in lactylation downstream functions await biochemical validation; lactylation may act as an 'amplifier' or 'stabilizer' rather than as a 'master switch' of M2 polarization.

Studies have identified additional histone lactylation sites involved in macrophage polarization regulation, revealing the bidirectional regulatory potential of this modification. For example, H3K23la and H4K5la have been found to participate in the transcriptional repression of pro-inflammatory genes in M1 macrophages (12,14). In LPS-stimulated macrophages, as glycolysis is enhanced and lactate accumulates, H3K23la levels gradually increase and become enriched in the promoter regions of pro-inflammatory genes such as *TNF-α* and *IL-6*, suppressing their sustained expression and preventing tissue damage caused by excessive inflammatory responses (12,14). This finding suggests that histone lactylation may precisely control the dynamic balance and temporal transition of macrophage polarization through dual, bidirectional regulation of both M1 and M2 genes. Furthermore, in an atherosclerosis model, macrophage MCT4 deficiency led to intracellular lactate accumulation and elevated H3K18la levels, activating anti-inflammatory and repair-related gene expression (such as *IL-10 and TGF-β*), thereby alleviating plaque inflammation and delaying atherosclerotic plaque development and progression (21).

The associations between lactylation and macrophage phenotypes in the aforementioned studies remain largely correlative observations rather than strictly causal relationships. For example, enrichment of H3K18la at M2-related gene promoters does not directly prove that this modification is sufficient or necessary to drive M2 polarization, the observed phenotypic changes in some studies may simultaneously depend on other synergistic modifications (such as H3K27ac or H3K4me3) or changes in upstream transcription factor activity, with lactylation potentially merely accompanying these events. To date, only a few studies have preliminarily established causality through genetic interventions (such as site-directed mutagenesis of lactylation sites, conditional p300 knockout, or use of lactylation-specific inhibitors), but these experiments are mostly limited to cell lines or ectopic expression systems, with very limited validation in primary macrophages and *in vivo* physiological models. Notably, a study in an ischemia-induced muscle regeneration model found, through CUT and Tag sequencing, that changes in the macrophage H3K18la genomic landscape could predict subsequent gene expression changes, rather than merely reflecting prior transcriptional states; providing direct evidence for the functional driving role of histone lactylation *in vivo* (28). Therefore, readers should interpret current evidence with caution: Lactylation in most contexts is more likely a downstream marker of metabolic

reprogramming or a co-regulatory factor and its universality and independence as a polarization-driving factor require more rigorous gain- and loss-of-function experiments for confirmation.

Furthermore, the regulation of macrophage polarization by histone lactylation exhibits significant cell-type specificity and stimulus dependence. For example, in intestinal inflammation models, lactylation primarily regulates the anti-inflammatory functions of macrophages, promoting mucosal healing; whereas in the tumor microenvironment, it primarily promotes immunosuppressive M2 polarization, facilitating immune evasion (23,29). This specificity may be associated with differences in lactate sources (endogenous vs. exogenous), concentrations (mM vs. μM), exposure duration (acute vs. chronic), and synergistic effects of other signaling molecules (such as cytokines, metabolites and pathogen-associated molecular patterns) across different microenvironments. In intestinal inflammatory conditions, exogenous lactate produced by lactic acid bacteria can be taken up by macrophages, activating anti-inflammatory gene expression through histone lactylation and suppressing excessive immune responses, reflecting the immunomodulatory function of host-microbe metabolic interactions (23,29). In the tumor microenvironment, despite different metabolic characteristics of tumor cells, they all exhibit high lactate production and efflux, maintaining persistently high microenvironmental lactate concentrations (10-40 mM), which not only promotes M2 polarization through histone lactylation but also synergistically enhances immunosuppressive phenotypes through other mechanisms such as HIF-1α activation and T cell function suppression (25,30,31). However, a previous study found decoupling between lactylation and M2 gene expression signatures, with *Arg1* expression depending on IL-6/Stat3 signaling rather than lactylation (32).

Effects of non-histone lactylation on macrophage signal transduction. Before investigating the specific mechanisms, clarifying the functional hierarchical differences between histone and non-histone lactylation is necessary. Histone lactylation primarily acts at the chromatin level, influencing the transcriptional activity of specific genes by altering nucleosomal spatial conformation and DNA accessibility. It therefore represents epigenetic regulation at the transcriptional level, with relatively slow but sustained effects (12,14). By contrast, non-histone lactylation directly modifies key proteins in signal transduction pathways, such as the transcription factors NF-κB and HIF-1α, metabolic enzymes PKM2 and GAPDH, pyroptosis-related protein NLRP3 and DNA repair protein MRE11. By altering the activity, stability, subcellular localization, protein-protein interactions, or enzyme kinetics of these proteins, non-histone lactylation can affect the intensity and duration of signaling pathways, thereby enabling relatively rapid regulation at the signal transduction level that can alter cellular function within minutes to hours (33,34). These two classes of lactylation events are not independent but are closely functionally coupled. Histone lactylation can indirectly affect the levels of non-histone lactylation substrates or modify enzyme activities by altering the expression of cytokines, metabolic enzymes, or signaling molecules, whereas non-histone lactylation (such as PKM2 and LDHA lactylation) can also potentially influence lactyl-CoA availability for histone lactylation by regulating metabolic flux. Future research is needed to elucidate how these two classes of modifications cooperate in time and space to shape macrophage polarization decisions. Again, most current conclusions regarding non-histone lactylation-driven macrophage polarization remain based on correlative observations or mechanistic inferences from *in vitro* overexpression systems and lack quantitative validation of endogenous substrate modifications (such as stoichiometry) and *in vivo* genetic evidence (such as site-specific knock-in mice). Readers should distinguish between definitive findings validated by multiple orthogonal experimental approaches and preliminary inferences that are still in the exploratory stage.

The NF-κB signaling pathway is the core regulatory pathway for M1 macrophage polarization (Fig. 3), and its activity is finely regulated by multiple post-translational modifications, including phosphorylation, acetylation, ubiquitination and lactylation (12,35). In LPS-stimulated macrophages, lactylation has been identified at the K310 site of the NF-κB p65 subunit. Mechanistic studies have shown that lactylation at this site enhances the binding affinity between p65 and the inhibitory protein IκBα, promoting p65-IκBα complex formation and p65 nuclear export, thereby inhibiting p65 nuclear translocation, DNA-binding capacity and transcriptional activity and ultimately providing negative feedback to limit the expression of M1 pro-inflammatory genes (12). Recent research has revealed a non-enzymatic D-lactylation mechanism in activated macrophages. Downregulation of *GLO2* expression leads to the accumulation of its substrate SLG, which can directly induce D-lactylation at the RelA K310 site, similarly exerting inhibitory effects on NF-κB transcriptional activity and providing a new molecular explanation for the negative feedback regulation of p65 K310 lactylation (16). These findings indicate that under specific contexts (such as the late phase of LPS-induced acute inflammatory responses), p65 K310la exerts inflammation-suppressive functions, revealing lactylation as an endogenous negative regulatory mechanism ('brake') of the NF-κB signaling pathway that plays an important role in inflammation resolution and temporal control (Fig. 4). Furthermore, in *Treponema pallidum*-infected macrophages, the bacterial lipoprotein TpF1 can induce host methyltransferase-like 14 *(METTL14)* expression, which indirectly promotes NF-κB p65 lactylation, inhibits its activity and promotes macrophage M2 polarization, thereby facilitating bacterial immune evasion and intracellular survival (35). This study suggests that pathogens may manipulate host cell lactylation to interfere with macrophage polarization and evade immune clearance. Notably, although both involve p65 lactylation, the upstream induction mechanisms, site specificity, and downstream functional outputs may differ between LPS stimulation and *T. pallidum* infection, again emphasizing the context-dependence of lactylation regulation.

Notably, in addition to the aforementioned enzymatic lactylation pathway dependent on lactyl-CoA, recent studies have revealed a completely novel non-enzymatic lactylation mechanism. Zhao *et al* (16) found that SLG (S-D-lactoylglutathione), the substrate of *GLO2*, can accumulate in large amounts under inflammatory stimulation and directly transfer D-lactyl groups to lysine residues through non-enzymatic reactions, forming D-lactylation modifications. This finding not only

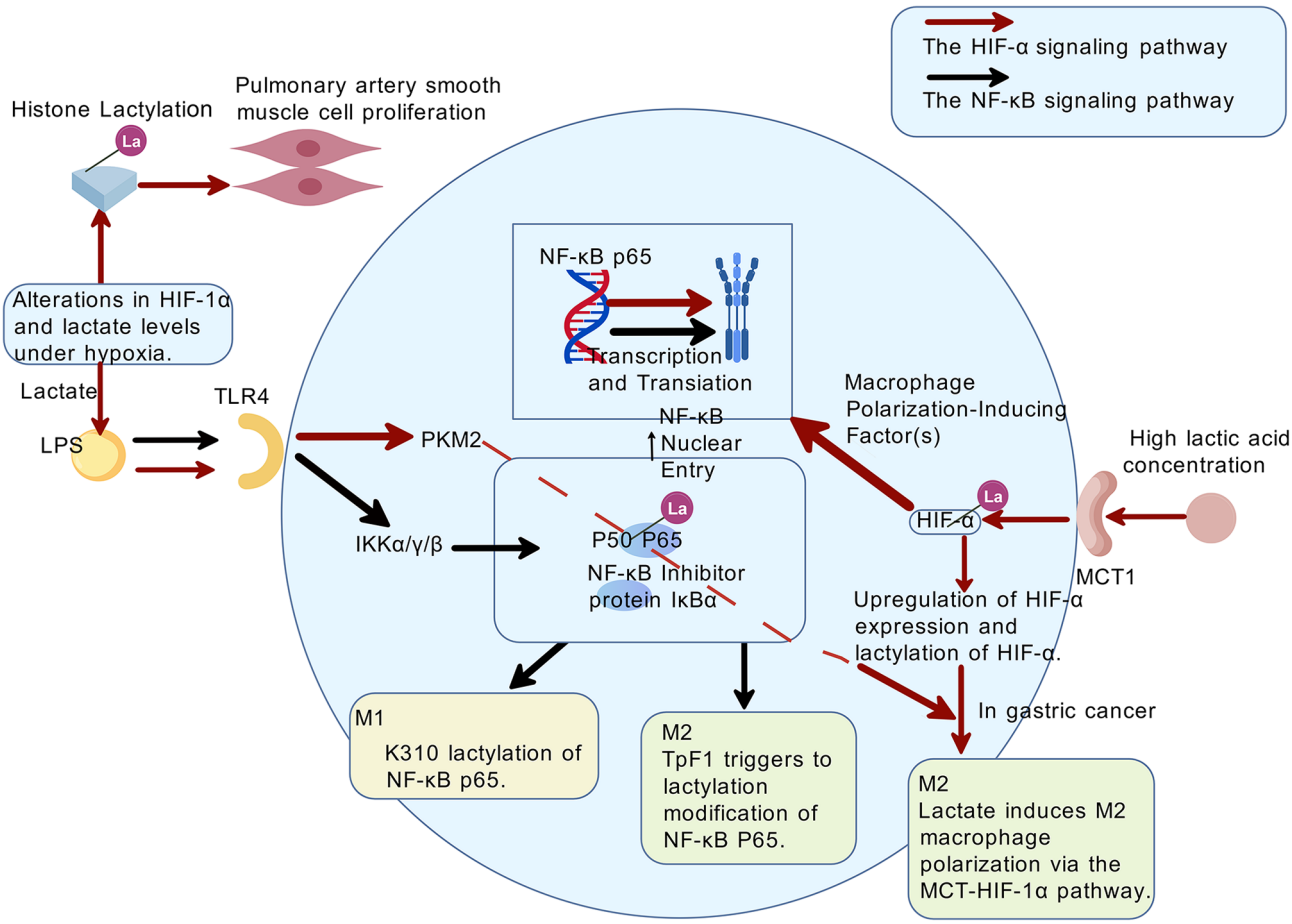


Figure 3. Lactylation crosstalk with NF-κB and HIF-1α signaling pathways in macrophage polarization. Illustration of the interplay between lactylation and canonical signaling pathways. Lactate, taken up via MCT1 or produced intracellularly, functions as a substrate for lactylation of both histones and non-histone proteins, including NF-κB p65 and HIF-1α. Lactylation of NF-κB p65 (such as at K310) modulates its interaction with the inhibitory protein IκBα, regulating its nuclear entry and transcriptional activity. Meanwhile, HIF-1α lactylation enhances its stability and transactivation capacity. These signaling events orchestrate the dynamic balance between M1 and M2 polarization. The figures were created with BioGDP (biogdp.com). La, lactylation; PKM2, pyruvate kinase M2; TLR4, Toll-like receptor 4; LPS, lipopolysaccharide. HIF-1, hypoxia-inducible factor 1; PKM2, pyruvate kinase M2; IKKα/γ/β, IκB kinase; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; La, lactyl group; K310, lysine 310; TpF1, *Treponema pallidum* factor 1; MCT1, monocarboxylate transporter 1.

demonstrates that the donor source of lactylation is not limited to lactyl-CoA but also suggests that non-enzymatic chemical pathways may confer faster response kinetics on lactylation than previously recognized, as SLG generation and accumulation are directly coupled to instantaneous fluctuations in cellular metabolic status without the delay of enzymatic catalytic reactions. Thus, the uniqueness of lactylation in 'real-time metabolic sensing' may derive both from the wide dynamic range of lactate concentrations and the ultra-fast response mode provided by non-enzymatic pathways.

Another key signaling pathway regulated by lactylation is the HIF-1α pathway (as shown in Fig. 3). In the tumor microenvironment, high concentrations of lactate are taken up by macrophages through MCT1, activating HIF-1α expression and activity, stabilizing HIF-1α protein even under normoxic conditions (pseudo-hypoxic effect) (12,27,33). Studies have found that HIF-1α itself can also undergo lactylation (such as at the K79 site), and this modification can enhance its protein stability (inhibiting PHD/VHL-mediated degradation) and promote its binding to target gene promoters and transcriptional activity (12,26,27). In gastric cancer models, lactate induces macrophage M2 polarization through the MCT-HIF-1α axis and non-histone HIF-1α lactylation has been found to participate in this process. However, it should be noted that HIF-1α activity is also regulated by multiple other post-translational modifications, including PHD-dependent oxygen sensing, phosphorylation, acetylation and SUMOylation. Lactylation is only one regulatory dimension and its relative contribution depends on cell type, oxygen tension and lactate concentration gradients (27). Inhibition of non-histone HIF-1α lactylation can markedly attenuate its transcriptional activation of M2 marker genes *ARG1 and CD163*, thereby reversing the immunosuppressive phenotype of tumor-associated macrophages (12,27,31,36). Chen *et al* (37) found that in a hypoxic model, reactive oxygen species-driven glycolytic shift remodeled HIF-1α and lactate levels *in vivo*, with histone lactylation promoting pulmonary artery smooth muscle cell proliferation; moreover, lactate could activate *PKM2* in LPS-induced macrophages, promoting their transition toward a reparative phenotype (6,30,37).

In addition to the aforementioned signaling pathways, studies have identified other non-histone lactylation targets involved in macrophage polarization regulation.

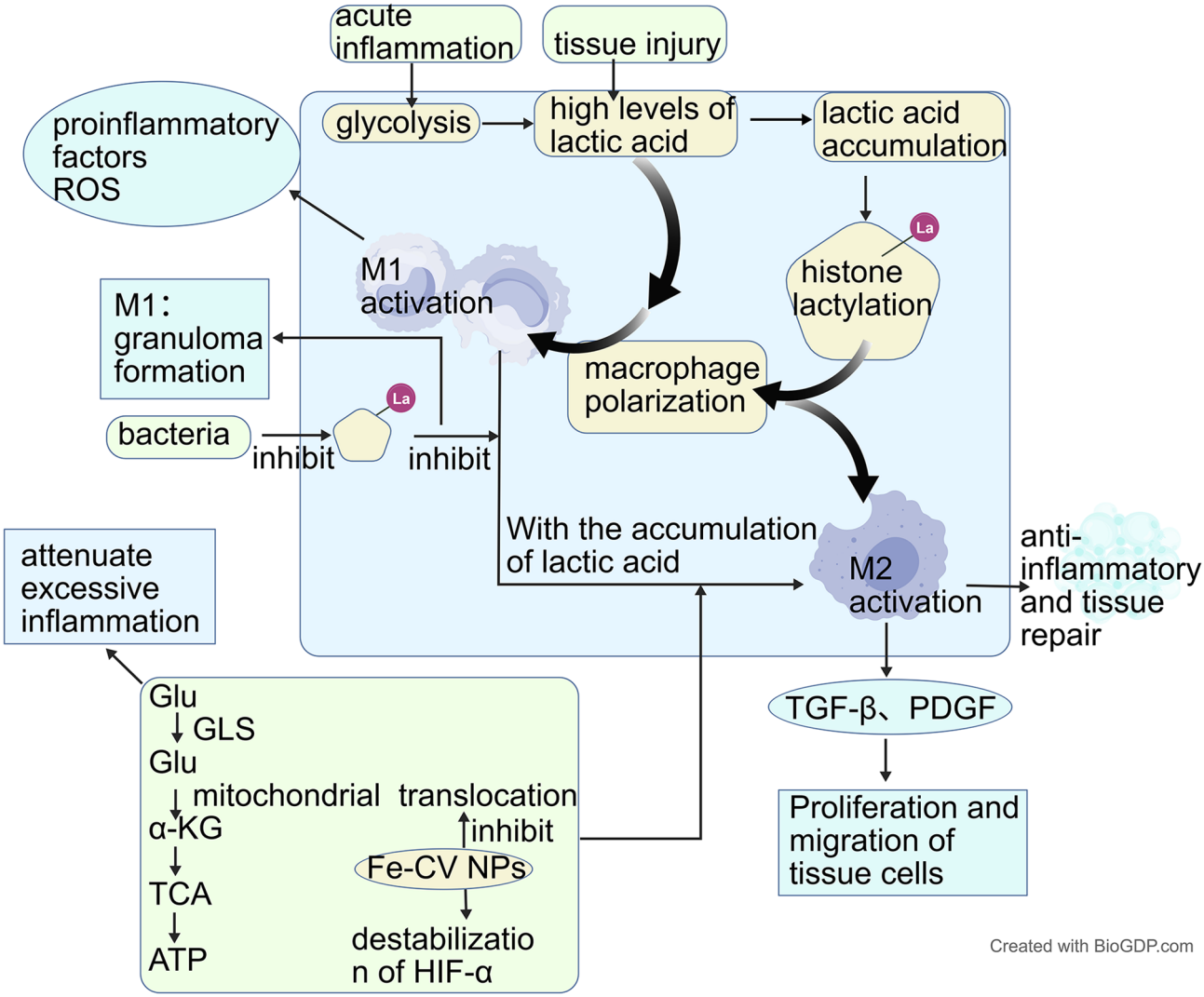


Figure 4. Temporal regulation of macrophage polarization by histone lactylation during acute inflammation and tissue repair. A time-course model depicting how histone lactylation acts as a 'metabolic brake' to govern the transition from inflammation to resolution. During early acute inflammation and tissue injury, glycolysis is upregulated, leading to high levels of lactic acid accumulation. This surge in lactate drives histone lactylation, which subsequently inhibits M1 pro-inflammatory activation and granuloma formation while promoting M2 activation. The M2 phenotype subsequently secretes growth factors (*TGF-β, PDGF)* to stimulate the proliferation and migration of tissue cells, thereby facilitating tissue repair and attenuating excessive inflammatory damage. Notably, the accumulation of lactic acid can be influenced by interventions (such as Fe-CV NPs), which inhibit mitochondrial translocation and HIF-1α destabilization, further modulating the M1/M2 equilibrium. The figures were created with BioGDP (biogdp.com). ROS, reactive oxygen species; La, lactyl group; Glu, glutamine; GLS, glutaminase; α-KG, ketoglutarate; TCA, tricarboxylic acid; ATP, adenosine triphosphate; Fe-CV NPs, iron-curcumin nanoparticles; HIF-α, hypoxia-inducible factor alpha; TGF-β, transforming growth factor-beta; PDGF, platelet-derived growth factor.

For example, in bladder cancer cells, histone H3K18 lactylation can activate *PRKN* gene expression; PRKN is a key mitophagy regulatory protein that enhances M2 polarization of macrophages by promoting clearance of damaged mitochondria through mitophagy. In tumors, non-histone lactylation of p53, PD-L1 and MRE11 has also been implicated, directly affecting tumorigenesis, immune evasion and DNA damage repair resistance (3,18,38,39). In diabetic ulcer models, lactylation of NLRP3 inflammasome components has been found to inhibit its assembly and activation, thereby reducing macrophage pyroptosis and release of pro-inflammatory cytokines such as *IL-1β* and *IL-18*, promoting wound healing (34). However, functional studies of non-histone lactylation are currently mostly limited to overexpression systems of single candidate proteins, lacking quantitative analysis of endogenous substrate modification stoichiometry. Future research should more extensively employ endogenous mass spectrometry quantification, site-specific antibodies, CRISPR/Cas9-mediated site-directed mutant knock-in mouse models, and conditional knockout tools to rigorously validate the pathophysiological significance of non-histone lactylation, avoiding false-positive conclusions caused by overexpression artifacts.

Crosstalk between lactylation and epigenetic modifications. The intracellular epigenetic modification network is highly complex, dynamic and interconnected; extensive crosstalk exists between different types of modifications, collectively determining gene expression patterns and cell fates (12). As an emerging epigenetic modification, lactylation interacts with other known modifications including acetylation, methylation and phosphorylation, which play important roles in

regulating macrophage polarization and constitute a multilayered regulatory network.

The crosstalk between lactylation and acetylation is among the most extensively studied, as both modifications utilize metabolite-CoA derivatives as substrates and share regulatory enzymes (such as p300/CBP and SIRTs). Histone lysine acetylation and lactylation directly compete for the same lysine residues; high concentrations of lactate or lactyl-CoA can inhibit acetyltransferase activity or competitively bind to deacetylases, thereby affecting the overall acetylation levels (12). During M1 macrophage polarization, enhanced glycolysis in the early phase results in limited lactate accumulation, while histone acetylation (such as H3K9ac and H3K27ac) predominates and promotes rapid expression of pro-inflammatory genes, including *TNF-α*. In the later phase, substantial lactate accumulation increases lactylation marks such as H3K9la and H3K18la, which gradually replace acetylation and contribute to the suppression of pro-inflammatory gene expression and activation of repair-associated gene expression (10,12). This 'acetylation-to-lactylation' temporal switch not only regulates the intensity and duration of inflammatory responses but also participates in the orderly transition of macrophages toward a reparative phenotype, representing an important molecular basis for inflammatory self-limitation. Furthermore, lactylation and acetylation can jointly participate in disease progression: in septic acute kidney injury (SAKI), excessive acetylation and inactivation of PDHA1 K385 increases lactate production, which promotes lactylation of the mitochondrial fission protein Fission 1 at K20, exacerbating mitochondrial dysfunction and SAKI and forming a pathological acetylation-lactylation positive feedback loop (19).

The crosstalk between lactylation and methylation is primarily achieved by influencing the activity or recruitment of methyltransferases (KMTs) and KDMs. In macrophages, lactylation can inhibit the activity of certain KMTs, leading to reduced levels of activating methylation marks, such as H3K4me3, and thereby suppressing M1 gene expression (12). Conversely, lactylation promote the activity or recruitment of certain KDMs to remove repressive methylation marks, such as H3K27me3, and activate M2 gene transcription (27). For example, in TAMs, H3K18la can recruit the H3K27 demethylase KDM6B to specifically remove H3K27me3 repressive modifications in the *IL-10* promoter region, promoting *IL-10* expression and enhancing immunosuppressive function (27). This lactylation-methylation crosstalk provides new explanations for how the metabolic status finely regulates macrophage polarization through epigenetic mechanisms and suggests that lactylation may exert long-term regulatory effects by remodeling the methylation landscape.

Phosphorylation, a rapidly responsive post-translational modification, exhibits functional synergy with lactylation. During macrophage activation, extracellular signals activate kinases such as MAPK and MSK1/2, leading to phosphorylation of histone H3 at S10 and other sites, thereby promoting chromatin opening and pro-inflammatory gene expression (12). H3S10 phosphorylation can enhance the efficiency or stability of lactylation at the adjacent K14 site; this 'phosphorylation-lactylation' synergy markedly increases the transcriptional activity of pro-inflammatory genes (12). Conversely, during the inflammation resolution phase, H3S10 phosphorylation levels decrease, leading to reduced K14 lactylation and suppression of pro-inflammatory gene expression (12,14). This synergistic regulation may participate in the rapid switching of macrophage polarization, enabling flexible responses to microenvironmental changes.

As well as crosstalk between histone modifications, non-histone lactylation can also indirectly regulate gene expression by affecting the functions of other epigenetic regulatory factors. For example, in macrophages, lactylated *PKM2* can bind to histone deacetylase HDAC1, inhibiting its deacetylase activity, thereby increasing histone acetylation levels and promoting M2 gene expression, forming a non-histone lactylation → histone acetylation → gene expression cascade. In addition, lactylated GAPDH can transition from a glycolytic enzyme to an RNA-binding protein, interacting with epigenetic regulatory factors such as enhancer of zeste homolog 2 (the catalytic subunit of the polycomb repressive complex 2 complex) to regulate its chromatin-binding capacity and H3K27me3 modification levels, thereby affecting macrophage differentiation and polarization. In summary, histone and non-histone lactylation operate at different functional levels but are tightly coupled in macrophage polarization regulation: the former remodels the chromatin landscape, establishing a 'permissive' or 'repressive' background for the transcription of specific polarization-related genes; the latter directly regulates the activation thresholds and kinetics of signaling proteins, rapidly responding to microenvironmental stimuli. Positive or negative feedback loops may exist between them, but the detailed mechanisms, temporal relationships and context specificity of this synergistic network await systematic investigation.

5. Pathophysiological significance of lactylation-regulated macrophage polarization

Inflammatory responses and tissue repair. As discussed in the Introduction, the regulatory effects of lactylation on macrophage polarisation are not fixed but exhibit significant context dependence. This variation is primarily influenced by factors including lactate concentration and exposure duration, cell type and tissue microenvironment, disease stage, and crosstalk with other epigenetic modifications (10,12,40). Lactylation regulates the temporal switching of macrophage polarisation and plays a critical role in the initiation, persistence and resolution of inflammatory responses and subsequent tissue repair. Its core functions can be summarised in three aspects: The 'temporal brake' in acute inflammation, the 'phenotypic switch driver' in tissue repair, and the 'dysregulation amplifier' in chronic inflammation. The physiological and pathological implications of lactylation-modulated macrophage polarisation are summarised in Table II.

Lactylation-regulated macrophage polarisation plays a critical role in the initiation, progression, and resolution of inflammatory responses and subsequent tissue repair (10,29,40). Glycolytic metabolites are closely linked to the initiation and resolution of acute inflammation. In the early stages of the disease, macrophages are rapidly activated to the M1 phenotype, clearing pathogens or damaged cells through the release of pro-inflammatory cytokines and ROS. This process is accompanied by a significant increase in glycolytic

Table II. Physiological pathological implications of lactylation-modulated macrophage polarization.

Classification	Biological context	Lactylation change	Macrophage phenotype shift	Core biological function	(Refs.)
Physiological process	Tissue injury and repair	Upregulated	M2 dominant	Promote tissue regeneration, limit excessive inflammation	(10,25,28, 40,41)
Physiological process	Metabolic homeostasis (adipose/liver)	Moderate elevation	Balanced M1/M2	Maintain tissue metabolic stability	(25,53,56)
Pathological disease	Malignant tumor (TME)	Highly elevated	M2/TAMs polarization	Suppress anti-tumor immunity; accelerate tumor proliferation, metastasis	(11,18,25, 27,30,33, 45-47)
Pathological disease	Chronic inflammatory disorders (arthritis, colitis)	Reduced global lactylation	M1 hyperactivation	Exaggerate inflammatory injury	(23,29,61)
Pathological disease	Organ fibrosis (lung/liver/kidney)	Increased H3K18la	M2 macrophage accumulation	Secrete collagen, aggravate extracellular matrix deposition	(42,43,56)
Pathological disease	Sepsis and acute systemic inflammation	Insufficient lactylation	Overactive M1	Massive release of TNF-α, IL-6; induce cytokine storm	(8,10,19)

H3K18la, histone H3 lysine 18 lactylation; TAM, tumor-associated macrophages; TME, tumor microenvironment; TNF-α, tumor necrosis factor-α.

activity and lactate production (10,15,25). As inflammation progresses, intracellular lactate accumulation leads to elevated histone lactylation levels, such as H3K18la, which suppresses M1 pro-inflammatory gene expression while activating the transcription of M2 anti-inflammatory and repair-associated genes, thereby promoting M2 polarisation (10). This metabolic-epigenetic regulatory switch ensures the timely termination of inflammatory responses and prevents tissue damage caused by excessive inflammation (Fig. 4).

In bacterial infection models, macrophage intracellular lactate levels, together with histone lactylation and methylation crosstalk, influence disease progression (10,12,17). In the early stage of bacterial infection, macrophages predominantly exhibit M1 polarization, exerting host defense functions through phagocytosis and bacterial killing (2). As infection is controlled, macrophage intracellular lactate levels rise, activating anti-inflammatory gene expression through modifications such as H3K18la, promoting the switch toward M2 polarization and initiating tissue repair processes (10). Dysregulation of this switching process may lead to persistent chronic inflammation or infection. For example, in *Treponema pallidum* infection, the pathogen can suppress macrophage lactylation or manipulate its shift toward M2, leading to prolonged inflammation or immune evasion and granuloma formation (35). In liver fibrosis models, CM272 treatment reduced DNA methylation and histone methylation levels in hepatic stellate cells; it has been speculated that CM272-induced reduction in lactate production may also decrease histone lactylation, thereby inhibiting hepatic stellate cell (HSC) activation and exerting anti-fibrotic effects (41). This finding provides new perspectives for understanding the pathogenesis of chronic infections and suggests that targeting lactylation may represent a novel strategy for treating chronic inflammatory diseases. In a silicosis fibrosis model, silica nanoparticles could drive macrophage M1 polarization and promote pulmonary fibrosis progression through SIRT3 downregulation leading to H3K18la accumulation and direct activation of *NOS2* transcription. Notably, SIRT3 plays a dual role in this model, both as a delactylase directly removing H3K18la and indirectly affecting lactylation levels through regulation of lactate metabolism, further supporting the therapeutic potential of targeting erasers in inflammatory disease (42). This suggests that the functional output of the same histone lactylation site is highly dependent on cell type (alveolar macrophages vs. plaque macrophages), upstream regulatory mechanisms (delactylase SIRT3 downregulation vs. transporter MCT4 deficiency) and the temporal features of the disease microenvironment. This apparent contradiction precisely confirms the repeatedly emphasized view of the present review: Lactylation is a context-dependent co-regulatory factor, not a fixed pro-M1 or pro-M2 signal.

During tissue injury repair, injury-induced lactate elevation promotes macrophage M2 polarization through lactylation, favoring tissue regeneration and repair. In an acute kidney injury model, folate-induced kidney injury promoted macrophage M2 polarization, accelerating injury repair through secretion of growth factors such as *TGF-β* and *PDGF* that promote renal tubular epithelial cell proliferation and migration; inhibition of lactylation markedly reduced M2 macrophage infiltration and delayed renal function recovery (40). Similarly, in a zebrafish

fin regeneration model, lactate participated in early inflammatory responses by promoting M1 macrophage polarization, subsequently regulating the switch toward M2 through lactylation and promoting the regeneration process (25). Studies have revealed the evolutionary conservation of lactylation in the temporal regulation of macrophage polarization (23,29). In intestinal inflammatory disease such as ulcerative colitis, dysregulation of lactylation-regulated macrophage polarization is a key factor in disease progression (23,29). Lactylation levels in intestinal mucosal macrophages are markedly reduced in ulcerative colitis patients, leading to persistent M1 pro-inflammatory phenotypes and failure of inflammation resolution (23,29). The use of lactate-producing probiotics can increase intestinal lactate levels, promote macrophage histone lactylation, inhibit NLRP3 inflammasome activation and pyroptosis, thereby alleviating inflammatory responses (43). This finding provides new approaches for the treatment of ulcerative colitis, restoring normal polarization switching of macrophages through regulation of lactylation to promote inflammation resolution and tissue repair.

Tumour microenvironment and immune evasion. In the tumour microenvironment, LDH in macrophages not only participates in lactate production but may also directly interact with histones to regulate their lactylation levels, suggesting that metabolic enzymes may directly participate in the regulation of lactylation. The dysregulation of lactylation-regulated macrophage polarisation is a key mechanism in tumour immune evasion and progression (18,25,30,33). Recent reviews have systematically summarised the molecular mechanisms by which lactylation promotes immunosuppression by remodelling the metabolic-epigenetic axis of macrophages in the tumour microenvironment (44,45). Tumour cells produce large amounts of lactate through the Warburg effect, leading to markedly elevated lactate concentrations in the tumour microenvironment (46). Lactate is taken up by TAMs through transporters such as MCT1, resulting in elevated intracellular lactate levels and enhanced lactylation (25,46). Lactylation promotes M2 polarisation of TAMs through multiple mechanisms, forming an immunosuppressive microenvironment that promotes tumour growth, invasion and metastasis (18,45,47). In a colorectal cancer liver metastasis model, microbial signals could induce lactylation at the K852 site of macrophage RIG-I, suppressing NF-κB signalling and promoting macrophage polarisation toward the M2-like phenotype, thereby constructing an immunosuppressive microenvironment favourable for tumour metastasis (48). In gastric cancer models, tumour cell-secreted lactate induced macrophage M2 polarisation through the MCT-HIF-1α signalling axis (33) (Fig. 5). Further mechanistic studies revealed that HIF-1α K79 lactylation enhanced its binding to the promoters of the M2 marker genes *ARG1* and *CD163*, promoting their transcription (33). Knockout of MCT1 or inhibition of non-histone HIF-1α lactylation markedly reduced M2 polarisation of TAMs, enhanced their antitumour activity, and suppressed tumour growth (31,33,36). Similarly, in bladder cancer cells, H3K18la can activate *PRKN* gene expression, thereby enhancing M2 polarisation and the immunosuppressive function of TAMs by promoting mitophagy (18). These studies revealed the diverse mechanisms by which lactylation regulates macrophage polarisation in the tumour microenvironment, providing multiple potential targets for the development of therapeutic strategies.

Lactylation further promotes tumor immune evasion by regulating the interactions between TAMs and other immune cells (30). M2 TAMs can secrete anti-inflammatory cytokines such as *IL-10* and *TGF-β*, suppressing the activity of cytotoxic T cells and natural killer (NK) cells (2,30,49). In addition, TAMs can consume key amino acids such as arginine in the tumor microenvironment through expression of metabolic enzymes such as arginase-1, further suppressing T cell proliferation and function (30). These immunosuppressive functions are partially dependent on the regulation of lactylation. For example, in a non-small cell lung cancer model, *DNMT3A i*nhibited *SLIT2* expression through methylation, thereby promoting macrophage M2 polarization and immunosuppression (30). The expression of *SLIT2* itself is regulated by histone lactylation, and the reduction of histone delactylation caused by high lactate levels in the tumor microenvironment is an important reason for *SLIT2* silencing (30).

These studies provide new ideas and potential targets for tumor immunotherapy, with the potential to improve the response rates and efficacy of current immunotherapies. Currently, targeting lactylation-regulated macrophage polarization has emerged as a new strategy for tumor immunotherapy, focusing on the following aspects: Inhibition of tumor cell lactate production, such as using *LDHA* inhibitors (45); ii) blockade of lactate transport, such as using MCT1/4 inhibitors (21,33); iii) direct inhibition of lactylation 'writers' or activation of 'erasers' (14,18); and iv) specific interference with the regulation of key transcription factors such as HIF-1α and NF-κB by lactylation (12,25). For example, in melanoma models, lactylation at the K503 site of LSD1 in drug-tolerant cells triggers ferroptosis, remodel the tumor immune microenvironment and sensitize responses to PD-1 inhibitor therapy (50,51); in hepatocellular carcinoma models, inhibition of histone lactylation enhanced the antitumor function of NK cells, overcoming immunosuppression in the tumor microenvironment (11); in gastric cancer mouse models, studies found that lactate enhanced DNA repair and resistance to DNA damage-based therapies, suggesting that lactate intervention may improve chemotherapy outcomes and increase patient survival rates (1,2,9). In addition, non-histone SUMOylation forms indirect regulatory networks with lactylation. For example, a circRNA-encoded PIAS1 variant could influence immunogenic ferroptosis by regulating the balance between SUMOylation and phosphorylation of STAT1 (52), suggesting SUMOylation may functionally interact with lactylation in tumor immune regulation.

Metabolic disease. Lactylation-regulated macrophage polarisation also plays important roles in the development and progression of metabolic diseases such as obesity, type 2 diabetes and atherosclerosis (21,23,53). In obesity, adipose tissue is infiltrated by macrophages, which polarise toward the pro-inflammatory M1 phenotype, releasing inflammatory cytokines such as TNF-α and IL-6, leading to chronic low-grade inflammation and insulin resistance (23). During obesity, adipocytes exhibit enhanced glycolysis and produce large amounts of lactate, which can be taken up by macrophages

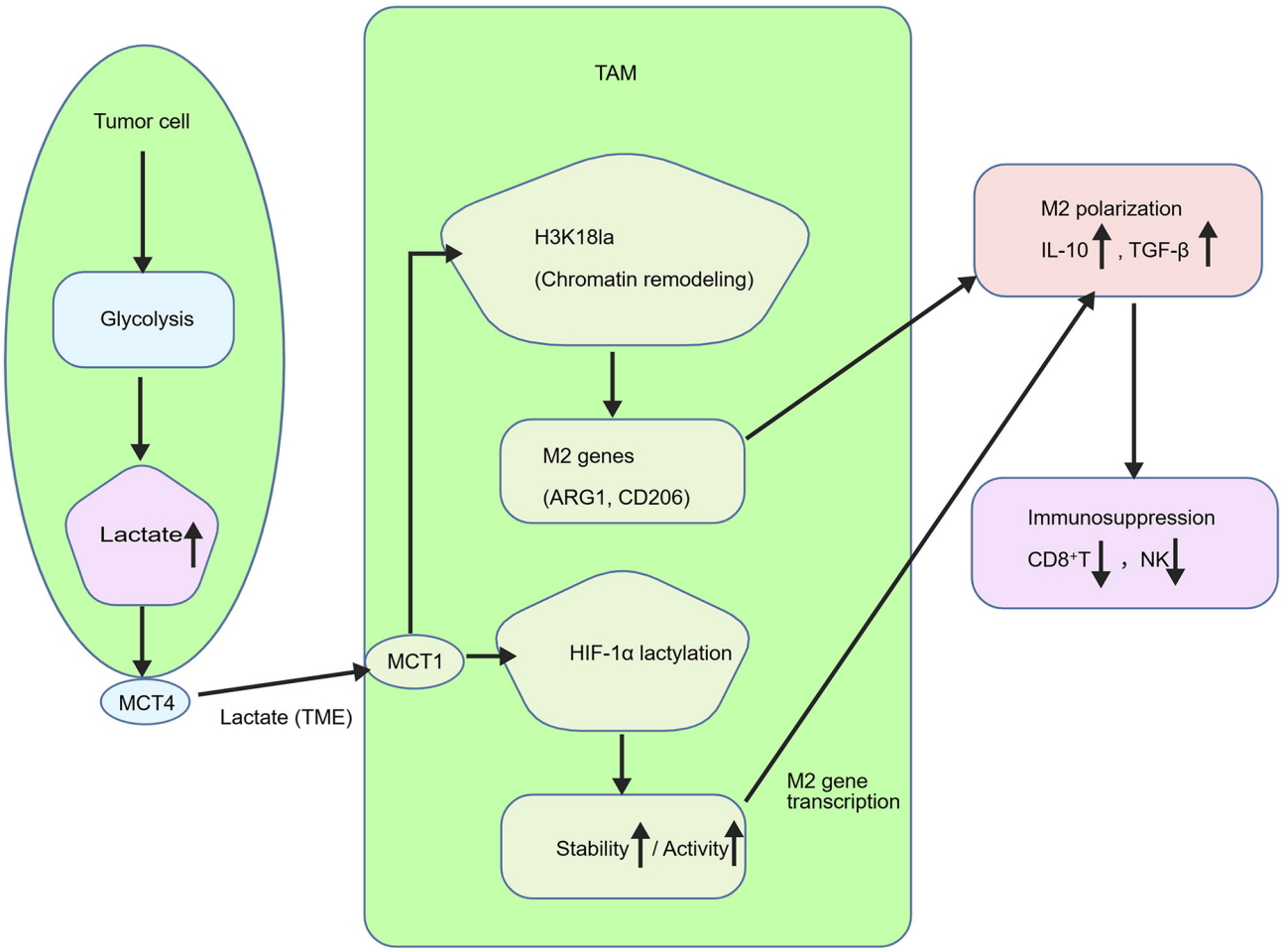


Figure 5. Lactate-driven M2 polarization of TAMs promotes immunosuppression in the tumor microenvironment. Mechanistic model illustrating lactate-mediated immunosuppression in cancer. Tumor cells exhibit enhanced glycolysis and secrete large amounts of lactate into the TME via MCT4. This exogenous lactate is imported into TAMs via MCT1, serving as a trigger for both epigenetic and post-translational modifications. On one hand, it induces histone H3K18la, promoting chromatin remodeling and the expression of M2-related genes *(ARG1, CD206)*. On the other hand, it drives HIF-1α lactylation, enhancing its stability and activity to further promote M2 gene transcription. The resulting M2 polarization leads to upregulated IL-10 and TGF-β secretion, which suppresses the cytotoxic activity of $CD8^+$ T cells and NK cells, culminating in profound immunosuppression and tumor progression. The figures were created with BioGDP (biogdp.com). TME, tumor microenvironment. TAM, tumor-associated macrophage; MCT1, monocarboxylate transporter 1; H3K18la, histone H3 lysine 18 lactylation; ARG1, arginase 1; HIF-1α, hypoxia-inducible factor 1-alpha; IL-10, interleukin-10; TGF-β, transforming growth factor-beta; $CD8^+$ T, CD8-positive T cells; NK, natural killer cells.

through MCT1, activating HIF-1α and inducing its lactylation, thereby promoting M1 polarisation (18,23). Furthermore, free fatty acids secreted by adipocytes can further increase lactate production and lactylation by enhancing macrophage aerobic glycolysis, forming a vicious metabolic-inflammatory cycle that exacerbates insulin resistance and metabolic disorders (39). In diabetic models, under hyperglycaemic conditions, histone lactylation participates in gene regulation and may contribute to ferroptosis in diabetic nephropathy. In patients with diabetic retinopathy, high glucose promotes histone lactylation, upregulates *ALKBH5* expression, and ultimately inhibits RNF123-mediated *PKM2* ubiquitination and degradation, thereby regulating glycolysis and lactate production in Müller glial cells and the release of inflammatory factors, leading to disease exacerbation (54,55) (Fig. 6).

In atherosclerosis models, macrophages are the major cellular components of atherosclerotic plaques and studies have reported that low-density lipoproteins can induce M2 polarisation, with the polarisation status directly affecting plaque stability and disease progression (21,53). Macrophage MCT4 deficiency leads to elevated H3K18la levels, thereby activating anti-inflammatory and repair-related gene expression and promoting macrophage polarisation toward a reparative phenotype, which reduces intraplaque inflammation, increases fibrous cap thickness, and enhances plaque stability (21). This finding reveals the critical role of the MCT4-H3K18la axis in atherosclerosis progression and provides new therapeutic targets for this disease.

Lactylation-regulated macrophage polarization is associated with the development and progression of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) (23,56). In NAFLD/NASH models, M1 polarization of hepatic macrophages (Kupffer cells) is the primary driver of hepatic inflammation and fibrosis. Studies have shown that *IL-25* inhibits the STAT3/Notch-1 pathway to negatively regulate the NF-κB/Jagged-1 axis, preventing M1 macrophage polarization (56). Studies found that hepatocytes under lipid overload conditions exhibit enhanced glycolysis and increased

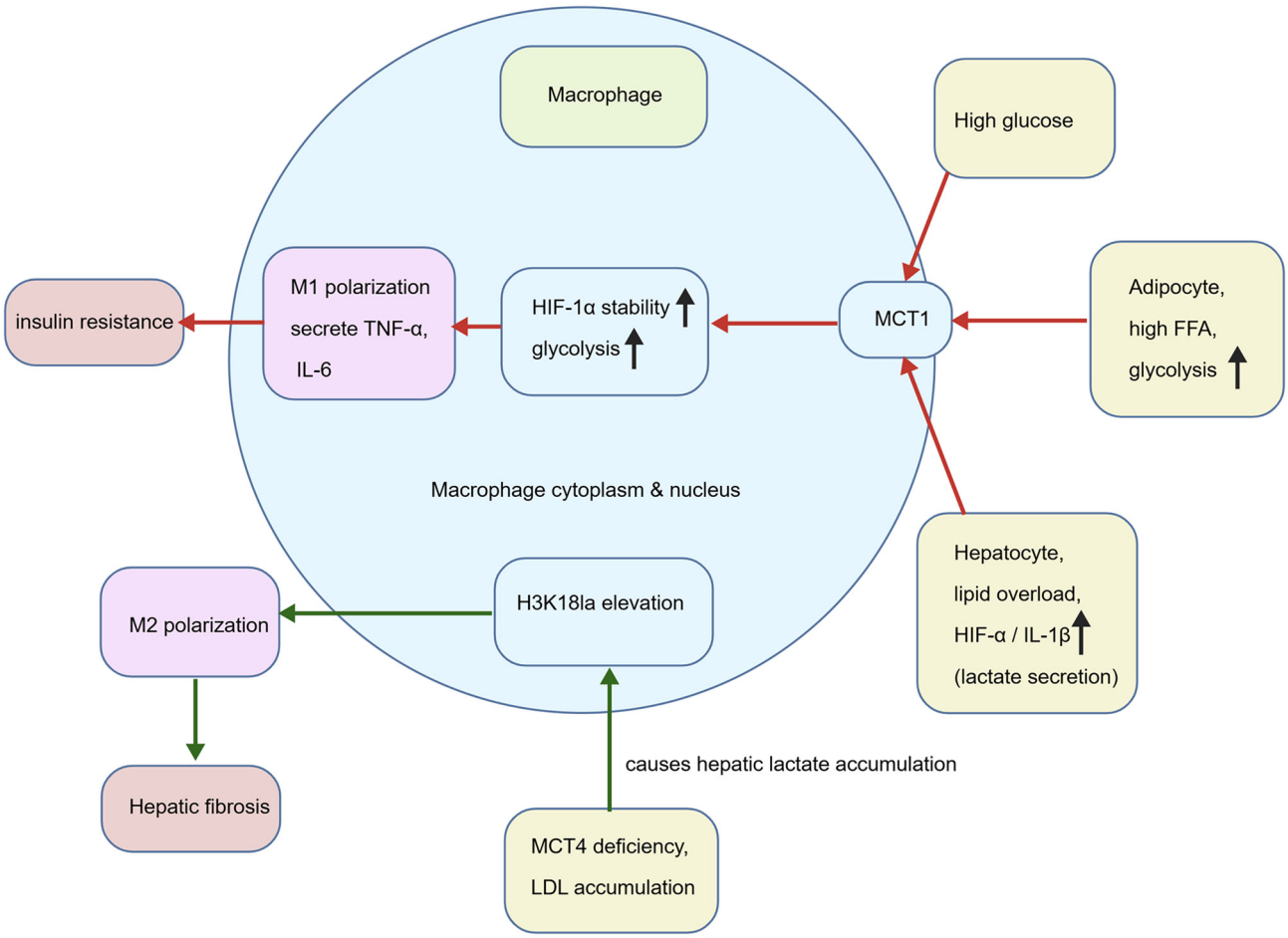


Figure 6. The MCT1-centered lactylation network in metabolic disorders and hepatic pathogenesis. Schematic depicting the pathological role of lactylation in metabolic diseases. Under high-glucose conditions, or in the presence of high FFAs and hepatocyte lipid overload, MCT1 expression on macrophages is upregulated. Increased lactate uptake via MCT1 stabilizes HIF-1α and enhances glycolysis, driving M1 polarization and the secretion of *TNF-α* and *IL-6*, which exacerbates systemic insulin resistance. Conversely, elevated H3K18la levels promote M2 polarization, which is associated with hepatic fibrosis in the context of MCT4 deficiency and LDL accumulation. This schematic highlights the context-dependent and dualistic roles of lactate signaling and histone lactylation in driving both inflammatory damage and fibrotic progression in liver and adipose tissues. The figures were created with BioGDP (biogdp.com). FFAs, free fatty acids; MCT1, monocarboxylate transporter 1; HIF-1, hypoxia-inducible factor 1-alpha; TNF-α, tumor necrosis factor-alpha; H3K18la, histone H3 lysine 18 lactylation; LDL, low-density lipoprotein.

lactate production, which can promote M1 polarization of Kupffer cells in a paracrine manner (23,56). Lactate promotes hepatic inflammation and fibrosis progression through activation of HIF-1α and its downstream target genes such as *IL-1β* (23,56). Inhibition of lactylation or blockade of HIF-1α signaling markedly attenuated M1 polarization of Kupffer cells and alleviated hepatic inflammation and fibrosis (56). These studies indicate that lactylation-regulated macrophage polarization is a critical link in the development of metabolic diseases, and targeting this process may represent a new strategy for treating metabolic diseases.

Roles in other pathological conditions. In addition to the major pathological conditions aforementioned, lactylation-regulated macrophage polarisation plays an important role in various other diseases, including neurodegenerative, autoimmune, and infectious diseases, as well as psoriasis (53,56,57). In neurodegenerative disease such as Alzheimer's disease (AD), abnormal activation and polarisation of microglia (resident macrophage-lineage immune cells of the central nervous system) are key factors in disease progression (12,56). Recent reviews have summarised the regulatory roles of histone lactylation in AD and other neurological diseases, covering key mechanisms, including H3K18la-driven neuroinflammation through NF-κB signalling and H4K12la involvement in microglial metabolic reprogramming (7,58,59). In AD animal models, multiple original studies have elucidated the molecular mechanisms underlying these effects: Pan *et al* (60) found that H4K12la promotes microglial activation and exacerbates inflammation through a 'glycolysis/H4K12la/PKM2' positive feedback loop; Wei *et al* (58) confirmed that H3K18la activates the NF-κB signalling pathway by binding to the *Rela* and *NF-κB1* promoters, increasing the release of SASP components such as IL-6 and IL-8, thereby accelerating AD pathological progression. These findings suggest that lactylation is an important epigenetic mechanism regulating the balance between M1- and M2-like microglial phenotypes in AD (56). Notably, microglia-specific knockout of SR promotes an anti-inflammatory phenotype by upregulating H3K18la expression and improving cognitive function in 5XFAD mice (60), suggesting that lactylation in AD

is bidirectional and context-dependent, with its ultimate effects depending on specific modification sites and pathological stages.

In autoimmune diseases, such as rheumatoid arthritis (RA), aberrant lactylation may provide a basis for exploring therapeutic strategies. For example, in RA, macrophages in synovial tissues are abnormally polarised toward the M1 phenotype, continuously releasing pro-inflammatory cytokines such as TNF-α and IL-6, leading to joint inflammation and destruction (61). Lactate levels in the synovial fluid of patients with RA are markedly elevated and positively associated with disease activity (61). Lactate is taken up by synovial macrophages through MCT1, inducing lactylation and activating NF-κB and MAPK signalling pathways, thereby promoting M1 polarisation. Notably, the pro-M1 effect of lactylation is primarily mediated through the MAPK pathway, and the modification site may differ from p65 K310 (16). These findings suggest that lactylation at different sites may exert distinct or even opposing effects on the NF-κB signalling (16,22), consistent with the p65 K310 lactylation-mediated negative feedback 'brake' mechanism, highlighting the site- and pathway-specific effects of lactylation (61).

In infectious diseases, pathogens can interfere with macrophage polarization phenotypes through regulation of host macrophage lactylation, thereby evading immune clearance (35). In addition to regulating macrophage polarization through lactylation, lactate can also suppress RLR-mediated type I interferon production by directly binding to the transmembrane domain of the MAVS protein, thereby weakening host antiviral innate immune responses (5). This mechanism has been confirmed to participate in immune evasion in various viral infections, including HBV and PRRSV. For example, in *Treponema pallidum* infection, the bacterial lipoprotein TpF1 induces *METTL14* expression in macrophages, which enhances NF-κB p65 lactylation, inhibits its activity, promotes macrophage M2 polarization, and facilitates bacterial survival and replication (35). Similarly, in viral infections such as HIV, viral proteins can enhance macrophage glycolysis and lactate production, inducing polarization toward the immunosuppressive M2 phenotype and thereby evading host immune responses. These findings not only deepen our understanding of pathogen immune evasion mechanisms but also provide potential targets for developing novel anti-infection strategies, such as restoring macrophage anti-pathogen activity through modulation of lactylation.

6. Summary and perspectives

As an emerging post-translational modification, lactylation has attracted widespread attention in recent years because of its role in regulating macrophage polarisation. Since the first report of histone lactylation in 2019, numerous studies have revealed the complex regulatory network by which this modification regulates macrophage polarisation through epigenetic mechanisms as well as its critical roles in various pathophysiological processes, including inflammation, tumours and metabolic diseases. The present review systematically summarised the discovery, regulatory mechanisms, and roles of lactylation in macrophage polarisation, as well as its pathophysiological significance.

Existing studies have shown that the dynamic balance of lactylation is jointly maintained by three classes of regulatory factors: 'writers', 'erasers' and 'readers'. Although HATs such as p300/CBP have been identified as potential 'writers', HDACs such as SIRT2 as potential 'erasers' and transcription factors such as PU.1 and PPARγ as potential 'readers', the specificity and mechanisms of action of a number of key regulatory factors remain to be further clarified. In particular, the identification of specific HLTs and delactylases is an important direction for future research, providing key clues for understanding the specific regulatory mechanisms of lactylation.

Notably, lactylation co-ordinately regulates macrophage polarisation at both the epigenetic and signal transduction levels through histone and non-histone modifications. Histone lactylation such as H3K18la primarily regulates polarisation-related gene expression by altering chromatin structure and transcription factor binding; non-histone lactylation such as that of NF-κB and HIF-1α primarily participates in signal transduction regulation by affecting their activity, stability, or localisation. Notably, most evidence regarding lactylation-driven macrophage polarisation is correlative observations or mechanistic inferences based on *in vitro* experiments (22), particularly in the field of non-histone lactylation, where studies often rely on screening candidate proteins in overexpression systems, with limited quantitative validation of endogenous substrates and *in vivo* genetic evidence.Future research should combine high-resolution mass spectrometry with specific antibodies to map the landscape of lactylation during macrophage polarisation, identify new modification targets, and elucidate their functions and regulatory mechanisms.

Mechanistic studies have revealed that lactylation-regulated macrophage polarisation serves a critical role in various physiological and pathological processes with potential clinical translational significance (7,14). Manipulating lactylation can regulate macrophage polarisation and improve disease phenotypes in tumors (12,13,57), inflammatory (17,22,42), and metabolic disease models (21,41). However, most research remains at a basic stage, with substantial challenges remaining for clinical translation (7,14,45). Notably, the function of lactylation is context-dependent. In *T. pallidum* infection, the lipoprotein TpF1 can induce *METTL14* expression in macrophages, thereby enhancing NF-κB p65 lactylation. Although the specific modification site remains to be identified, its functional effect differs markedly from the negative regulatory mechanism associated with p65 K310 lactylation induced by LPS. In this context, p65 lactylation is associated with sustained expression of pro-inflammatory cytokines and induces M1 polarisation, which is exploited by *T. pallidum* for immune evasion (35). This suggests that the functional interpretation of lactylation must consider specific pathogen infection types and pathological contexts and that therapeutic strategies targeting lactylation must also consider its differential effects across different disease backgrounds.

On this basis, the following key scientific questions and technical challenges merit attention in future research. First, the establishment of causality is the most urgent task. Most current studies have only reported correlations between lactylation levels and specific polarisation phenotypes, and causality requires more direct genetic evidence. Future research should systematically employ conditional gene knockouts (such

as conditional p300 knockout to block lactylation writing), CRISPR/Cas9-mediated site-specific mutations of lactylation sites (mutating specific lysine residues to arginine or glutamine to simulate delactylation or constitutive lactylation states) and optogenetic tools (enabling spatiotemporally controllable manipulation of lactylation levels) to validate the sufficiency and necessity of lactylation for macrophage polarisation under physiological conditions *in vivo*. Furthermore, developing experimental designs that distinguish between effects 'driven directly by lactylation' and those that are 'merely concomitant with metabolic reprogramming' will be a key step toward establishing causal mechanisms in this field.

Second, the source and metabolic regulation of lactylation substrates remain one of the most fundamental yet critical knowledge gaps. As the direct donor of lactylation, the intracellular source and metabolic flux of lactyl-CoA have yet to be systematically elucidated. Future work needs to develop highly sensitive lactyl-CoA detection methods (such as liquid chromatography-tandem mass spectrometry), systematically characterize its concentration dynamics in various cell types and metabolic states, simultaneously identify the specific enzymes responsible for its synthesis, and elucidate the complete metabolic flux of lactyl-CoA, thereby providing metabolic-level intervention nodes for targeting lactylation.

Identification and functional validation of 'writers', 'erasers' and 'readers' require continued efforts. Although p300/CBP and SIRT1/2 exhibit lactylation writing or erasing activities, their *in vitro* catalytic efficiencies, substrate preferences and physiological relevance all remain in significant question. Future research should utilize activity-based chemical probes and affinity purification-mass spectrometry approaches to systematically identify the enzymes that truly mediate lactylation writing and erasing from macrophage lysates; employ cryo-electron microscopy and X-ray crystallography to resolve the three-dimensional structures of lactylation-specific recognition domains, elucidating the molecular basis of 'reader' recognition of lactylated lysine; and develop specific small-molecule inhibitors or activators targeting different regulatory enzymes to dissect the functional contributions of each enzyme in specific pathological contexts. In addition, whether cell type- or tissue-specific lactylation regulatory enzyme systems exist deserves in-depth exploration.

Fourth, the synergistic network between histone and non-histone lactylation also requires more systematic analysis. Future research should use multi-omics integrative analysis (such as combining ChIP-seq, RNA-seq and lactylation proteomics) to simultaneously delineate the genome-wide distribution of histone lactylation and the global landscape of non-histone lactylation in the same cellular model and reveal the temporal dynamics of lactylation events during macrophage polarization through time-series experiments. Concurrently, the functional coupling between histone and non-histone lactylation in signaling pathways should be explored; for example, whether histone H3K18la synergizes with non-histone HIF-1α lactylation to drive M2-type gene expression programs.

Finally, the targetability of lactylation and translational medicine challenges should not be overlooked. Future translational research should focus on the following technical challenges: How to target lactylation without affecting structurally and functionally similar acetylation (given that they share some regulatory enzymes); this requires the development of lactylation-specific antibodies or small-molecule inhibitors; how to precisely deliver lactylation modulators to target tissues to reduce systemic side effects, nanoparticle drug carriers and antibody-drug conjugates are directions worth exploring; which lactylation sites can serve as biomarkers for disease diagnosis or therapeutic response prediction, this requires validation in large-scale clinical cohorts; and whether long-term intervention of lactylation affects the immune surveillance functions or tissue repair capabilities of normal macrophages, this requires systematic toxicological and pharmacodynamic evaluation in primate models.

In addition, a number of important scientific questions remain to be explored. For example, the mechanism by which lactylation coordinately regulate macrophage polarization with other metabolite modifications (such as succinylation and crotonylation); the specific regulatory mechanisms of macrophage lactylation in different tissue microenvironments; and the role of lactylation in macrophage lineage differentiation and maintenance of tissue-resident macrophage function. The development of technology such as single-cell sequencing, spatial metabolomics, and ultra-high-resolution imaging, are expected to reveal the spatiotemporal dynamics of lactylation-regulated macrophage polarization at the single-cell and subcellular levels, providing new perspectives for comprehensively understanding this complex regulatory network.

Finally, it should be noted that the NF-κB p65 lactylation effects reviewed present a consistent direction in the existing literature; that is, lactylation at the K310 site (including both enzymatic L-lactylation induced by LPS and non-enzymatic D-lactylation mediated by GLO2/SLG during immune activation) exerts inhibitory functions on NF-κB transcriptional activity. Under LPS stimulation, p65 K310 lactylation exerts a negative feedback braking function. Therefore, the core function of p65 K310 lactylation is an endogenous 'brake' mechanism of NF-κB signaling; its different effects in M1/M2 polarization are essentially downstream extensions of this 'brake' being triggered in different pathological contexts. When interpreting p65 lactylation function, the modification site (K310) and regulatory mechanisms should be clearly identified and it should be recognized that lactylation at the same site may produce differential downstream effects through regulating p65 interactions with other transcription factors under different cell types and stimulation conditions. However, it should be noted that lactylation effects at other sites (such as non-K310 sites) or mediated through other pathways (such as MAPK) may produce completely different functional outputs, as exemplified by the RA model described in *Roles in other pathological conditions* where lactylation promotes M1 polarization through MAPK; this further emphasizes the need to identify the modification site and signaling pathway specificity when interpreting lactylation functions.

In summary, although the importance of lactylation in macrophage polarization regulation has been preliminarily confirmed, numerous fundamental scientific and technical challenges remain between mechanistic understanding and clinical translation. It is reiterated that lactylation should be viewed as an important link in the complex regulatory network of macrophage

polarization, acting synergistically with cytokine signals, metabolic reprogramming, transcription factor networks and microenvironmental signals, rather than an isolated or dominant determinant. Future research requires sustained breakthroughs at multiple levels, including causality establishment, metabolic substrate tracing, regulatory enzyme identification, synergistic network dissection and targeted therapeutic strategy development. With continuous advances in chemical genetics, structural biology and multi-omics integrative approaches, there is reason to expect that these challenges will be progressively addressed, thereby laying a solid theoretical and experimental foundation for the clinical translation of lactylation.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant no. 32471419), National Key Clinical Specialty Project (grant no. 41792113) and Independent Innovation Project of General Hospital of Western Theater Command (grant no. 2024-YGLC-B03).

Availability of data and materials

Not applicable.

Authors' contributions

YW and QQH wrote the initial draft of the manuscript. XYW designed the key mechanistic diagrams and revised the figures. XYW, DXL, LY and QX contributed to the study design and final manuscript preparation. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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