How lactate and lactylation shape the immunity system in atherosclerosis (Review)

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Abstract. Atherosclerosis is a leading cause of cardiovascular diseases, causing significant morbidity and mortality. This review article examines the role of lactate and lactylation in atherosclerosis, a chronic inflammatory disease closely linked to lipid metabolism and immune system activation. Lactate, a metabolic byproduct and signaling molecule, has emerged as a key regulator of immune cell functions and epigenetic modifications. The article explores the mechanisms through which lactate and lactylation influence macrophage polarization, T-cell differentiation and B-cell metabolism, highlighting their complex dual roles in the progression of atherosclerosis. By modulating metabolic reprogramming, functional polarization and epigenetic regulation, lactate and lactylation significantly impact plaque formation and stability. These findings provide a foundation for developing novel therapeutic strategies targeting lactate metabolism and lactylation pathways.

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Contents

1. Introduction

Cardiovascular diseases (CVDs), the leading cause of death worldwide, claims ~18 million lives each year and has high morbidity rates (1-4). Atherosclerosis is the main pathologic mechanism of most CVDs (5). These chronic plaques in vessel, composed mainly of cholesterol, fat, calcium and blood cells, gradually harden over time, leading to arterial stenosis and thereby restricting the flow of oxygen-rich blood to various parts of the body (6). Atherosclerosis has been found to be the central mechanism of this pathological process and the leading cause of CVDs worldwide (7).

In recent years, atherosclerosis has been recognized as a chronic inflammatory disease and leads to arterial stenosis and plaque formation due to the accumulation of lipids and inflammatory cells within the arterial wall (8-11). The role of adaptive immunity in atherosclerosis has increasingly attracted attention (12). The adaptive immune system participates in the development of atherosclerosis through various cellular and molecular mechanisms, including the interactions of T cells (13), B cells (14), antigen-presenting cells (15) and cytokines (16). Inflammation plays a key role in the progression of atherosclerosis, and adaptive immune responses influence plaque formation and stability by modulating the activity of inflammatory cells and the secretion of cytokines. These studies further confirm the key role of inflammation and immunity in atherosclerosis and provide a theoretical basis for immune-modulating therapies.

Epigenetics focuses on heritable changes in gene expression that are not derived from alterations in the nucleotide sequence, such as DNA or RNA methylation modifications,

as well as post-translational modifications of proteins (17). Lactylation, an emerging post-translational modification, has garnered widespread attention in biological and medical research (18-20). Lactylation plays a crucial role in various biological processes, including the regulation of macrophage function, modulation of glycolytic activity and the promotion of tumorigenesis (21). As a key regulatory factor in numerous biological processes and disease mechanisms, lactylation modification has become a hot topic in molecular biology studies (22,23).

Although the potential role of lactylation modification in CVD has been demonstrated (24), its role in regulating immunity in the context of atherosclerosis remains largely elusive. During the pathological process of atherosclerosis, the accumulation of lactate in local tissues obviously impacts this process. Therefore, vast research efforts have explored the interaction between lactylation modifications and adaptive immunity within the atherosclerotic microenvironment. This review aims to clarify the role of lactylation in immunity in the context of atherosclerosis and summarize the driving mechanisms. This article not only explores the roles of lactate and lactylation in atherosclerosis but also systematically analyzes their impacts on various components of the immune system, such as macrophages, T cells and B cells. To the best of our knowledge, this multidimensional perspective is relatively rare in previous reviews (12,25-27), as most studies have focused solely on a single cell type or mechanism. By closely integrating the metabolic characteristics of lactate with the regulation of immune responses, the article highlights the crucial role of metabolic reprogramming in atherosclerosis. This integrative approach provides a more comprehensive framework for understanding the pathogenesis of atherosclerosis. These innovative aspects not only enrich our understanding of the pathogenic mechanisms of atherosclerosis but also offer new directions for future therapeutic strategies.

2. Lactate and atherosclerosis

Lactate exists in two isomeric forms: D-lactate and L-lactate, with L-lactate being the most common form in living organisms (28). Lactate transport mainly relies on monocarboxylate transporters (MCTs) (29,30). In organisms, glucose is metabolized to lactate via the glycolytic pathway under a short supply of oxygen. Although only 2 ATP molecules are generated per glucose molecule during this process, the energy output is relatively low and the rapid production of lactate quickly provides energy under hypoxic conditions to maintain normal cellular functions (31). As an acidic substance, lactate plays an important role in the acid-base balance of the body. Furthermore, tumor cells often exhibit aerobic glycolysis, producing large amounts of lactate even in the presence of oxygen (32,33). This metabolic phenomenon is known as the 'Warburg effect' and the accumulation of lactate facilitates the growth and invasion of tumor cells (34,35).

Under normal physiological conditions, the production and clearance of lactate are in a dynamic equilibrium. It has been found that lactate is a metabolic byproduct of glycolysis and an important signaling molecule (36-39). The metabolic pathways of lactate vary with the cell type and environment. Lactate can be produced through anaerobic glycolysis, leading to its accumulation, or it can be oxidized to acetyl-coenzyme A (CoA) and enter the tricarboxylic acid cycle (TCA) cycle during aerobic respiration (40). Additionally, lactate can be generated from pyruvate via the Warburg effect (41). These distinct metabolic fates highlight the versatile roles of lactate in different physiological contexts. For instance, in the immune system, lactate modulates the activity of immune cells, inhibiting the overactivation of certain immune cells while promoting the proliferation and differentiation of others (42-44). In addition, lactate is involved in various physiological and pathological processes as an energy source and a signaling molecule and participate in epigenetic modifications (e.g., lactylation) (19).

In the heart, lactate is a byproduct of glycolysis and a key energy source for cardiomyocytes. Under normal physiological conditions, lactate oxidation provides >50% of the energy demands of cardiomyocytes. Even at rest, the proportion of energy supplied by lactate oxidation can reach 10%, and during exercise, this proportion can exceed 50% (45-47). Lactate enters the mitochondria through the lactate oxidation complex, is converted into pyruvate, and then enters the TCA cycle to ultimately generate ATP. Furthermore, lactate activates a series of transcriptional networks, affecting the expression and subcellular localization of metabolism-related proteins in cardiomyocytes, such as hexokinase-2, pyruvate kinase M2 (PKM2) and lactate dehydrogenase A/B, thereby regulating metabolic homeostasis in cardiomyocytes (48-52). Lactate and pyruvate can also scavenge free radicals, protecting cardiomyocytes from oxidative stress damage (53-55). A cross-sectional study involving 1,496 participants reported that blood lactate levels were independently associated with carotid atherosclerosis, suggesting that lactate is involved in atherosclerosis development (56). During the progression of atherosclerosis, lactic acid accumulates in the microenvironment of atherosclerotic plaques as an end product of glycolysis and leads to local acidification. This acidic microenvironment facilitates the binding of oxidized low-density lipoprotein (oxLDL) to aortic proteoglycans, triggers local immune responses and recruits immune cells, thereby exacerbating inflammatory reactions (57). Furthermore, lactic acid stabilizes hypoxia-inducible factor 1α (HIF-1α) and N-myc downstream regulated gene 3. This further promotes the expression of pro-angiogenic factors such as vascular endothelial growth factor and forms a positive feedback loop that promotes atherosclerosis development (58) (Fig. 1).

Lactate participates in cellular metabolism to provide energy, serves as a donor for lactylation modification and contribute to the regulation of the local tissue microenvironment.

3. Immunity and atherosclerosis

Atherosclerosis is a chronic inflammatory disease triggered by lipid metabolism disorders and characterized by the formation of atherosclerotic plaques beneath the intima of large and medium-sized arteries (5,11,12). During the progression of atherosclerosis, the glycolysis levels of cells within the plaque significantly increase, leading to excessive production and release of lactic acid, which in turn acidifies the extracellular environment (59-61). This metabolic change further influences the development of atherosclerosis through multiple mechanisms.

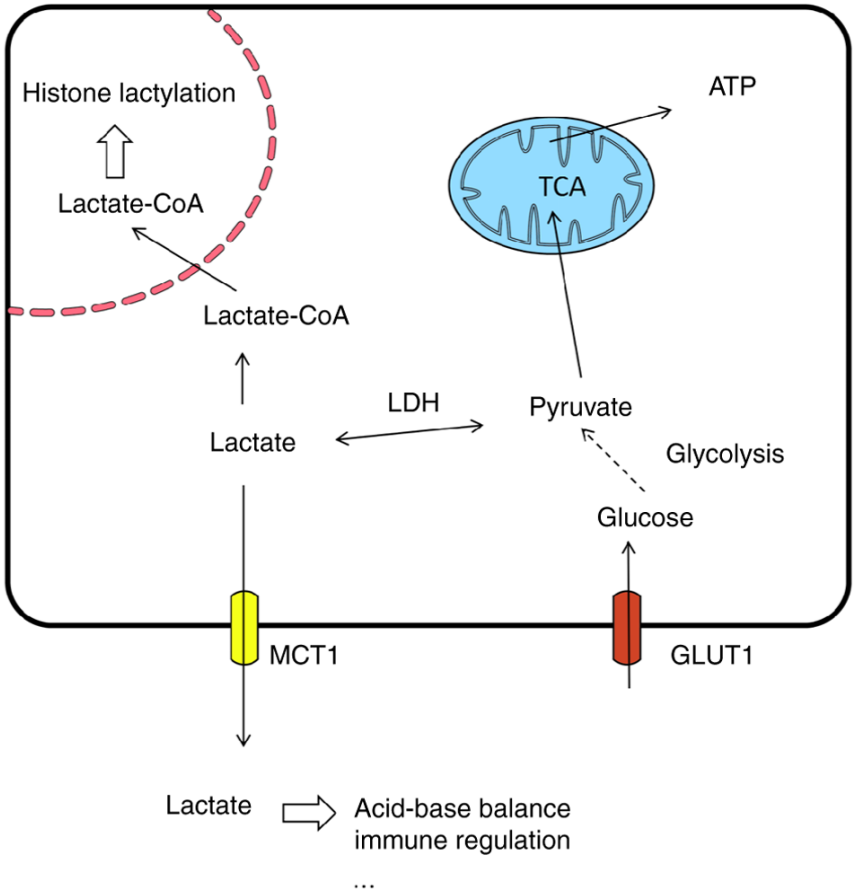

Figure 1. Lactate metabolism. As a pivotal metabolic intermediate, lactate exerts pleiotropic effects in cellular physiology: Firstly, it participates in cellular energy metabolism through mitochondrial oxidative pathways, serving as a substrate for ATP synthesis. Secondly, functioning as a crucial donor molecule for post-translational modifications, lactate can covalently modify target proteins such as histones via lactylation, thereby modulating gene expression profiles. Furthermore, lactate contributes to the homeostatic regulation of local tissue microenvironments through mechanisms including extracellular pH modulation and intercellular signaling. These three interconnected functions collectively establish lactate's multifaceted role in cellular metabolic regulation networks. The figure was created using Adobe Illustrator 2020 (Adobe Inc.). ATP, adenosine triphosphate; LDH, lactate dehydrogenase; CoA, coenzyme A; TCA, tricarboxylic acid cycle; MCT1, monocarboxylate transporter 1; GLUT1, glucose transporter 1F.

There is a close and complex interrelationship between atherosclerosis and the immune system (25,62,63). As a chronic inflammatory disease, the inflammatory process in atherosclerosis is typically initiated by the deposition of oxLDL and damage to endothelial cells. After endothelial injury, cytokines and chemokines are released as inflammatory mediators and then attract monocytes and other inflammatory cells into the vascular wall, thereby initiating the inflammatory response (Fig. 2) (64). The immune system plays a critical role in atherosclerosis through the interplay of innate and adaptive immune responses, immune cell metabolism and cytokine networks, driving inflammation and plaque progression.

The involvement of various immune cells plays a crucial role in atherosclerosis. Macrophages engulf oxLDL to form foam cells that accumulate within the vascular wall and serve as the foundation for plaque formation (65-67). Lipidomics and transcriptomics analyses have shown that foam cells themselves do not possess pro-inflammatory properties. However, the increased oxidative stress in the arterial wall and the accumulation of modified lipoproteins reprogram the metabolic processes of macrophages, thereby triggering inflammatory responses that promote atherosclerosis (68,69). After cell death, lipid-overloaded macrophages are usually phagocytized by other macrophages (70). However, when phagocytic cells become overwhelmed, they release pro-inflammatory components. The retention of macrophages in the arterial wall is promoted by adhesion molecules (e.g., vascular cell adhesion molecule 1) and neuroguidance factors (such as netrin 1), while high-density lipoprotein facilitates the egress of macrophages from plaques through a C-C motif chemokine receptor (CCR)7-mediated mechanism (71-74). Macrophages in atherosclerotic plaques exhibit pro-inflammatory or anti-inflammatory characteristics but do not follow the classical M1/M2 classification (25,75). Single-cell studies have identified at least five distinct macrophage subpopulations in the mouse aorta, including inflammatory macrophages, type I interferon-inducible cells, foam cells with high expression of triggering receptor expressed on myeloid cells 2, aortic intima-resident macrophages and embryonic-derived resident macrophages (68,69,76,77). These subpopulations play diverse roles in atherosclerosis. These cells exert both pro-inflammatory and anti-inflammatory effects during disease progression and their functions are regulated by multiple factors, such as cholesterol metabolism, oxidative stress and cell-to-cell interactions. Efforts

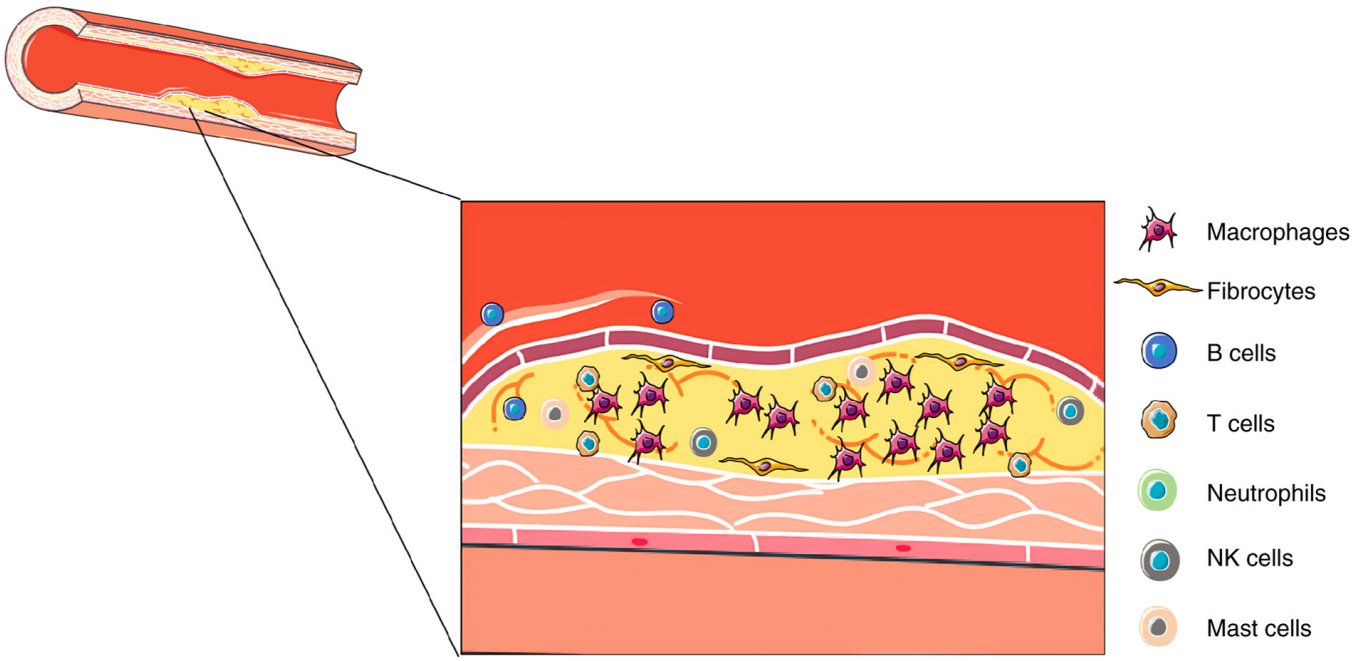

Figure 2. Immune system in atherosclerosis. The immune system critically regulates atherosclerosis through coordinated innate and adaptive immune responses. Key immune cells (macrophages, T cells, dendritic cells) undergo metabolic reprogramming that modulates their inflammatory activation within plaques. Concurrently, cytokine networks amplify pro-inflammatory signaling, promoting endothelial dysfunction and foam cell formation. These interconnected immunometabolic processes sustain vascular inflammation, driving plaque progression and destabilization. Therapeutic targeting of these mechanisms holds promise for atherosclerosis treatment. The figure was created using Adobe Illustrator 2020 (Adobe Inc.). NK, natural killer.

should be invested to further characterize the functions of these macrophage subpopulations and explore their specific mechanisms of action in atherosclerosis.

Adaptive immunity is a key modulator of atherosclerosis. T cells play a complex role in atherosclerosis and different subsets influence disease progression through numerous mechanisms. Type 1 T-helper (Th1) cells are the most prominent $CD4^+$T-cell subset in atherosclerotic plaques, promoting lesion development and plaque instability by secreting IFNγ and expressing T-bet (78,79). The mechanisms include inducing the uptake of oxLDL, foam cell formation, polarization of macrophages to a pro-inflammatory phenotype and proliferation of vascular smooth muscle cells (13,80,81).

Regulatory T (Treg) cells. Treg cells are negatively correlated with atherosclerosis (82). IL-35 maintains the suppressive function of Treg cells by enhancing their migratory capacity, inhibiting signaling pathways that weaken their function and promoting the expression of inhibitory receptors. This helps counteract atherosclerosis induced by hyperlipidemia (83). Depletion of Treg cells increases the lesion size and exacerbates atherosclerosis by altering plasma cholesterol profiles through impaired liver lipoprotein metabolism (84). During plaque regression, Treg cell numbers are restored, especially those of peripherally induced Treg cells that do not express neuropilin 1. This is associated with the formation of an anti-inflammatory microenvironment and tissue repair (85).

Th2 cells. Th2 cell-related cytokines have diverse effects on atherosclerosis (86,87). IL-5 and IL-13 exert anti-atherosclerotic effects by promoting antibody-dependent clearance of apoptotic cells, increasing collagen formation, inhibiting monocyte infiltration and inducing M2-type macrophages, while IL-4 has more complex functions (88-91). IL-4 has been reported to promote the regression of atherosclerosis (88).

Th17 cells. The role of Th17 cells in atherosclerosis remains controversial. In mouse models, the number of T cells expressing IL-17 is positively correlated with atherosclerosis. Depletion of Th17 cells inhibits the production of pro-inflammatory cytokines and chemokines, as well as leukocyte infiltration and plaque formation (92). In addition to its pro-inflammatory effects, IL-17A has a plaque-stabilizing role in atherosclerosis (93).

B cells. B lymphocytes have dual roles in atherosclerosis (14). B cell-derived cytokines play a complex dual role in the development of atherosclerosis. Anti-inflammatory cytokines (e.g., IL-10) exert protective effects against atherosclerosis by suppressing inflammatory responses, thereby reducing the formation of foam cells and the instability of plaques (94,95). On the other hand, pro-inflammatory cytokines (such as TNF-α) exacerbate the progression of atherosclerosis by activating inflammatory responses, promoting the formation of foam cells and causing damage to the arterial wall (96). In addition, IL-6 enhances inflammatory reactions and activate immune cells as a pro-inflammatory cytokine. In the context of atherosclerosis, elevated levels of IL-6 are closely associated with plaque instability and an increased risk of cardiovascular events (97,98). OxLDL is immunogenic and is recognized by the immune system as oxidation-specific epitopes (OSEs), thereby triggering inflammatory responses. B cell-derived antibodies modulate inflammation by neutralizing oxLDL or

activating the complement system. IgM antibodies typically exhibit anti-atherosclerotic effects by recognizing OSEs on oxLDL and apoptotic cell debris, thereby limiting inflammatory reactions (99). By contrast, immune complexes formed by IgG antibodies and oxLDL promote inflammatory responses, although their specific roles in atherosclerosis remain to be fully elucidated (100-102). In addition, IgE antibodies further promote the development of atherosclerosis by activating mast cells and macrophages (103,104).

Neutrophils, natural killer (NK) cells and mast cells. Neutrophils are mainly associated with events following plaque rupture or erosion, releasing various enzymes and cytokines that participate in the inflammatory response and tissue repair process (105-107). NK cells modulate the activity of other immune cells by releasing cytokines and cytotoxic granules, thereby influencing the immune response within atherosclerotic plaques (108). Mast cells, primarily located in the adventitia of arteries, release histamine, enzymes and cytokines, degrade the extracellular matrix, promote the further recruitment of inflammatory cells and enhance local inflammation, increasing the complexity and potential rupture risk of atherosclerotic plaques (109,110) (Table I).

During the progression of atherosclerosis, the persistent inflammatory response significantly impacts the immune system. Chronic inflammation can lead to overactivation or dysfunction of the immune system, thus increasing the risk of autoimmune diseases. Furthermore, vascular changes caused by atherosclerosis can affect the transport and distribution of immune cells, thereby influencing the normal function of the immune system (111-113). Considering the close relationship between atherosclerosis and the immune system, immune regulation strategies have potential in treating atherosclerosis. By modulating the function of immune cells, inhibiting the production of pro-inflammatory cytokines or enhancing the effects of anti-inflammatory cytokines, it is possible to reduce the inflammatory response, stabilize atherosclerotic plaques and thereby reduce the risk of cardiovascular events, offering new potential therapeutic options for atherosclerosis.

4. Lactylation

Lactylation is an epigenetic modification that involves post-translational modifications of both histone and non-histone proteins and plays a key role in the regulation of gene transcription and protein function (114). There are three isomers generated in this process: Lysine L-lactylation (Kl-la), N-ε-(carboxyethyl) lysine and D-lactyl lysine. It has been shown that Kl-la is the primary form of lactylation within cells and significantly contributes to glycolysis and the Warburg effect (115). Lactylation tends to occur at nucleophilic sites, such as amino groups ($-NH_2$), interacting with corresponding functional groups, and this high level of selectivity allows lactylation to precisely target specific proteins, causing significant changes in their properties and functions (114) (Fig. 3).

Induced by the accumulation of lactate, lactylation modifies proteins and alters the spatial conformation of histones, thereby affecting gene transcription and the regulation of gene expression. Similarly, it affects the function of non-histone proteins by altering their spatial conformation. Lactylation involves a series of enzyme-catalyzed, reversible chemical reactions, rather than spontaneous chemical activity (116). The 'writers' of lactylation refer to enzymes or proteins capable of catalyzing lactylation reactions, transferring lactoyl groups to target proteins after lactate is converted into lactoyl-CoA. The known lactylation 'writers' proteins mainly include histone acetyltransferases Sirtuin (SIRT)1 (117), P300 (117), lysine acetyltransferase 2A (KAT2A) (118), Tat-interactive protein 60 kDa (119,120) and KAT8 (121,122). 'Erasers' include enzymes or proteins that remove or erase lactoyl groups through hydrolysis, restoring the target molecule to its original state, with histone deacetylases (123) and SIRTs (124,125) being known 'erasers' that remove lactylation modifications. In biology, 'readers' are defined as proteins or domains capable of recognizing and interacting with lactoyl groups. Although no specific lactylation readers have been discovered, this may be related to the recent discovery of lactylation and an incomplete understanding of its underlying molecular mechanisms. Lactylation, a post-translational modification first reported in 2019 by Professor Yingming Zhao's group at the University of Chicago, has a shorter research history compared to classical modifications like acetylation and phosphorylation (19). Although the identification of specific 'reader' proteins for lactylation is still in progress, their functional roles have been confirmed through various studies. For instance, histone H3K18 lactylation influences macrophage polarization and tumor microenvironment regulation (126), lactylation of cyclic GMP-AMP synthase inhibits its immune activity, and lactylation in NK cells causes mitochondrial dysfunction (127). The lack of identified 'readers' does not diminish lactylation's biological significance but rather highlights the field's rapid development. Current evidence underscores its crucial roles in gene regulation, immune responses and disease. Future technological advancements and in-depth research are expected to uncover lactylation-specific 'readers', further clarifying its molecular mechanisms. As research progresses, more information about lactylation readers will be revealed in the future, leading to a more comprehensive understanding of the molecular mechanisms of lactylation.

Lactylation is an important epigenetic modification mechanism that plays a key role in various physiological and pathological processes by affecting protein stability, enzyme activity, protein-protein interactions, protein distribution, structure and function (128). Specifically, lactylation involves a series of complex physiological activities, including somatic cell reprogramming (129,130), embryonic development (131-133), neural excitation (134), osteoblast differentiation (135,136), pyroptosis (137,138), macroautophagy (139), decidualization (140), homologous recombination (119,141), cuproptosis (142), myogenesis (143) and oxidative phosphorylation (52,144). In addition, lactylation is closely related to the occurrence and development of various diseases, including but not limited to malignant tumors (22,119), inflammation-related diseases (145-147), fibrosis-related diseases (148,149), Alzheimer's disease (150), heart disease (60,117,151), insulin resistance (152), non-alcoholic fatty liver disease (153), cerebral infarction (154,155), viral infections (156,157) and endometriosis (158).

Table I. Immune cell impacts on atherosclerosis.

Immune cell type	Mechanism	Roles
Macrophages	- Engulfment of oxLDL to form foam cells, which accumulate in the vascular wall and promote plaque formation. - Oxidative stress and modified lipoproteins reprogram macrophage metabolism, triggering inflammatory responses. - Subpopulations (e.g., inflammatory macrophages, TREM2hi foam cells) exhibit pro-inflammatory or anti-inflammatory properties.	Pro-inflammatory: Promotion of plaque formation and inflammation. Anti-inflammatory: Some subpopulations may contribute to tissue repair and inflammation resolution.
Th1 cells	- Secretion of IFN-γ, promoting oxLDL uptake, foam cell formation, macrophage polarization to a pro-inflammatory phenotype, and vascular smooth muscle cell proliferation. - Expression of T-bet, promoting plaque instability.	Pro-inflammatory: Promotion of plaque development and instability.
Treg cells	- Secretion of IL-35, enhancing migratory capacity, inhibiting pro-inflammatory signaling pathways and expressing inhibitory receptors. - Depletion of Treg cells exacerbates atherosclerosis by altering plasma cholesterol profiles. - During plaque regression, Treg cell numbers are restored, promoting an anti-inflammatory microenvironment and tissue repair.	Anti-inflammatory: Suppression of inflammation and promotion of plaque stability and tissue repair.
Th2 cells	- Secretion of IL-5 and IL-13, promoting antibody-dependent clearance of apoptotic cells, increasing collagen formation, inhibiting monocyte infiltration and inducing M2-type macrophages. - The role of IL-4 is complex and may promote atherosclerosis resolution.	Anti-inflammatory: IL-5 and IL-13 exert anti-atherosclerotic effects. Complex: IL-4 may promote plaque resolution.
Th17 cells	- Secretion of IL-17, promoting inflammation and plaque formation. - IL-17A may have a plaque-stabilizing role in certain contexts.	Pro-inflammatory: Promotion of inflammation and plaque formation. Complex: IL-17A may stabilize plaques in certain cases.
B cells	- Secretion of anti-inflammatory cytokines (e.g., IL-10), stabilizing suppressing inflammation, reducing foam cell formation and plaques. - Secretion of pro-inflammatory cytokines (e.g., TNF-α, IL-6), activating inflammation, promoting foam cell formation and damaging the arterial wall. - IgM antibodies neutralize oxLDL to inhibit inflammation, while IgG and IgE antibodies may promote inflammation.	Dual role: Anti-inflammatory: IL-10 and IgM antibodies. Pro-inflammatory: TNF-α, IL-6, IgG and IgE antibodies.
Neutrophils	- Release of enzymes and cytokines following plaque rupture or erosion, participating in inflammation and tissue repair.	Pro-inflammatory: Promotion of inflammation. Repair: Participation in tissue repair.
NK cells	- Modulation of the activity of other immune cells by releasing cytokines and cytotoxic granules, influencing immune responses within plaques.	Regulatory: May promote or suppress inflammation, with roles requiring further clarification.
Mast cells	- Release of histamine, enzymes and cytokines, degradation of the extracellular matrix, recruitment of inflammatory cells, enhancement of local inflammation and increase of plaque complexity and rupture risk.	Pro-inflammatory: Promotion of local inflammation and plaque instability.

NK, natural killer; Th, T helper; Treg, T-regulatory cell; TREM2hi, triggering receptor expressed on myeloid cells 2 high expression; oxLDL, oxidized low-density lipoprotein.

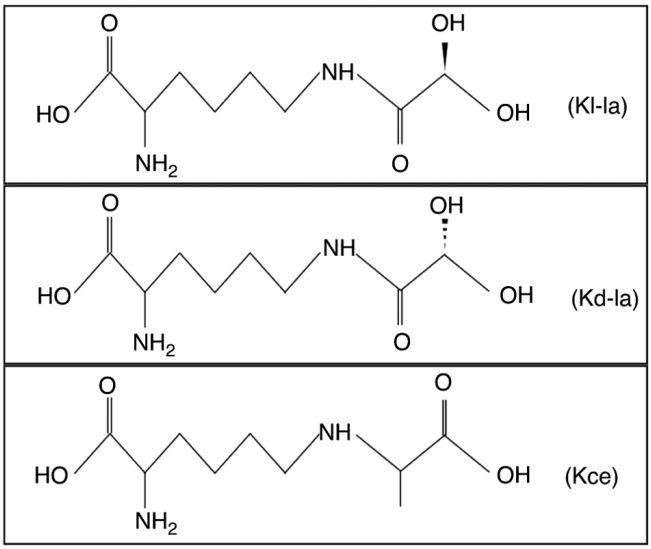

Figure 3. Three isomers of lysine lactylation modification. The lactylation process generates three distinct lysine isomeric modifications: i) Kla, formed by covalent conjugation of L-lactate to the ε-amino group of lysine; ii) Kce, characterized by carboxyethylation at the ε-position of lysine; and iii) Kd-la, representing the stereospecific D-lactate adduct. These modifications exhibit unique structural characteristics: While both Kla and Kd-la demonstrate the stereospecificity of their respective L- and D-lactate precursors, Kce displays distinct electronic properties due to its carboxylated side chain. The figure was created using Adobe Illustrator 2020 (Adobe Inc.). Kla, lysine L-lactylation; Kce, N-ε-(carboxyethyl)-lysine; Kd-la, D-lactyl-lysine.

5. Lactate and lactylation: Involvement in the immune system of atherosclerosis

Lactate, lactylation and macrophages. In atherosclerotic plaques, high concentrations of lactate induce metabolic reprogramming in macrophages, shifting their metabolism from glycolysis to oxidative phosphorylation (159-161). This metabolic remodeling significantly impacts the functional status of macrophages: The accumulation of lactate inhibits mitochondrial function, reduces ATP production and consequently diminishes the activity and functional performance of macrophages (111,162,163). Furthermore, lactate induces the polarization of macrophages towards the M2 phenotype while inhibiting M1 polarization, thereby promoting their anti-inflammatory and immunosuppressive functions (164,165). Besides, lactate attenuates inflammatory responses by reducing the phosphorylation levels of NF-κB, thereby suppressing the transcription of inflammation-related genes (166).

More critically, lactate can induce histone lactylation, a modification that regulates macrophage metabolism and phenotypic transformation by acting on both histones (such as H3K18la) and non-histone proteins (such as PKM2) (167-169). For instance, H3K18la modification activates the expression of M2-related genes and drives the transformation of M1 macrophages towards the M2 phenotype. Macrophage activation is one of the key features of atherosclerosis, typically accompanied by a shift in core metabolism from oxidative phosphorylation to glycolysis (19). It has been found that histone lactylation mediated by MCT4, which is associated with lactate efflux, is closely related to atherosclerosis. In the absence of MCT4, histone lactylation at lysine 18 of histone H3 activates the transcription of anti-inflammatory and TCA cycle genes, thereby initiating local repair and homeostasis (170). This finding indicates that lactylation plays an important role in regulating macrophage function and the progression of atherosclerosis.

Lactate, lactylation and T cells. Lactate is a byproduct of glycolysis and usually accumulates in large amounts in the tumor microenvironment, creating an acidic ecological niche. In the acute inflammatory phase, lactate primarily exerts anti-inflammatory effects by activating the G protein-coupled receptor 81 receptor, thereby inhibiting the production of inflammatory mediators and alleviating the inflammatory response (171,172). However, the acidic environment caused by lactate accumulation exacerbates the persistence of inflammation and promotes tissue damage in the chronic inflammatory phase. Nevertheless, lactate also induces the polarization of immune cells and modulates metabolic pathways to facilitate the resolution of inflammation and exert certain anti-inflammatory effects (173,174).

The activation and differentiation of T cells are accompanied by metabolic reprogramming, one of the metabolic hallmarks being aerobic glycolysis, which refers to the conversion of glucose to lactate in the presence of oxygen (175). T cells undergo metabolic reprogramming in different states of differentiation (176). For instance, effector T cells primarily rely on glycolysis, whereas regulatory T cells and memory T cells mainly depend on oxidative phosphorylation (177,178). T cells sense lactate through the expression of specific transporters, which leads to the inhibition of their migratory capacity. This 'stop signal' for migration depends on the interference of lactate with intracellular metabolic pathways, particularly glycolysis. Lactate promotes the differentiation of CD4+ T cells into the IL-17+ subset while reducing the cytotoxic capacity of CD8+ T cells. These phenomena lead to the formation of ectopic lymphoid structures at sites of inflammation and the production of autoantibodies (43,179). Lactate triggers the nuclear translocation of the PKM2 via an active transmembrane influx mediated by the sodium-coupled monocarboxylate transporter 2 (also known as solute carrier family 5 member 12). Within the nucleus, PKM2 forms a complex with phosphorylated signal transducer and activator of transcription 3, synergistically enhancing the transcriptional activity of the IL-17 gene, thereby markedly promoting IL-17 secretion by Th17 cells (180-182). The activity of Tregs relies on the metabolic reprogramming from glycolysis to oxidative phosphorylation, a process strictly regulated by the transcription factor forkhead box P3. Lactate promotes the accumulation of Tregs at inflammatory sites and activates the HIF-1α-dependent CCL20/CCR6 signaling axis, facilitating Treg migration to the lesion area. In addition, Tregs utilize lactate as a substrate for the TCA cycle, further enhancing their immunosuppressive function (164,183,184). Nevertheless, in chronic inflammatory responses, the persistent accumulation of lactate causes local tissue damage and drives the progression of chronic inflammation, which significantly exacerbates the pathological impact on atherosclerotic lesions and accelerates disease progression (173,179). Lactate plays a complex dual role in inflammation and immune responses. It

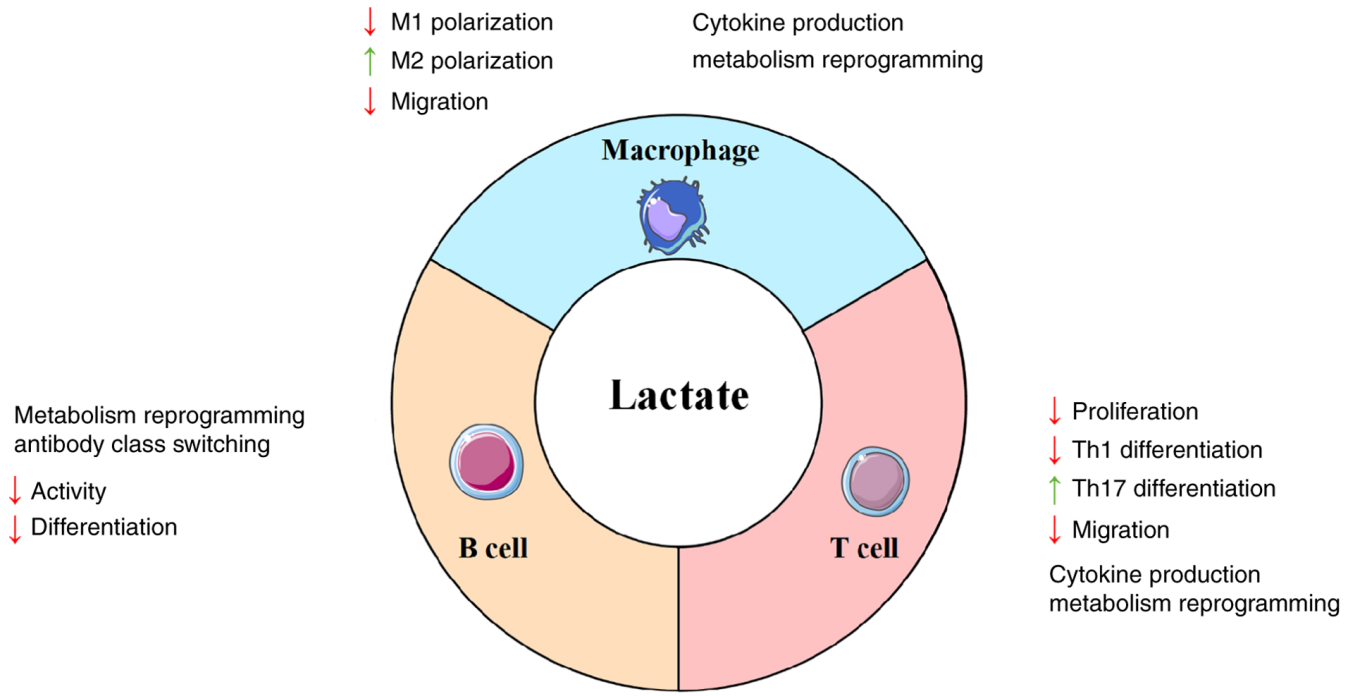

Figure 4. Lactate and Lactylation: Their involvement in the immune system of atherosclerosis. Lactate and its mediated lactylation modifications play a complex dual role in atherosclerosis by regulating metabolic reprogramming, functional polarization and epigenetic modifications of macrophages, T cells and B cells. Lactate and lactylation exerts multifaceted effects on immune cell functions, including metabolic reprogramming, cellular polarization, differentiation, activation, proliferation and migration. These regulatory effects may play crucial roles in modulating immune responses, particularly in inflammation-related and immune-regulated diseases. The figure was created using Adobe Illustrator 2020 (Adobe Inc.).

exerts anti-inflammatory effects by regulating metabolism and immune cell functions, but it exacerbates tissue damage and disease progression in chronic inflammation.

Lactylation promotes Th17 differentiation and participates in the development of autoimmune diseases and inflammatory responses by regulating site-specific modifications of key proteins such as IKAROS family zinc finger 1, which directly modulates the expression of Th17-related genes (185). In the tumor microenvironment, lactate regulates the generation of Treg cells through lactylation modification at lysine 72 of the MOESIN protein. This process enhances the interaction between MOESIN and transforming growth factor-β receptor I, activates the downstream SMAD3 signaling pathway and significantly improves the stability and function of Treg cells (186). This discovery provides an important reference for understanding the regulatory mechanisms of lactate accumulation on Treg cells in the context of atherosclerotic tissue environments.

Lactate, lactylation and B cells. Lactate significantly inhibits the proliferation capacity and antibody production of B cells by reducing the extracellular pH (159,187). Additionally, lactate modulates the metabolic pathways of B cells, particularly by enhancing the glycolytic process, which provides rapid energy supply to support their proliferation and differentiation. At the same time, lactate suppresses oxidative phosphorylation and results in significant alterations in the metabolic state of B cells (28,188). At the molecular level, lactate promotes the growth and metabolic activities of B cells by activating the mammalian target of rapamycin signaling pathway (189,190). Under hypoxic conditions, lactate enhances the adaptability of B cells to low oxygen environments by stabilizing HIF-1α (191-193). Furthermore, lactate activates the NF-κB signaling pathway, promoting the secretion of pro-inflammatory cytokines by B cells, thereby participating in the regulation of inflammatory responses (194,195). These findings demonstrate that lactate plays a multifaceted role in the functional regulation of B cells, influencing metabolic reprogramming, signaling pathway activation and environmental adaptability, among other aspects. Lactylation modulates the antibody class switch recombination (CSR) in B cells by influencing metabolic pathways. For instance, the MCT1-mediated lactate transport and pyruvate metabolism regulates the acetylation modification of histone H3K27, thereby affecting the transcriptional efficiency of activation-induced cytidine deaminase, which ultimately impacts the CSR in B cells (196) (Fig. 4).

Lactate and its mediated lactylation modifications play a complex dual role in atherosclerosis by regulating metabolic reprogramming, functional polarization and epigenetic modifications of macrophages, T cells and B cells.

6. Conclusions

In summary, this review comprehensively analyzes the multifaceted roles of lactate and lactylation in shaping the immune system within the context of atherosclerosis. As a chronic inflammatory disease, atherosclerosis is characterized by the complex interplay between lipid metabolism, immune cell infiltration and the local microenvironment. The results highlight the critical roles of lactate and lactylation in modulating immune cell functions, metabolic

reprogramming and epigenetic regulation, thereby influencing the progression and stability of atherosclerotic plaques.

The involvement of lactate and lactylation in the regulation of macrophage polarization, T cell differentiation and B cell metabolism underscores their potential as therapeutic targets. Specifically, lactate-induced metabolic reprogramming and lactylation modifications have been shown to significantly impact the phenotypes and functions of immune cells and contribute to pro-inflammatory and anti-inflammatory responses. These insights provide a deeper understanding of the immune metabolic mechanisms underlying atherosclerosis and pave the way for novel therapeutic strategies targeting lactate metabolism and lactylation pathways.

However, despite the progress made in elucidating the roles of lactate and lactylation in atherosclerosis, several gaps remain in our knowledge. The complex microenvironment of atherosclerotic plaques, characterized by hypoxia, nutrient deprivation and acidosis, is likely to influence the behavior of immune cells and the efficacy of potential treatments. Yet, the precise mechanisms through which these microenvironmental factors interact with lactate and lactylation to modulate immune responses are still not fully understood. Additionally, the diverse metabolic profiles and functional states of immune cells within plaques suggest that a more detailed characterization of immune cell subsets and their specific roles is needed.

Furthermore, the dynamic changes in the atherosclerotic microenvironment over time, from plaque initiation to rupture, add another layer of complexity to the study of immune regulation. The impact of these temporal changes on lactate production, lactylation modifications and immune cell function remains elusive. Furthermore, the potential compensatory mechanisms and feedback loops involving other metabolic pathways and epigenetic modifications in response to lactate accumulation and lactylation need further investigation.

In conclusion, although significant advancements have been made in understanding the roles of lactate and lactylation in atherosclerosis, the intricate interplay between the microenvironment, metabolic changes and immune regulation remains an area of considerable research need. Future studies should focus on unraveling the detailed mechanisms through which the atherosclerotic microenvironment influences lactate metabolism and lactylation, as well as their downstream effects on immune cell function. These will enhance our understanding of the pathophysiology of atherosclerosis and provide new avenues for developing targeted therapies aimed at modulating immune responses and improving clinical outcomes.

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Authors' contributions

YX was involved in the conceptualization of the review, data curation, investigation, methodology and writing-original draft. JZ was responsible for data curation and project administration. JW contributed to the conceptualization, data curation and methodology. HH was involved in conceptualization, data curation, investigation, methodology and writing-original draft, writing-review & editing. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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