DOI: 10.26599/FSHW.2026.9250951

Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

China Food Publishing Co.

Lactylation at the Crossroads of Metabolism and Immunity: Epigenetic Reprogramming in Allergic Inflammation

Ruiqi Zhang[1, 2], Qianwei Wang[1, 2], Jiao Xu[3, *], Huilian Che[1, 2, *]

[1]*College of Food Science and Nutritional Engineering, China Agricultural University, Beijing, PR China, 100083*

[2]*Key Laboratory of Food Nutrition and Health Evaluation Technology，State Administration for Market Regulation, Beijing, PR China, 100091*

[3]*Nutrition and food hygiene, China National Center for Food Safety Risk Assessment, Beijing, PR China, 100022*

ABSTRACT: Food allergies are increasingly prevalent worldwide, yet the underlying immunometabolic mechanisms remain incompletely elucidated. Lactylation, as an emerging post-translational modification, has recently been identified as a critical regulator of immunometabolic reprogramming and inflammatory responses in allergic diseases. This review synthesizes current evidence on the role of lactylation in modulating immune cell dynamics, including macrophage polarization, dendritic cell antigen presentation, T-cell differentiation, mast cell activation, and neutrophil function. By systematically integrating lactate metabolism with lactylation-mediated epigenetic regulation, this review highlights their central role in shaping allergic inflammation, thereby linking metabolism to immune regulation in food allergies. Despite the research progress, challenges remain in understanding the transient nature of lactylation and tissue-specific dynamics. Future research should combine spatial omics, lactylation-specific imaging, and physiologically relevant models to clarify its spatiotemporal regulation. Meanwhile, dietary strategies, microbiota-based interventions, and pharmacological regulation may provide practical approaches for modulating lactate metabolism and lactylation.

Keywords: Allergic inflammation; Lactylation; Lactate metabolism; Immunometabolism

1. Introduction

Food allergies, one of the most common forms of allergic diseases, are highly prevalent worldwide. Epidemiological studies estimate that approximately 5% of adults and 8% of children in developed countries are affected[1]. An allergic reaction is an abnormal response of the immune system to a harmless antigen, which primarily includes IgE-mediated and non-IgE-mediated reactions. IgE-mediated allergic reactions typically depend on IL-4-induced B-cell class switching and the production of IgE antibodies; allergens then cross-link with IgE bound on mast cells and basophils, triggering degranulation and release of histamine and cytokines[2,3]. In contrast, non-IgE-mediated reactions involve other immune pathways, such as Treg/Th17 imbalance that influences gut immune tolerance, and typically present with delayed symptoms, including gastrointestinal disturbances and skin inflammation[4]. In contrast, non-IgE-mediated reactions involve other

***Corresponding author**
Jiao Xu (xujiao@cfsa.net.cn), Huilian Che(chehuilian@cau.edu.cn).

Received 26 June 2025
Received in revised from 22 September 2025
Accepted 10 October 2025

immune pathways, such as Treg/Th17 imbalance that influences gut immune tolerance, and typically present with delayed symptoms, including gastrointestinal disturbances and skin inflammation.

Lactylation is a novel post-translational modification that has been identified in recent years, and it involves the addition of lactate, a by-product of cellular metabolism, to lysine residues located in proteins through an enzymatic or non-enzymatic process, ultimately altering the function of the protein. In earlier studies, lactate was regarded as a metabolic waste product, produced mainly through anaerobic glucose metabolism, and viewed as a temporary energy source for cells with potentially harmful effects[5]. However, Otto Warburg discovered the Warburg effect that cancer cells can also produce significant amounts of lactate through glycolysis under aerobic conditions. The discovery of this effect prompted researchers to reconsider the role of lactate in cellular metabolism[6]. Furthermore, the Warburg effect occurs not only in cancer cells, but also in intensely proliferating cells and activated immune cells characterized by a high energy demand[7]. Zhang et al.[8] in 2019 discovered and demonstrated that lactate modifies histones through lactylation, which in turn modulates gene expression and cellular function. They also confirmed that lactate, in addition to serving as a metabolic intermediate, plays a critical role in the regulation of transcriptional processes within cells. Based on this insight, lactylation may influence immune metabolic reprogramming by modulating immune cell function. Recent studies have shown that lactylation targets a variety of proteins, including histones and key metabolic enzymes, thereby influencing immune cell activation, differentiation, and inflammatory responses through metabolic reprogramming[9,10].

As the significance of metabolic pathways, such as glycolysis and lactate production in allergic reactions is gradually recognized. Lactylation, as a novel immunomodulatory mechanism, potentially plays an important role in modulating immune responses in food allergies and other allergies. The discovery of lactylation has established lactate as a key regulator of cellular metabolism, gene expression, and immune regulation. In particular, lactate regulates immune cell function and influences the intensity and type of immune response through lactylation during the allergic processes and the cellular metabolism reprogram. This phenomenon has broadened researchers' understanding of metabolites while providing new insights[11].

The aim of this review is to provide an update on the research progress of lactylation in immunomodulation and allergic reactions. This review will also explore the potential association of lactylation with the analysis of immune cells and mechanisms of action involved in food allergy. By synthesizing recent research advances, we hope to elucidate the regulatory role of lactylation in allergic responses, clarify its function in IgE-mediated and non-IgE-mediated immune responses, and explore its potential application in immunotherapy. The review enriches the practical approach in this field of study and provides new perspectives and feasibility for future research.

2. Lactate Metabolism and Its Epigenetic and Immunological Implications

2.1 Formation of L-Lactate and D-Lactate

Lactic acid, as the end product of the glycolytic pathway, exists in two optical isomers: L-lactate (L+) and D-lactate (D-). L-lactate is primarily generated from pyruvate through the enzymatic action of lactate

dehydrogenase (LDH), particularly under conditions where oxygen availability is limited and mitochondrial oxidative phosphorylation is suppressed. As a result, during intense skeletal muscle contraction or under anaerobic and hypoxic conditions (e.g., strenuous exercise), the rate of L-lactate production significantly increases due to the heightened rate of glycolysis and the limited oxidation of pyruvate, resulting in its rapid accumulation in large amounts. Notably, following high-intensity exercise, plasma L-lactate concentrations can rise swiftly from approximately 1.0 mM in the resting state to over 15.0 mM[12]. In contrast to L-lactate, D-lactate arises at much lower concentrations in the human body and is closely linked to methylglyoxal (MGO) detoxification. Elevated D-lactate levels are often associated with metabolic acidosis and redox imbalance, thereby serving as an indirect indicator of metabolic health [13,14].

2.2 L-Lactate-Associated Enzymes and Their Roles in Metabolic and Epigenetic Regulation

Along with being a metabolic step, L-lactate also contributes to epigenetic control through lactylation changes, among other mechanisms. Multiple "writer" proteins have been identified as being involved in the lactylation process. Notably, p300 functions not only as a histone acetyltransferase (HAT) to mediate acetylation modifications but also serves as a writer protein that participates in lactylation modifications. Lactyl coenzyme A has been shown to bind specifically to p300 and its cognate protein CBP to promote histone lactylation[15]. Moreover, other validated writer proteins include AARS1, which responds to changes in lactate levels by translocating from the cytoplasm to the nucleus, thereby linking metabolic states to epigenetic regulation[16]. In contrast, HDACs 1–3 and SIRTs function as delactylases, removing lactyl groups from proteins within the cell[17,18].

Lactylation modifications and acetylation may either compete or synergize at specific sites to regulate chromatin state and gene transcription[19]. For instance, a study by Rho et.al[20] found that there is competition between lactylation and acetylation at the histone H3K18 sites during the activation of hepatic stellate cells and the progression of hepatic fibrosis. Lactylation promotes the expression of pro-inflammatory genes, while acetylation may counteract this effect. However, the study's conclusions are primarily based on a hepatocellular carcinoma cell model, where metabolic abnormalities may arise from the competitive advantage of lactylation modifications, exacerbated by lactate overaccumulation due to the Warburg effect. Immune cells may be more dependent on microenvironmental signals, indicating that further validation is necessary to determine the relevance of these findings. It is important to note that lactylation modifications play a synergistic role with other post-translational modifications, such as acetylation, in metabolic regulation and immune responses. Zhou et al. [21] pointed out that lactylation may influence macrophage function and gene expression through overlapping or synergistic effects with acetylation and propionylation. Although related histone modifications may share overlapping modification sites, they serve distinct functions and collectively contribute to a complex epigenetic regulatory network.

Furthermore, lactylation is not only regulated by lactate levels but is also catalyzed by specific enzymes. Recent study has revealed that acetyl-coenzyme A synthetase 2 (ACSS2) functions as a bona fide lactyl-CoA synthetase, converting lactate into lactyl-CoA. Epidermal Growth Factor Receptor (EGFR) activation induces

extracellular signal-regulated kinase (ERK)-mediated phosphorylation of ACSS2 at Ser267, which facilitates its nuclear translocation and binding to lysine acetyltransferase 2A (KAT2A). The ACSS2–KAT2A complex then acts as a lactyltransferase, driving histone H3 lactylation at specific lysine residues[22]. The mechanism explains why lactylation is selectively regulated in certain cell types rather than being based purely on lactate concentrations. Although the discovery of the ACSS2-KAT2A complex expands the regulatory model of lactylation, questions remain. The dynamic regulation of lactylation modifications and their physiopathological roles can be further explored in the future, potentially providing a new theoretical foundation for immunotherapy and metabolic intervention strategies.

2.3 D-Lactate Generation and Its Role in Protein D-Lactylation

In contrast to L-lactate synthesized by lactate dehydrogenase (LDH), D-lactate in humans is mainly generated via the glyoxalase system, a detoxification pathway targeting methylglyoxal (MGO). MGO, a reactive three-carbon aldehyde generated as a byproduct of glycolysis, tends to accumulate under hyperglycemic conditions. This molecule spontaneously reacts with proteins and nucleic acids through non-enzymatic glycation, resulting in the formation of advanced glycation end products (AGEs) that contribute to glycotoxicity.

The glyoxalase system mitigates this damage through a series of coordinated enzymatic steps. Glyoxalase I (GLO1) first catalyzes the isomerization of a hemithioacetal adduct, which is spontaneously formed between methylglyoxal (MGO) and glutathione (GSH), into S-D-lactoyl-glutathione (LGSH). Subsequently, glyoxalase II (GLO2) hydrolyzes LGSH to release D-lactate while regenerating GSH. Emerging evidence suggests that S-D-lactoyl-glutathione (LGSH) can also act as a donor of D-lactyl groups, which non-enzymatically modify lysine residues on proteins, leading to D-lactylation and potentially affecting protein function[23,24]. This pathway not only neutralizes MGO but also maintains cellular redox homeostasis by recycling GSH, thereby linking detoxification to metabolic balance. Thus, the glyoxalase system serves as a crucial metabolic defense mechanism against MGO-induced cytotoxicity, with D-lactate as the final product of neutralization (Figure 1). It should be noted that while emerging studies have proposed D-lactylation through the glyoxalase pathway, most current evidence supports L-lactate–derived lactyl-CoA as the predominant driver of protein lactylation, with the role of D-lactylation remaining preliminary and requiring further validation.

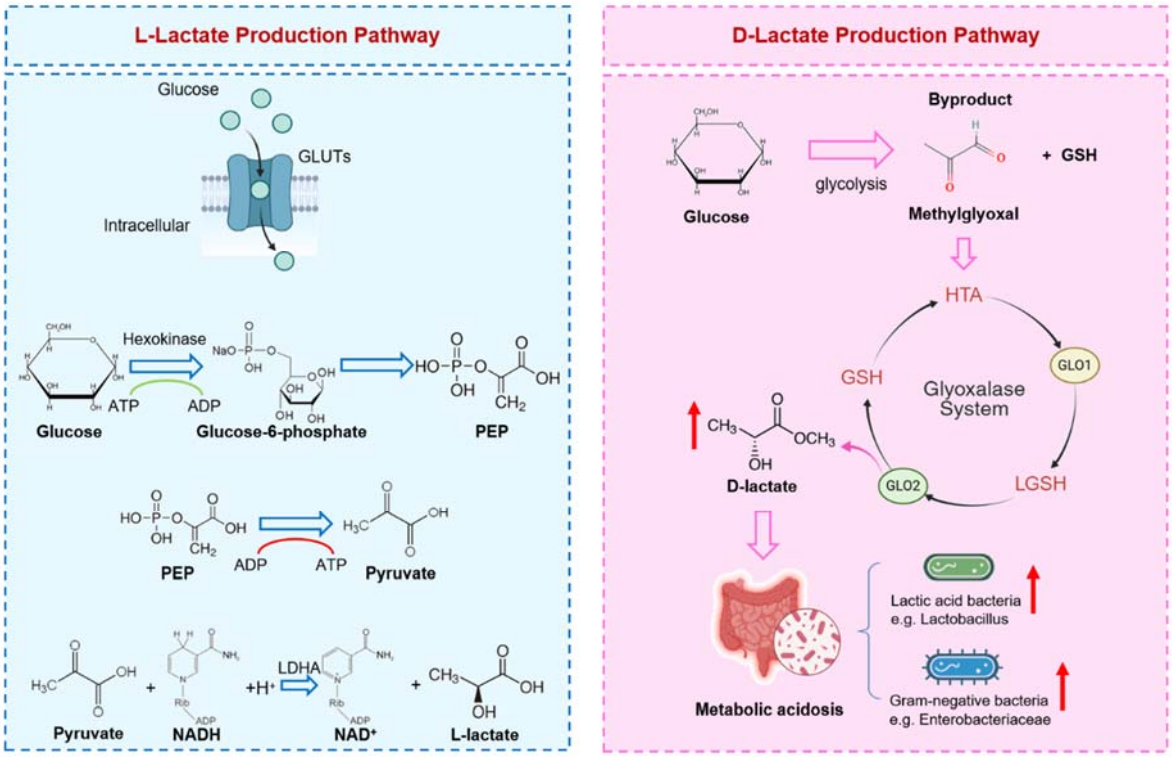

Figure 1 Pathways of Production for Different Types of Lactic Acid

3. Effect of Lactate on Allergic Reactions

Far from being a mere metabolic waste product, lactate serves as a crucial end product of glycolysis. It plays a central regulatory role in allergic diseases through its dynamic accumulation in the immune microenvironment and its bidirectional interactions with inflammatory signals. It has been shown that lactate levels are elevated in localized inflammatory tissues in diseases with a predominantly Th2 immune response, such as bronchial asthma and atopic dermatitis. Increased lactate affects macrophage polarization, dendritic cell antigen-presenting function, T-cell differentiation, and secretion of inflammatory factors by associated effector cells. These processes further modulate the intensity and type of immune response.

3.1 Macrophages

Macrophages are essential components of the immunoregulatory network and can be polarized into two distinct phenotypes: M1 (pro-inflammatory) and M2 (anti-inflammatory). M1 macrophages rely on glycolysis as the preferred source of energy, and M2 macrophages support its function mainly through oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO). Accumulated lactate, a major byproduct of glycolysis, reinforces macrophage polarization toward the M1 phenotype by amplifying pro-inflammatory signaling, thereby linking glycolytic metabolism to inflammatory activation. It is worth noting that inhibition of glycolysis interferes with macrophage polarization toward the M1 phenotype, which has strong pro-inflammatory properties essential for pathogen defense but can also cause tissue damage and chronic inflammation if excessively activated[25,26].

Additionally, the lactate-rich environment is critical in regulating macrophage polarization. It has been observed that macrophages in the lungs undergo considerable metabolic reprogramming in the context of

OVA-induced asthma. Notably, elevated levels of HIF-1α were predominantly identified in F4/80-positive macrophages within the lungs of mice subjected to OVA exposure, alongside a significant increase in the expression of key glycolytic enzymes such as HXKI, HXKII, LDH, and PFK-1. This suggests that lung macrophages undergo substantial glycolytic reprogramming during asthma, characterized by heightened lactate production, which is closely associated with airway inflammation[27]. Significantly, lactate accumulation not only drives a shift toward glycolysis but also reprograms macrophage function by enhancing pro-inflammatory cytokine production and sustaining chronic inflammatory signaling, thereby exacerbating associated allergic diseases.

3.2 Dendritic Cell

Lactate not only participates in the regulation of macrophage polarisation but also strongly modulates the function and metabolism of antigen-presenting cells (APCs) like dendritic cells (DCs). In allergic responses, environmental antigens are sampled by DCs. By processing and presenting these antigens, DCs play a pivotal role in initiating the adaptive immune response, including Th2 cell differentiation and IgE production. Thus, DCs serve as a critical initiator of allergic inflammation. Wang et al.[28] discovered that lactate modulates the antigen-presenting capacity of DCs through the lysosomal pathway. When the HK2 pathway is inhibited, lactate production decreases, leading to the activation of the lysosomal pathway, which promotes CHOP gene expression and enhances DC function, thereby impacting the immune response. However, lactate regulates the metabolic state of DCs through the HIF-1α-mediated NDUFA4L2 signaling pathway, which reduces mitochondrial reactive oxygen species (mtROS) production, consequently limiting the pro-inflammatory response of DCs[29]. Moreover, high concentrations of lactate can suppress antigen presentation by downregulating MHC-II expression on DCs and other immune cells via GPR81, and further inhibit T cell activation through HIF-1α–NDUFA4L2 signaling, thereby enhancing IL-23/IL-17-mediated inflammation[30]. This bidirectional regulation reflects the dose-dependent nature of lactate signaling. At low concentrations, lactate enhances antigen presentation and immune activation, while at high concentrations, it promotes immunosuppression and inflammation through metabolic and epigenetic reprogramming.

3.3 T cell

Studies have shown that lactate can modulate inflammatory responses by activating signaling pathways related to immune cell metabolism and function via GPR81[31]. For instance, the activation of GPR81 has been shown to alter the metabolic state of DCs, impacting their antigen-presenting function and promoting Th2 cell differentiation, which is closely associated with the development of allergic reactions[30]. Interestingly, the effects of lactate on immunomodulation show a significant dose-dependent relationship; however, the underlying mechanism has not been fully elucidated. Kenison et al.[32] noted that low doses of lactate promote the differentiation of T regulatory cells, thereby maintaining cellular tolerance through PD-L1/PD-L2 signaling.

In general, lactate-mediated reprogramming of DCs and T cells can either enhance or decrease the expression of allergic reactions[33,34]. Lactylation in DCs is more inclined to influence antigen presentation

functions compared to eosinophils and mast cells, which primarily depend on glycolysis to enhance pro-inflammatory effects. The acidic environment influences inflammation through dual pathways. It is worth noting that tissue acidification in the inflammatory microenvironment affects immune cell metabolism through pH sensing mechanisms, and may also regulate immune cell function through post-translational modifications of proteins by lactate[35].

3.4 Mast cells and Basophils

Mast cells and basophils are critical effector cells in allergic responses, which can be activated through two primary receptor pathways: the classical IgE-mediated pathway via the high-affinity IgE receptor (FcεRI) and the immunoglobulin-independent pathway via receptors such as MRGPRX2. These distinct pathways converge on a common energetic demand. To fuel rapid proliferation and degranulation during inflammation, these cells enhance glycolysis, leading to lactate accumulation in the microenvironment[7,36,37]. This metabolic reprogramming is tightly linked to inflammatory processes, further highlighting lactate as a key modulator of mast cell function. Elevated lactate can, in turn, modulate immune responses by activating G protein-coupled receptors on the cell surface[5]. The functional outcome of lactate signaling, however, is pathway-dependent. For example, in the context of MRGPRX2 activation, lactate suppresses the release of pro-inflammatory cytokines such as CCL2 and IL-8, highlighting a unique regulatory role specific to this pathway[38].

3.5 Eosinophil

Lactate may influence the inflammatory process by modulating eosinophil function, such as enhanced cytokine secretion and chemotaxis. Unlike basophils, eosinophils primarily infiltrate tissues during chronic allergic inflammation (e.g., eosinophilic esophagitis, eosinophilic gastroenteritis) or parasitic infections, conditions that often exist in a state of hypoxia and active glycolysis, leading to locally elevated levels of lactate. A recent study by Lv et al.[39] suggests that eosinophils upregulate glycolysis upon activation to compensate for the inhibition of reactive oxygen species (ROS) production and the decrease in TCA cycle intermediates. IL-3, IL-5, and granulocyte–macrophage colony-stimulating factor (GM-CSF) also regulate glycolysis and mitochondrial respiration via the STAT5/PI3K/Akt axis to maintain eosinophil activation and maturation[37] (Figure 2).

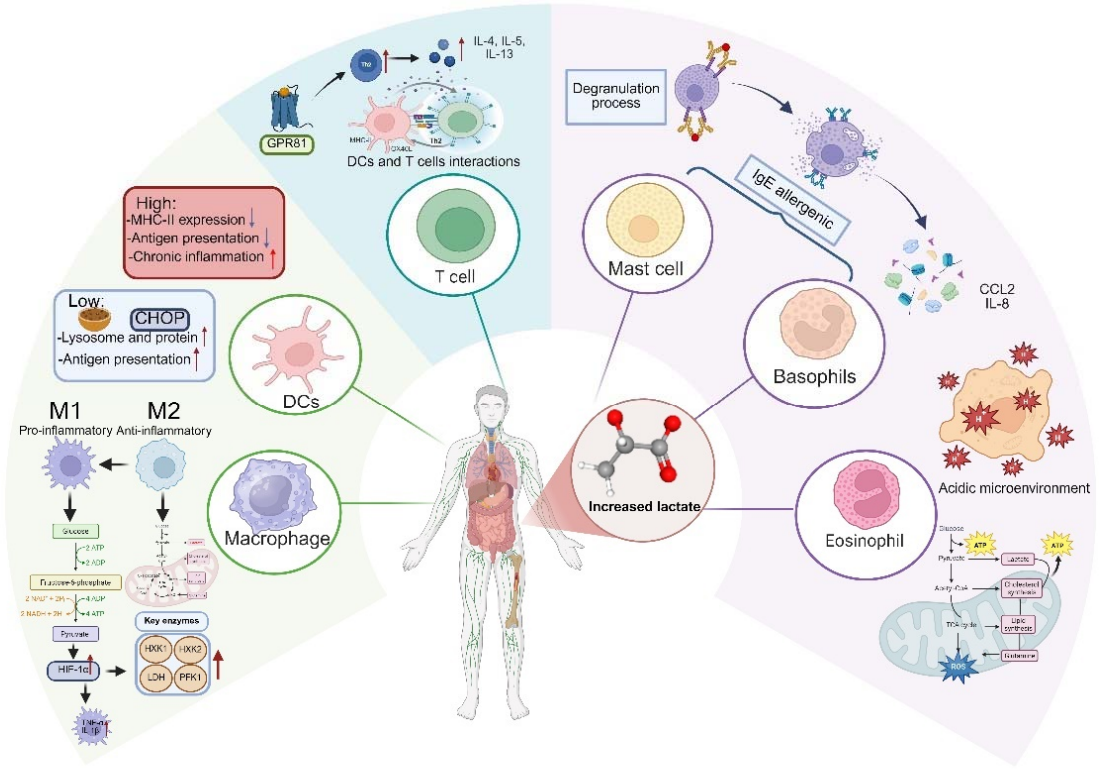

Figure 2 Lactate-Mediated Modulation of Immune Cells in Allergic Inflammation

4. Lactylation and remodeling of immune cell metabolic networks

The process of metabolic reprogramming is not only reflected in influencing cellular processes through the metabolite level, but also involves the regulation of multiple mechanisms such as epigenetics and post-translational modifications. For instance, upregulation of HK2, a crucial enzyme involved in glycolysis, enhances glycolytic flux and lactate production, which in turn promotes histone lactylation, thereby reinforcing metabolic reprogramming and inflammatory responses[40]. Furthermore, lactylation modifications regulate LDH, potentially affecting the dynamic equilibrium of lactate within the local microenvironment[41]. These observations indicate that lactylation serves not only as a terminal outcome of lactate metabolism but also as a pivotal link between metabolic dysfunction and epigenetic dysregulation. Lactylation modifications can utilize lactate and its derivatives as signaling molecules to modulate immune cell function, remodel metabolic pathways to meet the demands of inflammation, and influence the intensity and duration of allergic reactions. In this section, it will focus on the role of protein lactylation modifications on immune cell differentiation and activation.

4.1 Macrophage Polarization Regulated by Lactylation

In M1 macrophages, the process of lactylation markedly enhances the transcription of genes associated with inflammation, including TNF-α and IL-1β. Lactylation not only affects the pro-inflammatory response but also plays a crucial role in regulating M2 macrophage function. As previously demonstrated by Kawai and Taro[42], the Toll-like receptor (TLR) on macrophages triggers early inflammation and promotes M1

polarization primarily through NF-κB signaling. However,a recent study has identified that downstream regulatory mechanisms involving phosphatidylinositol 3-kinase adaptor protein 1 (BCAP) may inhibit forkhead box protein O1 (FOXO1) and glycogen synthase kinase 3β (GSK3β) during prolonged exposure to metabolic signals, such as lactate[43]. This exposure promotes histone lactylation, specifically at lysine 18 on histone H3 (H3K18la), in the promoter regions of reparative genes, including Arg1, Retnla, and Mrc1. These epigenetic modifications enhance chromatin accessibility and transcriptional activation of reparative gene programs, thereby facilitating the transition of macrophages from an M1 to M2 phenotype at a later stage in the immune response. These findings align with the results of Zhou et al. [21], which suggest that this metabolic shift, rather than conventional TLR signaling, could contribute to macrophage polarization towards the M2 phenotype by inhibiting TLR4/NF-κB signaling, particularly under conditions of higher lactate levels. These changes enhance the expression of anti-inflammatory genes, such as Arg1 and IL-10. M2 macrophages play a significant role in the context of allergic inflammation, as they are capable of modulating Th2 cell-mediated immune responses and influencing IgE-dependent allergic reactions[44]. Research conducted by Banafea et al.[45] demonstrated that M2 macrophages were shown to exacerbate allergic inflammatory responses by promoting the release of cytokines from Th2 cells, eosinophils, and mast cells. Consistently, Su et al. [46] reported that in G6PT-deficient macrophages, excessive lactate accumulation elevated H3K18la levels, which enhanced ALKBH5 expression and suppressed NLRP3 inflammasome activation through m6A demethylation of NLRP3 mRNA. Additionally, recent findings revealed that SIRT2 suppresses macrophage chemotaxis by removing lactylation at histone H4K8 (H4K8la), highlighting a distinct lactylation-dependent mechanism through which SIRT2 modulates macrophage immune phenotype following infection[47]. Further investigations have indicated that lactate-driven histone lactylation of histone H3 at lysine 18 (H3K18la) inhibits Toll-like receptor 4 (TLR4)-mediated pro-inflammatory signaling pathways, thereby facilitating macrophage polarization toward the M2 phenotype[48]. This shift also has implications for the pathological processes underlying airway inflammation, allergic asthma, and food allergies[27].

Collectively, these findings demonstrate that lactylation acts as a pivotal epigenetic mechanism linking lactate metabolism to macrophage polarization, thereby shaping inflammatory and allergic outcomes and highlighting macrophages as a promising therapeutic target in allergic inflammation through lactylation-mediated regulation of their dynamic transition between M1 and M2 phenotypes (Figure 3).

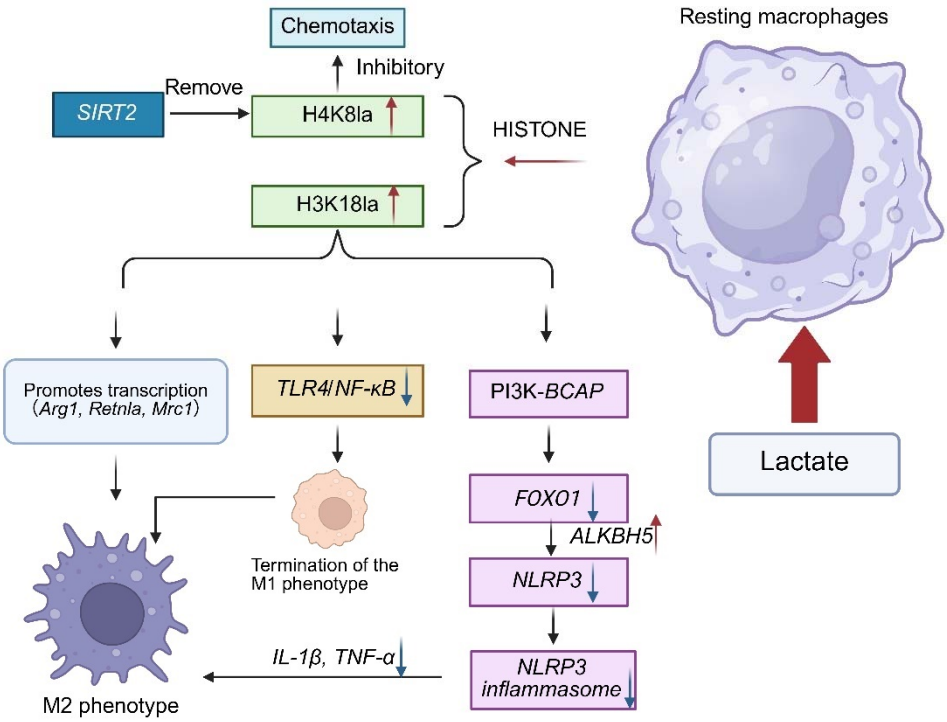

Figure 3 Regulation of Macrophage Polarization by Lactate-Driven Histone Lactylation

4.2 T Cell Differentiation and Immune Fate Shaped by Lactylation

A study by Sun et al.[49] demonstrated that the lactylation of H3K18la in T cells modulates immune responses by suppressing CD39 promoter activity and downregulating CCR8 expression. This modulation affects T cell activation and cytokine signaling in inflammatory environments. Notably, there is a strong correlation between T cell activation and metabolism, suggesting that metabolic changes are not only the result of activation but may also determine T cell types. For example, CD4+ effector memory T cells rely on glycolysis to evade apoptosis under hypoxic conditions[50]. T cells may experience metabolic changes mediated by monocarboxylate transporters (MCTs) that affect their capacity to proliferate and secrete cytokines after DCs complete antigen presentation. These modifications can lead to T cell dysfunction, which may exacerbate Th2-mediated inflammatory responses in a chronically inflamed environment[51,52]. Lactylation at lysine 72 (K72) of MOESIN enhances TGF-β-induced Foxp3 expression, thereby promoting Treg differentiation and modulating immune responses[53]. Taken together, these findings suggest that lactylation exerts a decisive influence on T cell fate by tipping the balance between pro-inflammatory Th2 responses and immunosuppressive Treg differentiation, thereby shaping allergic outcomes.

4.3 Mast Cell Activation and IL-33 Pathways under Lactylation Control

Research indicates that increased concentrations of lactate within the allergic microenvironment may directly affect the activation of inflammatory signaling pathways via histone lactylation modifications. IL-33 is pivotal in IgE-mediated hypersensitivity reactions, with its expression levels markedly heightened in individuals diagnosed with asthma and atopic dermatitis[54]. This upregulation is causally linked to lactate-driven histone lactylation, which remodels chromatin at the IL-33 promoter and directly enhances its

transcriptional activation. In turn, IL-33 enhances the expression of key glycolytic enzymes, specifically HK2 and PFKFB3, through the activation of the PI3K/AKT/mTOR signaling pathway via its interaction with the ST2 receptor (IL1RL1)[55,56]. Furthermore, PFKFB3 exerts direct regulatory effects on PFK-1, a rate-limiting enzyme in the glycolytic pathway, thereby facilitating glycolytic metabolism and increasing ATP production[57]. This metabolic reprogramming has been linked to increased secretion of pro-inflammatory cytokines, including IL-6 and TNF-α, in mast cells. Both IL-6 and TNF-α are well-recognized mediators of airway inflammation and tissue remodeling in allergic diseases. Lactate-driven histone lactylation of IL-33 forms a feed-forward loop that enhances mast cell activation, thereby linking metabolic reprogramming to allergic diseases such as asthma and atopic dermatitis.

4.4 Regulation of Neutrophil Function by Lactylation

In addition, researchers have found that lactylation also affects neutrophils in the latest studies. Zhu et al. [58] discovered that lactate enhances the release of neutrophil extracellular traps (NETs) by promoting the lactylation of HMGB1 (high-mobility group protein B1). The overaccumulation of NETs has been suggested as a significant driving factor in various inflammatory diseases. Furthermore, allergy reactions may be influenced by the positive feedback environment of ROS and lactylation at the H3K18 locus. Lactate-induced H3K18 lactylation enhances the production of ROS, which, in turn, facilitates the recruitment of neutrophils to sites of inflammation. This indicates the presence of a pro-inflammatory lactate–lactylation–ROS axis in innate immunity[59].Recent studies using zebrafish models have further confirmed this mechanism, demonstrating that lactate-induced H3K18 lactylation promotes the transcription of the duox gene, thereby enhancing ROS production. This amplification loop further recruits neutrophils and aggravates inflammatory responses, while interventions such as metformin treatment can reduce H3K18 lactylation and ROS levels, alleviating neutrophil-mediated inflammation[60].These findings suggest that neutrophils may act as key responders to lactate metabolism and lactylation regulation, driving cellular inflammatory responses and epigenetic modulation, thereby highlighting the potential therapeutic value of lactate-mediated histone modifications in innate immune diseases. This evidence link metabolism to innate immune-driven inflammation by connecting lactate, lactylation and ROS.

Table 1 Effects of Lactylation on Immune Cell Metabolism and Function

Immune cell type	Functional regulation	Metabolic pathways or mechanisms	Effects on allergic reactions
Macrophages	Polarization between pro-inflammatory M1 and anti-inflammatory M2 phenotypes; Cytokine production; Regulating autophagy.	M1: Enhanced glycolysis, lactate accumulation, and histone lactylation to promote inflammatory gene expression; M2: FAO and OXPHOS; high-lactate environment promotes polarization via inhibition of TLR4/NF-κB and activation of PI3K-BCAP-FOXO1 axis.	High lactate promotes macrophage polarization toward the M2[21]; Increased Hif-1α, HXKI-HXKIII, LDH, PFK1 expression[27]; Reduce allergic airway inflammation through TLR4 signaling.
Mast cell	Regulation of rapid proliferation and degranulation; Cytokine production	Lactate activates surface G protein-coupled receptors, modulating cytokine release (e.g., IL-6, TNF-α, CCL2, IL-8) and mast cell receptor	Modulates cytokine release and mast cell activation in an environment-dependent manner, exerting pro- inflammatory or

		signaling pathways, including FcεRI and MRGPRX2.	anti-inflammatory effects based on receptor pathways[5].
T cell	Regulation of proliferation, cytokine secretion and T cell types	Glycolysis supports $CD4^+$ effector memory T cells under hypoxia[50]; MOESIN at site 72 in T cells enhances TGF-β-induced Foxp3 expression, promoting Treg differentiation and immunosuppressive function.	May promote Th2 inflammation in chronic settings or enhance immune regulation via Treg differentiation, depending on the context[51–53].
Neutrophil	Lactylation promotes NETs release and enhances pro-inflammatory signaling	HMGB1 lactylation; lactate-induced H3K18 lactylation; lactate–lactylation–ROS axis	Exacerbated by enhancing the formation of NETs and facilitating their recruitment to sites of inflammation[58].

5. Future Perspectives on Lactylation in Allergic Responses

Emerging evidence highlights the critical regulatory role of lactylation, a novel post-translational modification, in allergic responses through modulating immunometabolic reprogramming and inflammatory cascades. Despite its potential significance, the mechanistic understanding of lactylation dynamics in allergy pathogenesis remains fragmented, underscoring the need for systematic investigations to elucidate its pathophysiological contributions and therapeutic implications.

Exercise-induced anaphylaxis (EIA) provides a compelling model for studying lactylation-mediated immunoregulation. Vigorous physical activity induces systemic lactate accumulation, which may facilitate protein lactylation in immune cells through non-enzymatic glycation mechanisms. Contemporary studies reveal significant elevation of lactylated proteins in hepatic and musculoskeletal tissues during the 24-hour recovery phase following high-intensity interval training (HIIT), suggesting its involvement in immunometabolic adaptations through glycolytic flux modulation and TCA cycle regulation[61,62]. Moreover, recent finding in the field of exercise immunology indicate that lactate functions as a central regulator of immune and inflammatory responses, with its effects varying depending on the physiological and pathological context[63]. Although direct evidence in allergic conditions is still limited, these insights support the plausibility that exercise-induced lactate accumulation may drive immune lactylation and influence allergic responses. However, methodological challenges persist due to the transient nature of lactylation events, interindividual variability in lactate metabolism, and dynamic immune fluctuations during exercise stress. Current limitations in standardized experimental models and specific detection methodologies further constrain progress in this field.

Recent advances in spatial omics technologies offer promising solutions to these challenges. As demonstrated by Yan et al.[64], the tissue-specific patterning and temporal dynamics of lactylation necessitate multimodal approaches. Future research directions should focus on developing physiologically relevant models, including exercise-mimetic in vivo systems and organoid platforms replicating hyperlactatemic microenvironments. Integration of single-cell spatial transcriptomics with matrix-assisted laser desorption/ionization (MALDI) mass spectrometry imaging could enable real-time tracking of lactylation patterns at cellular resolution, potentially unraveling its spatiotemporal regulation in allergic pathophysiology.

Beyond the directions highlighted in exercise immunology, dietary and microbiota-based interventions also hold significant promise in regulating lactate metabolism and lactylation during allergic responses. For

instance, functional foods rich in polyphenols or dietary fibers can improve gut microbiota composition and promote the production of short-chain fatty acids (SCFAs), thereby indirectly influencing energy metabolism pathways—including those involving lactate—and potentially modulating immune-related lactylation processes[65]. Probiotics and postbiotics are also recognized as important strategies for regulating lactate metabolism and lactylation, as they help maintain the dynamic balance of metabolites and consequently affect immune cell lactylation and inflammatory responses[66]. In addition, pharmacological interventions targeting lactate transporters (e.g., MCTs), lactyl-CoA synthetases, or delactylases (e.g., HDACs, SIRTs) may offer novel avenues for fine-tuning lactylation dynamics in allergic diseases[67,68]. Future studies integrating functional foods, microbiota-based strategies, and pharmacological approaches may provide multidimensional therapeutic avenues for the prevention and management of allergic disorders.

6. Conclusion

lactate is a significant factor for metabolism and immune regulation in food-allergic response and allergic inflammation. The main manifestation of this is an increase in lactate levels, which promotes glycolytic reactions and also drives the process of histone lactylation, exerting distinct effects on different immune cell types. However, current research remains limited by methodological challenges, such as the transient nature of lactylation, lack of standardized detection techniques, and the scarcity of allergy-specific models. Future studies integrating spatial metabolomics and lactylation-specific imaging, alongside interventions based on probiotics, postbiotics, functional foods, and dietary nutrients could help overcome these obstacles and provide promising avenues for modulating lactate metabolism and lactylation to manage and prevent allergic diseases.

Conflict of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding Resource

This work was supported by the National Key R&D Program of China (Grant No. 2023YFF1001600).

Reference

[1] Y. Fang, Z. Li, L. Yang, W. Li, Y. Wang, Z. Kong, J. Miao, Y. Chen, Y. Bian, L. Zeng, Emerging roles of lactate in acute and chronic inflammation, Cell Commun Signal 22 (2024) 276. https://doi.org/10.1186/s12964-024-01624-8.

[2] Z. Zhang, Y. Zhao, Y. Han, B. Yang, H. Lin, Z. Li, The natural substances with anti-allergic properties in food allergy, Trends in Food Science & Technology 128 (2022) 53–67. https://doi.org/10.1016/j.tifs.2022.07.004.

[3] G. Liu, M. Liu, J. Wang, Y. Mou, H. Che, The Role of Regulatory T Cells in Epicutaneous Immunotherapy for Food Allergy, Front. Immunol. 12 (2021). https://doi.org/10.3389/fimmu.2021.660974.

[4] P.N. Shah, G.A. Romar, A. Manukyan, W.-C. Ko, P.-C. Hsieh, G.A. Velasquez, E.M. Schunkert, X. Fu, I. Guleria, R.T. Bronson, K. Wei, A.H. Waldman, F.R. Vleugels, M.G. Liang, A. Giobbie-Hurder, A. Mostaghimi, B.A.R. Schmidt, V. Barrera, R.K. Foreman, M. Garber, S.J. Divito, Systemic and skin-limited delayed-type drug hypersensitivity reactions associate with distinct resident and recruited T cell subsets, J Clin Invest 134 (2024). https://doi.org/10.1172/JCI178253.

[5] M. Certo, C.-H. Tsai, V. Pucino, P.-C. Ho, C. Mauro, Lactate modulation of immune responses in inflammatory versus tumour microenvironments, Nat Rev Immunol 21 (2021) 151–161. https://doi.org/10.1038/s41577-020-0406-2.

[6] J. Pouysségur, I. Marchiq, S.K. Parks, J. Durivault, M. Ždralević, M. Vucetic, 'Warburg effect' controls tumor growth, bacterial, viral infections and immunity – Genetic deconstruction and therapeutic perspectives, Seminars in Cancer Biology 86 (2022) 334–346. https://doi.org/10.1016/j.semcancer.2022.07.004.

[7] A. Goretzki, Y.-J. Lin, S. Schülke, Immune metabolism in allergies, does it matter?—A review of immune metabolic basics and adaptations associated with the activation of innate immune cells in allergy, Allergy 76 (2021) 3314–3331. https://doi.org/10.1111/all.14843.

[8] D. Zhang, Z. Tang, H. Huang, G. Zhou, C. Cui, Y. Weng, W. Liu, S. Kim, S. Lee, M. Perez-Neut, J. Ding, D. Czyz, R. Hu, Z. Ye, M. He, Y.G. Zheng, H.A. Shuman, L. Dai, B. Ren, R.G. Roeder, L. Becker, Y. Zhao, Metabolic regulation of gene expression by histone lactylation, Nature 574 (2019) 575–580. https://doi.org/10.1038/s41586-019-1678-1.

[9] R. Li, Y. Yang, H. Wang, T. Zhang, F. Duan, K. Wu, S. Yang, K. Xu, X. Jiang, X. Sun, Lactate and Lactylation in the Brain: Current Progress and Perspectives, Cell Mol Neurobiol 43 (2023) 2541–2555. https://doi.org/10.1007/s10571-023-01335-7.

[10] F. Jing, J. Zhang, H. Zhang, T. Li, Unlocking the multifaceted molecular functions and diverse disease implications of lactylation, Biological Reviews n/a (2024). https://doi.org/10.1111/brv.13135.

[11] X. Li, Y. Yang, B. Zhang, X. Lin, X. Fu, Y. An, Y. Zou, J.-X. Wang, Z. Wang, T. Yu, Lactate metabolism in human health and disease, Sig Transduct Target Ther 7 (2022) 1–22. https://doi.org/10.1038/s41392-022-01151-3.

[12] W. Liu, Y. Wang, L.H.M. Bozi, P.D. Fischer, M.P. Jedrychowski, H. Xiao, T. Wu, N. Darabedian, X. He, E.L. Mills, N. Burger, S. Shin, A. Reddy, H.-G. Sprenger, N. Tran, S. Winther, S.M. Hinshaw, J. Shen, H.-S. Seo, K. Song, A.Z. Xu, L. Sebastian, J.J. Zhao, S. Dhe-Paganon, J. Che, S.P. Gygi, H. Arthanari, E.T. Chouchani, Lactate regulates cell cycle by remodelling the anaphase promoting complex, Nature 616 (2023) 790–797. https://doi.org/10.1038/s41586-023-05939-3.

[13] S. Xu, T. He, J. Li, Z. Huang, C. Hu, Enantioselective synthesis of D-lactic acid via chemocatalysis using MgO: Experimental and molecular-based rationalization of the triose's reactivity and preliminary insights with raw biomass, Applied Catalysis B: Environmental 292 (2021) 120145. https://doi.org/10.1016/j.apcatb.2021.120145.

[14] Y. Hou, D. Liu, Z. Guo, C. Wei, F. Cao, Y. Xu, Q. Feng, F. Liu, Lactate and Lactylation in AKI-to-CKD: Epigenetic Regulation and Therapeutic Opportunities, Cell Proliferation n/a (n.d.) e70034. https://doi.org/10.1111/cpr.70034.

[15] K. Xu, K. Zhang, Y. Wang, Y. Gu, Comprehensive review of histone lactylation: Structure, function, and therapeutic targets, Biochemical Pharmacology 225 (2024) 116331. https://doi.org/10.1016/j.bcp.2024.116331.

[16] J. Ju, H. Zhang, M. Lin, Z. Yan, L. An, Z. Cao, D. Geng, J. Yue, Y. Tang, L. Tian, F. Chen, Y. Han, W. Wang, S. Zhao, S. Jiao, Z. Zhou, The alanyl-tRNA synthetase AARS1 moonlights as a lactyltransferase to promote YAP signaling in gastric cancer, J Clin Invest 134 (2024). https://doi.org/10.1172/JCI174587.

[17] C. Moreno-Yruela, D. Zhang, W. Wei, M. Bæk, W. Liu, J. Gao, D. Danková, A.L. Nielsen, J.E. Bolding, L. Yang, S.T. Jameson, J. Wong, C.A. Olsen, Y. Zhao, Class I histone deacetylases (HDAC1–3) are histone lysine delactylases, Science Advances 8 (2022) eabi6696. https://doi.org/10.1126/sciadv.abi6696.

[18] H. Zu, C. Li, C. Dai, Y. Pan, C. Ding, H. Sun, X. Zhang, X. Yao, J. Zang, X. Mo, SIRT2 functions as a histone delactylase and inhibits the proliferation and migration of neuroblastoma cells, Cell Discov 8 (2022) 1–5. https://doi.org/10.1038/s41421-022-00398-y.

[19] M. Iozzo, E. Pardella, E. Giannoni, P. Chiarugi, The role of protein lactylation: A kaleidoscopic post-translational modification in cancer, Molecular Cell 0 (2025). https://doi.org/10.1016/j.molcel.2025.02.011.

[20] H. Rho, A.R. Terry, C. Chronis, N. Hay, Hexokinase 2-mediated gene expression via histone lactylation is required for hepatic stellate cell activation and liver fibrosis, Cell Metabolism 35 (2023) 1406-1423.e8. https://doi.org/10.1016/j.cmet.2023.06.013.

[21] Y. Zhou, L. Yang, X. Liu, H. Wang, Lactylation may be a Novel Posttranslational Modification in Inflammation in Neonatal Hypoxic-Ischemic Encephalopathy, Front. Pharmacol. 13 (2022). https://doi.org/10.3389/fphar.2022.926802.

[22] R. Zhu, X. Ye, X. Lu, L. Xiao, M. Yuan, H. Zhao, D. Guo, Y. Meng, H. Han, S. Luo, Q. Wu, X. Jiang, J. Xu, Z. Tang, Y.J. Tao, Z. Lu, ACSS2 acts as a lactyl-CoA synthetase and couples KAT2A to function as a lactyltransferase for histone lactylation and tumor immune evasion, Cell Metabolism 37 (2025) 361-376.e7. https://doi.org/10.1016/j.cmet.2024.10.015.

[23] H. Fang, R. Rodrigues e-Lacerda, N.G. Barra, D. Kukje Zada, N. Robin, A. Mehra, J.D. Schertzer, Postbiotic Impact on Host Metabolism and Immunity Provides Therapeutic Potential in Metabolic Disease, Endocrine Reviews 46 (2025) 60–79. https://doi.org/10.1210/endrev/bnae025.

[24] Q. Zhao, Q. Wang, Q. Yao, Z. Yang, W. Li, X. Cheng, Y. Wen, R. Chen, J. Xu, X. Wang, D. Qin, S. Zhu, L. He, N. Li, Y. Wu, Y. Yu, X. Cao, P. Wang, Nonenzymatic lysine d-lactylation induced by glyoxalase II substrate SLG dampens inflammatory immune responses, Cell Res 35 (2025) 97–116. https://doi.org/10.1038/s41422-024-01060-w.

[25] F. Guan, R. Wang, Z. Yi, P. Luo, W. Liu, Y. Xie, Z. Liu, Z. Xia, H. Zhang, Q. Cheng, Tissue macrophages: origin, heterogenity, biological functions, diseases and therapeutic targets, Sig Transduct Target Ther 10 (2025) 93. https://doi.org/10.1038/s41392-025-02124-y.

[26] L. Yan, J. Wang, X. Cai, Y.-C. Liou, H.-M. Shen, J. Hao, C. Huang, G. Luo, W. He, Macrophage plasticity: signaling pathways, tissue repair, and regeneration, (n.d.). https://doi.org/10.1002/mco2.658.

[27] N. Chen, Q.-M. Xie, S.-M. Song, S.-N. Guo, Y. Fang, G.-H. Fei, H.-M. Wu, Dexamethasone protects against asthma via regulating Hif-1α-glycolysis-lactate axis and protein lactylation, International Immunopharmacology 131 (2024) 111791. https://doi.org/10.1016/j.intimp.2024.111791.

[28] J. Wang, X. Guo, C. Chen, S. Sun, G. Liu, M. Liu, M. Hao, H. Che, Gender differences in food allergy depend on the PPAR γ/NF-κB in the intestines of mice, Life Sciences 278 (2021) 119606. https://doi.org/10.1016/j.lfs.2021.119606.

[29] L.M. Sanmarco, J.M. Rone, C.M. Polonio, G. Fernandez Lahore, F. Giovannoni, K. Ferrara, C. Gutierrez-Vazquez, N. Li, A. Sokolovska, A. Plasencia, C. Faust Akl, P. Nanda, E.S. Heck, Z. Li, H.-G. Lee, C.-C. Chao, C.M. Rejano-Gordillo, P.H. Fonseca-Castro, T. Illouz, M. Linnerbauer, J.E. Kenison, R.M. Barilla, D. Farrenkopf, N.A. Stevens, G. Piester, E.N. Chung, L. Dailey, V.K. Kuchroo, D. Hava, M.A. Wheeler, C. Clish, R. Nowarski, E. Balsa, J.M. Lora, F.J. Quintana, Lactate limits CNS autoimmunity by stabilizing HIF-1α in dendritic cells, Nature 620 (2023) 881–889. https://doi.org/10.1038/s41586-023-06409-6.

[30] T.P. Brown, P. Bhattacharjee, S. Ramachandran, S. Sivaprakasam, B. Ristic, M.O.F. Sikder, V. Ganapathy, The lactate receptor GPR81 promotes breast cancer growth via a paracrine mechanism involving antigen-presenting cells in the tumor microenvironment, Oncogene 39 (2020) 3292–3304. https://doi.org/10.1038/s41388-020-1216-5.

[31] S. Ishihara, K. Hata, K. Hirose, T. Okui, S. Toyosawa, N. Uzawa, R. Nishimura, T. Yoneda, The lactate sensor GPR81 regulates glycolysis and tumor growth of breast cancer, Sci Rep 12 (2022) 6261. https://doi.org/10.1038/s41598-022-10143-w.

[32] J.E. Kenison, N.A. Stevens, F.J. Quintana, Therapeutic induction of antigen-specific immune tolerance, Nat Rev Immunol 24 (2024) 338–357. https://doi.org/10.1038/s41577-023-00970-x.

[33] Q. Cai, W. Deng, Y. Zou, Z.-S. Chen, H. Tang, Histone lactylation as a driver of metabolic reprogramming and immune evasion, Medical Review (2024). https://doi.org/10.1515/mr-2024-0091.

[34] J. Zha, J. Zhang, J. Lu, G. Zhang, M. Hua, W. Guo, J. Yang, G. Fan, A review of lactate-lactylation in malignancy: its potential in immunotherapy, Front. Immunol. 15 (2024). https://doi.org/10.3389/fimmu.2024.1384948.

[35] X. Chen, A. Jaiswal, Z. Costliow, P. Herbst, E.A. Creasey, N. Oshiro-Rapley, M.J. Daly, K.L. Carey, D.B. Graham, R.J. Xavier, pH sensing controls tissue inflammation by modulating cellular metabolism and endo-lysosomal function of immune cells, Nat Immunol 23 (2022) 1063–1075. https://doi.org/10.1038/s41590-022-01231-0.

[36] L. Porter, N. Toepfner, K.R. Bashant, J. Guck, M. Ashcroft, N. Farahi, E.R. Chilvers, Metabolic Profiling of Human Eosinophils, Front. Immunol. 9 (2018). https://doi.org/10.3389/fimmu.2018.01404.

[37] N. Jones, E.E. Vincent, L.C. Felix, J.G. Cronin, L.M. Scott, P.S. Hole, P. Lacy, C.A. Thornton, Interleukin-5 drives glycolysis and reactive oxygen species-dependent citric acid cycling by eosinophils, Allergy 75 (2020) 1361–1370. https://doi.org/10.1111/all.14158.

[38] M. Syed, A.K. Kammala, B. Callahan, C.A. Oskeritzian, H. Subramanian, Lactic acid suppresses MRGPRX2 mediated mast cell responses, Cellular Immunology 368 (2021) 104422. https://doi.org/10.1016/j.cellimm.2021.104422.

[39] X. Lv, W. Wang, H. Dong, W. Li, Glycolysis in asthma: Its role and potential as a diagnostic or therapeutic target, International Immunopharmacology 148 (2025) 114143. https://doi.org/10.1016/j.intimp.2025.114143.

[40] J. Li, X. Chen, S. Song, W. Jiang, T. Geng, T. Wang, Y. Xu, Y. Zhu, J. Lu, Y. Xia, R. Wang, Hexokinase 2-mediated metabolic stress and inflammation burden of liver macrophages via histone lactylation in MASLD, Cell Rep 44 (2025) 115350. https://doi.org/10.1016/j.celrep.2025.115350.

[41] X. Yu, J. Yang, J. Xu, H. Pan, W. Wang, X. Yu, S. Shi, Histone lactylation: from tumor lactate metabolism to epigenetic regulation, International Journal of Biological Sciences 20 (2024) 1833. https://doi.org/10.7150/ijbs.91492.

[42] T. Kawai, S. Akira, The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors, Nat Immunol 11 (2010) 373–384. https://doi.org/10.1038/ni.1863.

[43] R.A. Irizarry-Caro, M.M. McDaniel, G.R. Overcast, V.G. Jain, T.D. Troutman, C. Pasare, TLR signaling adapter BCAP regulates inflammatory to reparatory macrophage transition by promoting histone lactylation, Proceedings of the National Academy of Sciences 117 (2020) 30628–30638. https://doi.org/10.1073/pnas.2009778117.

[44] H. Lou, Y. Huang, H. Chen, Y. Wang, L. Zhang, C. Wang, M2 macrophages correlated with symptom severity and promote type 2 inflammation in allergic rhinitis, Allergy 74 (2019) 2255–2257. https://doi.org/10.1111/all.13852.

[45] G.H. Banafea, Bakhashab ,Sherin, Alshaibi ,Huda F, Natesan Pushparaj ,Peter, M. and Rasool, The role of human mast cells in allergy and asthma, Bioengineered 13 (2022) 7049–7064. https://doi.org/10.1080/21655979.2022.2044278.

[46] Z. Su, J. Lan, Y. Wang, N. Ma, J. Yang, D. Liang, H. Zeng, M. Yang, Lactylation-driven ALKBH5 diminishes macrophage NLRP3 inflammasome activation in patients with G6PT deficiency, Journal of Allergy and Clinical Immunology (2025). https://doi.org/10.1016/j.jaci.2025.01.028.

[47] W. Song, Y. Tao, Y. Pan, X. Mo, Q. Cao, SIRT2 regulates macrophage chemotaxis by de-modifying histone H4K8 lactylation, Journal of Shanghai Jiao Tong University (Medical Science) 43 (2023) 1008. https://doi.org/10.3969/j.issn.1674-8115.2023.08.008.

[48] E. Galle, C.-W. Wong, A. Ghosh, T. Desgeorges, K. Melrose, L.C. Hinte, D. Castellano-Castillo, M. Engl, J.A. de Sousa, F.J. Ruiz-Ojeda, K. De Bock, J.R. Ruiz, F. von Meyenn, H3K18 lactylation marks tissue-specific active enhancers, Genome Biol 23 (2022) 207. https://doi.org/10.1186/s13059-022-02775-y.

[49] T. Sun, B. Liu, Y. Li, J. Wu, Y. Cao, S. Yang, H. Tan, L. Cai, S. Zhang, X. Qi, D. Yu, W. Yang, Oxamate enhances the efficacy of CAR-T therapy against glioblastoma via suppressing ectonucleotidases and CCR8 lactylation, J Exp Clin Cancer Res 42 (2023) 253. https://doi.org/10.1186/s13046-023-02815-w.

[50] H. Wu, H. Huang, Y. Zhao, Interplay between metabolic reprogramming and post-translational modifications: from glycolysis to lactylation, Front. Immunol. 14 (2023). https://doi.org/10.3389/fimmu.2023.1211221.

[51] V. Pucino, M. Certo, V. Bulusu, D. Cucchi, K. Goldmann, E. Pontarini, R. Haas, J. Smith, S.E. Headland, K. Blighe, M. Ruscica, F. Humby, M.J. Lewis, J.J. Kamphorst, M. Bombardieri, C. Pitzalis, C. Mauro, Lactate Buildup at the Site of Chronic Inflammation Promotes Disease by Inducing CD4+ T Cell Metabolic Rewiring, Cell Metabolism 30 (2019) 1055-1074.e8. https://doi.org/10.1016/j.cmet.2019.10.004.

[52] W.J. Quinn, J. Jiao, T. TeSlaa, J. Stadanlick, Z. Wang, L. Wang, T. Akimova, A. Angelin, P.M. Schäfer, M.D. Cully, C. Perry, P.K. Kopinski, L. Guo, I.A. Blair, L.R. Ghanem, M.S. Leibowitz, W.W. Hancock, E.K. Moon, M.H. Levine, E.B. Eruslanov, D.C. Wallace, J.A. Baur, U.H. Beier, Lactate Limits T Cell Proliferation via the NAD(H) Redox State, Cell Reports 33 (2020). https://doi.org/10.1016/j.celrep.2020.108500.

[53] J. Gu, J. Zhou, Q. Chen, X. Xu, J. Gao, X. Li, Q. Shao, B. Zhou, H. Zhou, S. Wei, Q. Wang, Y. Liang, L. Lu, Tumor metabolite lactate promotes tumorigenesis by modulating MOESIN lactylation and enhancing TGF-β signaling in regulatory T cells, Cell Reports 39 (2022). https://doi.org/10.1016/j.celrep.2022.110986.

[54] H.L. Caslin, M.T. Taruselli, T. Haque, N. Pondicherry, E.A. Baldwin, B.O. Barnstein, J.J. Ryan, Inhibiting Glycolysis and ATP Production Attenuates IL-33-Mediated Mast Cell Function and Peritonitis, Front. Immunol. 9 (2018). https://doi.org/10.3389/fimmu.2018.03026.

[55] K. Poels, J.G. Schnitzler, F. Waissi, J.H.M. Levels, E.S.G. Stroes, M.J.A.P. Daemen, E. Lutgens, A.-M. Pennekamp, D.P.V. De Kleijn, T.T.P. Seijkens, J. Kroon, Inhibition of PFKFB3 Hampers the Progression of Atherosclerosis and Promotes Plaque Stability, Front. Cell Dev. Biol. 8 (2020). https://doi.org/10.3389/fcell.2020.581641.

[56] J. Cao, F. Zeng, S. Liao, L. Cao, Y. Zhou, Effects of glycolysis on the polarization and function of tumor-associated macrophages (Review), International Journal of Oncology 62 (2023) 1–12. https://doi.org/10.3892/ijo.2023.5518.

[57] H. Zeng, T. Pan, M. Zhan, R. Hailiwu, B. Liu, H. Yang, P. Li, Suppression of PFKFB3-driven glycolysis restrains endothelial-to-mesenchymal transition and fibrotic response, Sig Transduct Target Ther 7 (2022) 303. https://doi.org/10.1038/s41392-022-01097-6.

[58] L. Zhu, Q. Zheng, X. Liu, H. Ding, M. Ma, J. Bao, Y. Cai, C. Cao, HMGB1 lactylation drives neutrophil extracellular trap formation in lactate-induced acute kidney injury, Front. Immunol. 15 (2025). https://doi.org/10.3389/fimmu.2024.1475543.

[59] Y. Zhou, J. Lou, Y. Tian, J. Ding, X. Wang, B. Tang, How lactate affects immune strategies in lymphoma, Front. Mol. Biosci. 11 (2024). https://doi.org/10.3389/fmolb.2024.1480884.

[60] C. Qiu, R. Zhou, H. Zhang, L. Zhang, Z. Yin, D. Ren, Histone lactylation-ROS loop contributes to light exposure-exacerbated neutrophil recruitment in zebrafish, Commun Biol 7 (2024) 1–12. https://doi.org/10.1038/s42003-024-06543-5.

[61] W. Huang, J. Su, X. Chen, Y. Li, Z. Xing, L. Guo, S. Li, J. Zhang, High-Intensity Interval Training Induces Protein Lactylation in Different Tissues of Mice with Specificity and Time Dependence, Metabolites 13 (2023) 647. https://doi.org/10.3390/metabo13050647.

[62] L.T. Izzo, K.E. Wellen, Histone lactylation links metabolism and gene regulation, Nature 574 (2019) 492–493. https://doi.org/10.1038/d41586-019-03122-1.

[63] M. Fasihiyan, Y. Asadi, R. Pakravan, S. Haji, M. Nourshahi, High-intensity exercise training and the immune system: A new role of lactate, Journal of Exercise & Organ Cross Talk 3 (2023) 93–98. https://doi.org/10.22034/jeoct.2023.391819.1074.

[64] L. Yan, Y. Wang, H. Hu, D. Yang, W. Wang, Z. Luo, Y. Wang, F. Yang, K.-F. So, L. Zhang, Physical exercise mediates cortical synaptic protein lactylation to improve stress resilience, Cell Metabolism 36 (2024) 2104-2117.e4. https://doi.org/10.1016/j.cmet.2024.07.018.

[65] Y. Xu, J. Song, Q. Huang, X. Wei, Z. Deng, Z. Song, H. Huang, C. Luo, D. Zhang, L. Han, Functional foods and nutraceuticals with anti-aging effects: Focus on modifying the enteral microbiome, Journal of Functional Foods 128 (2025) 106786. https://doi.org/10.1016/j.jff.2025.106786.

[66] H. Liu, S. Wang, J. Wang, X. Guo, Y. Song, K. Fu, Z. Gao, D. Liu, W. He, L.-L. Yang, Energy metabolism in health and diseases, Sig Transduct Target Ther 10 (2025) 69. https://doi.org/10.1038/s41392-025-02141-x.

[67] P. Louis, S.H. Duncan, P.O. Sheridan, A.W. Walker, H.J. Flint, Microbial lactate utilisation and the stability of the gut microbiome, Gut Microbiome 3 (2022) e3. https://doi.org/10.1017/gmb.2022.3.

[68] S. Kumar, N. Sahu, T. Jawaid, H.S. Jayasingh Chellammal, P. Upadhyay, Dual role of lactate in human health and disease, Front. Physiol. 16 (2025). https://doi.org/10.3389/fphys.2025.1621358.