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REVIEW

Zou et al: Lactylation in atherosclerosis

Protein lactylation in atherosclerosis – Mechanisms and therapeutic potential: A narrative review

Lijuan Zou[1#], Yingquan Zhu[1#], Yining Lan[1#], Yiheng Cheng[2], Bing Han[3], Jinglian Chen[4], Chao Qin[1*], Daobin Cheng[1*]

[1]Department of Neurology, The First Affiliated Hospital of Guangxi Medical University, Nanning, China;

[2]Department of Urology, The First Affiliated Hospital of Guangxi Medical University, Nanning, China;

[3]Department of Gastroenterology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China;

[4]Colorectal and Anal Disease Unit, Department of Gastrointestinal Surgery, Guangxi Medical University Cancer Hospital, Nanning, China.

*Correspondence to **Daobin Cheng**: chgdb@163.com and **Chao Qin**: mdqc2019@126.com.

[#]Equally contributed to this work: Lijuan Zou, Yingquan Zhu and Yining Lan.

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ABSTRACT

Protein lactylation, which links cellular metabolism to gene regulation and protein function, may influence atherosclerosis. This narrative review explores its cellular mechanisms and therapeutic potential. We searched PubMed from inception to September 30, 2026, for English-language studies and reviews. The synthesis differentiated lactylation from lactate signaling and distinguished direct evidence in atherosclerosis from findings in other disease models. Predominantly preclinical evidence suggests that both histone and non-histone lactylation are involved in endothelial inflammation, endothelial-to-mesenchymal transition, macrophage polarization and ferroptosis, and vascular smooth muscle cell senescence, phenotypic remodeling, and calcification. Depending on the cellular context, modification site, and downstream targets, lactylation can either promote vascular injury or support anti-inflammatory responses and plaque stabilization. Candidate interventions target lactate production, transport, and lactylation-related enzymes, but their effects often lack specificity for lactylation. Much of the therapeutic evidence originates from non-atherosclerotic models, and clinical validation is currently absent. Therefore, therapeutic development should consider cell type, disease stage, and modification site, with validation of causal mechanisms, selectivity, and safety in atherosclerosis models prior to clinical translation.

Keywords: Atherosclerosis, lactylation, cardiovascular and cerebrovascular diseases, glycolysis.

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INTRODUCTION

Cardiovascular and cerebrovascular diseases remain the leading causes of human mortality, with their common pathological basis—atherosclerosis (AS) is still an urgent problem to be solved[1]. AS is a multifaceted pathological process involving endothelial dysfunction and EndMT, macrophage activation and polarization, foam cell formation, and VSMC phenotypic remodeling[2]. Although traditionally attributed to lipid deposition and chronic inflammation, these pathological events are now recognized to be accompanied by, and in part driven by, metabolic reprogramming—particularly enhanced glycolysis[3] and local lactate accumulation[4]—which provides a rationale for investigating lactylation[5] in AS. In recent years, research perspectives have undergone a profound "metabolic shift"[6]: lactate, the end product of glycolysis, is no longer regarded merely as a metabolic waste product but rather as a key signaling molecule. In 2019, the discovery of lysine lactylation modification on histones completely overturned the traditional understanding of lactate's function, opening a new research field that bridges cellular metabolism and epigenetic regulation[7].

Lactylation has rapidly become a research hotspot in fields such as oncology and neurodegenerative diseases, with emerging evidence suggesting its involvement in AS[5, 8-10]. Studies have indicated that lactylation is not only present within AS plaques but may also participate in the progression of AS by regulating critical processes such as endothelial function, macrophage polarization, and smooth muscle cell phenotypic transformation. However, the precise role, molecular mechanisms, and translational potential of this emerging modification in AS remain largely unexplored, representing an "unknown territory" in need of investigation. This narrative review aims to summarize the current state of lactylation research, analyze its core mechanisms driving AS, and prospectively evaluate therapeutic strategies targeting lactylation Unlike recent reviews that broadly summarize lactylation in cardiovascular disease[4, 11], this review provides a cell-type-resolved and evidence-graded synthesis of lactylation in AS, with particular emphasis on direct versus indirect evidence, context-dependent protective and pathogenic effects, and the preclinical nature of current therapeutic data.

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Search strategy and Scope

A literature search was performed in PubMed from inception to September 30, 2026, using combinations of the following keywords: "lactylation", "lactate", "atherosclerosis", "endothelial cell", "macrophage", "vascular smooth muscle cell", "glycolysis", and "post-translational modification". Original studies, reviews, and preclinical studies published in English were considered.

Overview of lactate and lactylation modification

Lactate metabolism and lactylation modification

Lactate is a typical byproduct of glucose metabolism, and its primary production pathway within cells is dependent on glycolysis. Glucose transporters are responsible for the cellular uptake of glucose. Under the coordinated action of key rate-limiting enzymes in glycolysis—hexokinase, phosphofructokinase-1, and pyruvate kinase—glucose is converted into pyruvate. Instead of entering the mitochondria for the tricarboxylic acid cycle, pyruvate is directly reduced to lactate by lactate dehydrogenase[3]. In addition to glycolysis, glutamine catabolism serves as another source of lactate within cells[12]. The transport of lactate both inside and outside of cells is primarily mediated by monocarboxylate transporters (MCTs). MCT1 and MCT4 are bidirectional transporters whose direction depends on proton and concentration gradients[13]. Under typical glycolytic conditions, MCT1 often facilitates lactate uptake and MCT4 facilitates lactate efflux; however, this directionality is not absolute and varies by cell type, metabolic state, and microenvironment. Together, these transporters maintain intracellular lactate homeostasis and provide the substrate foundation for lactylation modification.

Lactate has two stereoisomers, D-lactate and L-lactate; DL-lactate is a racemic mixture of D- and L-lactate rather than a third stereoisomer[14]. Lysine lactylation-related modifications include L-lactylation (Kl-la), D-lactylation (Kd-la), and N-ε-carboxyethylation (Kce) modifications, although their biochemical relationships and formation pathways remain incompletely understood[15-16]. Among them, Kl-la is derived from L-lactate, whereas Kd-la is derived from D-lactate[15-16]. These three lysine modifications alter the chemical properties and spatial conformation of lysine residues, thereby exerting distinct effects on protein function. The specific impact

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depends on the type of protein, the modification site, and the cellular environment[10]. Currently, two major forms of lactylation are recognized: L-lactylation mediated by enzymatic reactions and D-lactylation mediated by non-enzymatic reactions[8, 17]. Among them, L-lactate is the predominant isomer in vivo, and its corresponding Kl-la represents an important glycolysis-responsive modification that has been extensively studied[15]. In contrast, Kd-la, generated through a non-enzymatic process involving lactoylglutathione, is observed only under conditions of impaired glycolytic enzyme systems and is closely associated with microbial metabolism or metabolic disorders[16].

Molecular mechanisms of lactylation modification

Enzyme-mediated L-lactylation is currently the most widely studied type of lactylation. Like other epigenetic modifications, the occurrence of L-lactylation also relies on the catalysis of specific enzymes, including "Writer" (modifying enzymes), "Reader" (modification-binding proteins), and "Eraser" (deconstruction enzymes). In this model, a writer is proposed to transfer a lactyl group from lactyl-CoA to the ε-amino group of lysine residues on histones or non-histone proteins, thereby triggering changes in the conformation and biological function of target proteins, although the formation of lactyl-CoA and the precise enzymatic routes remain incompletely understood[10, 18]. The "Reader" specifically recognizes the lysine modification state of the substrate, mediating the downstream signaling cascade and triggering corresponding biological effects. Once the signaling process concludes, the "Eraser" removes the lactylation modification from the lysine residue of the target protein, thereby terminating the modification process[10]. P300/CBP are among the most extensively studied candidate lactyltransferases, but their roles may be context-dependent and may overlap with acetylation[19-20]. The lactylation mediated by P300 has been implicated in regulating the progression of AS[20]. Whether these enzymes directly catalyze lactylation or indirectly regulate lactate metabolism requires further biochemical validation. In addition, several enzymes have been successively reported as novel lactyltransferases, including AARS1/2[21-23], Tip60/KAT5[24-25], YiaC[26], KAT7/HBO1[27], KAT8[28], GCN5/KAT2A[29], CBP[30], and NAA10[31]. Representative "Eraser" include class I–III histone deacetylases (HDAC1–3) and sirtuin proteins (SIRT1–3)[32]. Studies have

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demonstrated that HDAC2 overexpression reduces histone lactylation levels, thereby suppressing angiogenesis[33]; whereas HDAC3 may exert a protective role in AS by attenuating disease progression through the inhibition of histone lactylation[34]. It is noteworthy that no universally recognized "reader" of lactylation modifications has been identified to date. However, recent studies suggest that Brg1[35], DPF2[36], and TRIM33[37] may serve as potential "readers" involved in the recognition process. Previous research has demonstrated that TRIM33 plays a pivotal role in the activation of late-stage M1 macrophages[38], a process closely associated with histone lactylation[7]. Therefore, further investigations are warranted to elucidate the mechanistic roles of "reader" in lactylation recognition, which may provide deeper insights into the regulatory network of enzymatic lactylation modifications and represents a promising direction for future research in this field. (Figure 1)

Histone lactylation and non-histone lactylation

Similar to other post-translational modifications (PTM), lactylation can occur on both histone and non-histone proteins. Through synergistic regulation, histone and non-histone lactylation participate in multiple cellular processes, including cell proliferation, differentiation, senescence, and immune-inflammatory responses[4, 39-40], thereby serving as an important molecular mechanism linking metabolic states with cellular functions. Lactylation was initially discovered on lysine residues of histones in human HeLa cells and mouse bone marrow–derived macrophages, and in 2019, Zhao Yingming's team[7] identified 28 Kla sites in core histones, predominantly distributed on histone H3 and histone H4. Among these, histone H3 lysine 18 lactylation (H3K18la) is the most extensively studied modification. H3K18la is typically enriched at gene promoters and enhancer regions, where it not only serves as a marker of active gene expression but is also closely associated with diverse physiological and pathological processes, including transcriptional regulation, stem cell and embryonic development, macrophage polarization, and tumorigenesis[41-42]. In addition to H3K18, other histone lactylation sites with regulatory functions have also been reported, such as H2BK6[43], H3K9[27], H3K14[44], H3K23[45], H3K56[46], H4K5[32], H4K8[45], and H4K12[47], etc. Histone lactylation modifications exhibit widespread occurrence and evolutionary conservation, acting as a bridge between cellular metabolism and epigenetic

regulation, and their strong association with disease development highlights their potential as a therapeutic target. Figure 1 summarizes the enzymatic regulation of lactylation on both histones and non-histones.

Recent studies have shown that lactylation modifications are widespread and not limited to specific proteins. The development of mass spectrometry-based lactylation proteomics and proteomics technologies has not only enabled the precise identification of non-histone lactylation sites but also facilitated the discovery of numerous non-histone lactylation sites across different species. Overall, the study of non-histone lactylation contributes to a deeper understanding of various cellular functions and the progression of different diseases. Currently, the exploration of the mechanisms underlying non-histone lactylation remains a key research focus and hotspot in this field. Targeting specific lactylation modification sites to develop precise therapeutic strategies holds great promise for future applications.

Lactate and glycolytic imbalance in atherosclerosis

Previous studies have shown that glycolytic metabolism is significantly enhanced in AS[48]. This enhancement is essentially a glycolytic imbalance, characterized by the loss of normal regulation of glycolysis in cells, leading to excessive activation, sustained enhancement, or a state that does not match cellular demands, which in turn affects the onset and progression of AS. Multispecies studies have confirmed this phenomenon. For instance, in the ApoE−/− mouse model, Sarrazy et al.[49] found that compared to wild-type mice, glucose uptake and glycolysis were significantly increased in the AS plaques of ApoE−/− mice. Similarly, in a rabbit AS model, Yamashita et al.[50] observed significant accumulation of glycolytic metabolites. During the progression of AS, endothelial cells exhibit high glycolytic activity under homeostatic conditions, with their glycolytic rate comparable to that of tumor cells and significantly higher than that of other healthy cells[6]. Approximately 85% of ATP is derived from the glycolytic pathway[51]. However, excessive activation of glycolysis simultaneously induces a pro-inflammatory phenotypic transformation and abnormal proliferation in endothelial cells, stimulates angiogenesis, and ultimately leads to endothelial cell dysfunction, thereby accelerating the progression of AS[6, 52]. Additionally, hemodynamic factors that regulate endothelial cell glycolysis are also associated with AS. Laminar flow, by inhibiting glycolytic activity, induces a

resting endothelial cell phenotype, exerting an anti-AS effect[53]; in contrast, disturbed flow enhances glycolytic activity in endothelial cells, triggering vascular inflammation and promoting the development of AS[54-55]. It is currently widely accepted that the inflammatory activation of macrophages is accompanied by an increase in glycolysis, which serves as a key driving factor in the inflammatory response of AS[56]. Inhibiting glycolytic activity in macrophages can suppress the expression of inflammatory factors and the formation of foam cells, thereby alleviating AS[57-58]. Additionally, enhanced glycolysis also participates in the regulation of vascular smooth muscle cells (VSMCs) proliferation and migration[59-60], with excessive proliferation and migration of VSMCs being one of the primary causes of AS progression[61]. These findings collectively highlight the crucial role of glycolytic imbalance in the development of AS.

Lactate, as a central metabolic product of glycolysis, plays a critical role in AS. It is important to distinguish between the direct metabolic and signaling effects of lactate and the effects specifically mediated by protein lactylation[62]. It not only regulates gene transcription[63] but also activates inflammatory responses that exacerbate AS[64]. Lactate has specific regulatory mechanisms in different cell types. In macrophages, Colegio et al.[65] discovered that lactate promotes macrophage polarization toward the M2 phenotype through the mediation of hypoxia-inducible factor 1α, a mechanism that primarily reflects lactate signaling rather than lactylation. Research by Yang et al.[66] showed that lactate can trigger the transformation of VSMCs from a contractile to a synthetic phenotype, promoting their migration to the vascular endothelium, leading to intimal hyperplasia and stenosis[6]. Additionally, Zhu et al.[67] found that lactate accelerates the osteoblastic phenotypic transformation and calcium deposition in VSMCs, thereby promoting vascular calcification. It is noteworthy that lactate has a dual role in regulating endothelial cell inflammation: it can promote the inflammatory response by activating specific signaling pathways[63], but in certain cases, it can also inhibit inflammation. For instance, Sun et al.[68] confirmed that in endothelial cells exposed to oscillatory shear stress, lactate activates G protein-coupled receptor 81, inducing the expression of anti-AS transcription factors, thereby suppressing endothelial inflammation and slowing the progression of AS. Furthermore, a cross-sectional study involving 1496 participants reported that blood lactate levels were positively correlated with the severity of carotid

atherosclerosis, independent of other cardiovascular risk factors[69]. This suggests that lactate accumulation in plaques may regulate the pathological process of AS through lactylation modifications. In summary, glycolysis not only serves as a central regulator of energy balance in AS, but its metabolic product, lactate, also plays a critical role in determining the progression of AS. (Figure 2)

Mechanisms of lactylation modification in regulating atherosclerosis

Given the extensive regulatory functions of lactylation modifications, their role in AS is gradually being unveiled. AS is a chronic inflammatory process involving multiple cell types, including endothelial cells, VSMCs, monocytes, macrophages, and lymphocytes. Among these, endothelial cell dysfunction, macrophage polarization, foam cell formation, and VSMCs phenotypic transformation are core events driving the occurrence and progression of AS.

Involvement in endothelial cells dysfunction

Endothelial cells play a crucial role in maintaining vascular homeostasis, and their dysfunction is an initial response event in AS, significantly affecting the progression of the disease[70]. Studies have shown that lactate accumulation induced by exercise training promotes the lactylation of lysine 271 on methyl-CpG binding protein 2 (MeCP2) in AS mice (MeCP2 K271la). MeCP2 K271la inhibits the expression of epiregulin (EREG) by binding to chromatin, thereby regulating the mitogen-activated protein kinase (MAPK) signaling pathway. This, in turn, reduces the expression of vascular cell adhesion molecule-1, intercellular adhesion molecule-1, monocyte chemoattractant protein-1, interleukin-1β, and interleukin-6 in endothelial cells, while increasing endothelial nitric oxide synthase (eNOS) levels in the aortic tissues of mice, thus delaying the progression of AS[71]. Additionally, narciclasine was shown to inhibit H3K18la-mediated NF-κB activation by suppressing GLUT1/PFKFB3, reducing endothelial inflammation and early atherogenesis in ApoE−/− mice[72].

Endothelial-to-mesenchymal transition (EndMT) is the process by which endothelial cells lose their characteristic features and transform into mesenchymal cells with fibroblast-like or smooth muscle cell-like properties. This process is a key driver of endothelial cell dysfunction and AS. Transforming growth factor-β (TGF-β) is a critical regulator of EndMT[73]. Studies have shown that lactate itself can activate the

TGF-β/Smad2 signaling pathway, whereas lactylation of Snail1 (a specific post-translational modification) promotes its nuclear translocation, thereby promoting EndMT in endothelial cells[74]. These two effects—lactate signaling and Snail1 lactylation—are mechanistically distinct. Dong et al.[20] found that under the influence of oxidized low-density lipoprotein (ox-LDL), ASF1A-dependent P300 mediated H3K18la. H3K18la was enriched at the Snail1 promoter, activating Snail1 transcription, thus facilitating EndMT, exacerbating endothelial cell dysfunction, and accelerating AS progression. These studies indicate that histone lactylation plays a critical role in EndMT-induced AS; however, emerging evidence suggests that its pathogenic effects extend beyond EndMT. Ma et al.[75] reported that SLC22A6-dependent H3K9la promotes endothelial cell lipid oxidation and dysfunction by transcriptionally activating SCD1, thereby exacerbating AS. A recent study identified an H3K18la-SULF1 axis in endothelial cells, where metabolic stress induces HDAC3 downregulation and H3K18la enrichment at the SULF1 promoter, driving EndMT and plaque instability through HMOX1-mediated iron overload[76].

Both histone and non-histone lactylation modifications exert distinct roles in regulating the endothelial phenotype in AS, suggesting that different modification sites may perform different functions. Further research is needed to elucidate the precise role and mechanisms of lactylation modifications in the regulation of endothelial phenotypes in AS, providing a theoretical foundation for targeted interventions in AS. (Figure 3)

Regulation of macrophages polarization and inflammatory response

Macrophages within atherosclerotic plaques are highly heterogeneous and dynamic. Plaque macrophage phenotypes vary by plaque stage, lipid and cytokine environment, and metabolic state[77]. Beyond the traditional M1/M2 phenotypes, single-cell and spatial transcriptomics have identified resident-like, inflammatory, and TREM2^{high} foamy macrophages, as well as CD163^{+} M(Hb) macrophages, along with plaque-specific subsets such as Mox, Mhem, and M4[77-78]. The distinct plaque microenvironments and developmental stages drive fine-tuned transitions in macrophage phenotypes, which in turn profoundly influence disease progression[77]. A currently accepted view is that in advanced plaques, hypoxia stabilizes HIF-1α,

enhances glycolysis, and promotes an M1-like inflammatory state, whereas early, relatively oxygen-rich lesions tend toward oxidative phosphorylation and M2-like features[48]. Existing evidence suggests that lactylation in macrophages exerts context-dependent dual effects, either promoting reparative M2-like polarization and plaque stability or, under certain conditions, driving pro-inflammatory responses, senescence, and foam cell formation[79-81]. Given this heterogeneity and dynamism, the functional role of lactylation in these cells remains largely unresolved, particularly regarding the glycolysis–lactate–lactylation axis.

To examine this axis, we first consider how glycolysis and lactate influence macrophage phenotype. Glycolysis is widely present in AS macrophages, and its metabolic product, lactate, influences macrophage metabolic reprogramming and phenotypic polarization[7, 82]. Specifically, pro-inflammatory M1-like macrophages undergo metabolic reprogramming toward aerobic glycolysis to meet energy demands, leading to upregulation of glycolytic enzymes and significant lactate production[82]. Lactate not only serves as a metabolic end product of M1-like macrophages but also acts as an important signaling molecule that feedback-regulates macrophage fate. Lactate can induce macrophage senescence by activating the GPR132-Src signaling pathway, promoting oxidized low-density lipoprotein uptake and foam cell formation, thereby exacerbating atherosclerosis in the context of diabetes[83]. In addition, lactate directly drives M2-like macrophage polarization and promotes functional remodeling of tumor-associated macrophages (TAMs) through the ERK/STAT3 signaling pathway[84]; this effect is mediated by lactate signaling rather than by protein lactylation. Zhao et al.[7] observed an increase in lactate and upregulation of H3K18la modification in LPS and interferon-γ-treated pro-inflammatory M1-like polarized macrophages in mice. Inhibition of glycolysis in M1-like polarization led to a reduction in lactate production and histone lactylation. Notably, a set of M2-like genes specifically modified by H3K18la, such as arginase 1 (ARG1), were significantly upregulated during the later stages of inflammation. This suggests that the H3K18la modification in M1-like macrophages after inflammatory stimulation can drive their conversion to the anti-inflammatory M2-like phenotype, a process that is crucial for AS progression. Collectively, these findings suggest that the glycolysis-lactate-lactylation axis may serve as an integrated metabolic pathway regulating macrophage function.

Although lactylation modifications in macrophages have been extensively studied and yielded significant results in other fields, such as cancer, research on lactylation modifications in AS macrophages remains in its early stages, with a limited number of studies to date reporting the functional mechanisms of lactylation modifications in macrophages within the context of AS. One study showed that the deficiency and inhibition of macrophage MCT4 in AS lead to lactate accumulation and increased H3K18la modification. This process, in a P300-dependent manner, activates the transcription of anti-inflammatory genes and tricarboxylic acid cycle genes, inducing the transition of macrophages from the M1-like to M2-like phenotype, thereby ameliorating AS[79]. Furthermore, another study revealed the role of non-histone lactylation modifications in macrophage M2-like polarization. Through proteomic analysis, the study identified the specific lactylation site at lysine 271 (K271) of MeCP2 (MeCP2 K271la). The synergistic effect between MeCP2 K271la and H3K36me3 leads to increased chromatin accessibility and inhibits the expression of the pro-inflammatory transcription factor RUNX1. This enhances exercise-induced M2-like macrophage polarization and increases plaque stability in mice, ultimately improving AS[80]. Although current research on lactylation modifications in AS macrophages remains limited, existing evidence suggests that these modifications play a critical role in mediating M2-like macrophage polarization, anti-inflammatory responses, and plaque stability by regulating both histone and non-histone modifications, indicating that targeting lactylation modifications may represent a novel therapeutic strategy for AS intervention. (Figure 3)

Recent studies have further expanded our understanding of macrophage lactylation in AS. Chen et al. demonstrated that P300-mediated H3K18la promotes METTL3 expression, which accelerates SLC7A11 mRNA degradation via YTHDF2-dependent m6A modification, thereby inducing macrophage ferroptosis and exacerbating atherosclerosis[81]. Liang et al. developed a predictive model for subclinical atherosclerosis based on macrophage histone lactylation-related genes (AUC > 0.817) and showed that Ruan Jian Qing Mai formula reduced plaque area by 39% in ApoE−/− mice[85]. These findings reinforce the concept that macrophage lactylation is a dynamic regulator of AS, with effects depending on the target gene and modification site.

Smooth muscle cells remodeling

VSMCs play a critical role in maintaining vascular homeostasis and regulating blood flow[86-87]. In AS, VSMCs exhibit significant phenotypic plasticity[88], and their aberrant phenotypic transformation is a central pathological event in AS, regulated by lactylation modifications. Studies have shown that Sox10 lactylation drives the transdifferentiation of VSMCs into macrophage-like cells, influencing vascular inflammatory responses[89]. Moreover, VSMC-derived macrophage-like cells exhibit impaired capacity to clear lipids, dead cells, and necrotic debris, which may further contribute to the progression of AS[61]. Beyond transdifferentiation into macrophage-like cells, the phenotypic transition of VSMCs into osteoblast-like cells is also closely associated with lactylation modifications. During this process, VSMCs lose their characteristic smooth muscle features and acquire osteoblast-like properties, ultimately leading to vascular calcification[90]. Ma et al.[90] found that NR4A3 (Nuclear Receptor Subfamily 4 Group A Member 3) is significantly upregulated in calcified human aortas and in mouse models of arterial calcification. NR4A3 enhances glycolytic activity, increasing lactate production, and promoting histone lactylation (particularly H3K18la). This, in turn, activates the expression of Phospho1 (Phosphatase orphan 1), exacerbating VSMC calcification and promoting vascular calcification. Vascular calcification is a key pathological process in the progression of AS, suggesting that VSMCs may further accelerate AS development by promoting vascular calcification.

In addition to phenotypic plasticity, lactylation regulation during VSMCs senescence also contributes to the progression of AS. Previous studies have confirmed that senescent VSMCs promote AS and plaque instability[91-93]. Li et al.[34] found that in a VSMCs senescence model, tumor necrosis factor receptor-associated protein 1 (TRAP1) significantly enhances glycolysis, leading to increased lactate levels. The accumulated lactate promotes the enrichment of histone H4 lysine 12 lactylation (H4K12la) by downregulating the activity of histone deacetylase 3 (HDAC3). H4K12la is enriched in the promoter region of senescence-associated secretory phenotype (SASP) genes, and by activating SASP transcription, it exacerbates VSMCs senescence and accelerates the progression of AS. Similarly, Glut1 was found to be upregulated in mouse aortic VSMCs during AS progression, promoting

VSMC senescence through the glycolysis-lactate-H3K18la axis. Knockdown of Glut1 or reduction of intracellular lactate attenuated the senescence phenotype, whereas overexpression of Glut1 exacerbated it. Notably, knockout of the lactylation writer P300 or overexpression of the eraser HDAC1 also improved the premature senescence phenotype[94]. Together, these findings suggest that both TRAP1-H4K12la and Glut1-H3K18la axes contribute to VSMC senescence in AS, suggesting that these pathways may represent potential targets for further investigation. (Figure 3)

Context-dependent roles of lactylation in AS: A spatiotemporal and microenvironmental perspective

The functional consequences of lactylation in AS are shaped by the plaque microenvironment and disease stage. AS is a chronic, multi-stage, and spatiotemporally heterogeneous disorder in which endothelial cells, macrophages, and VSMCs are exposed to distinct local cues, including lipid accumulation, ox-LDL, laminar versus disturbed flow, hypoxia, inflammatory cytokines, necrotic debris, and lactate. These cues modulate glycolytic flux, lactate production and transport, and the expression or activity of lactylation writers, erasers, and readers, thereby determining cell type-specific and site-specific lactylation patterns.

Consequently, the same modification can exert protective or detrimental effects depending on cell type, plaque stage, local lactate concentration and gradients, subcellular localization, and downstream target genes. For example, MCT4 inhibition-induced H3K18la[79] and MeCP2 K271la[80] in macrophages suppress inflammation and promote plaque stability, whereas endothelial Snail1 lactylation[74] drives EndMT and VSMC TRAP1-driven H4K12la[34] promotes senescence.

Beyond these pathways, lactylation also play a role in angiogenesis[33, 95], valve calcification[96-97], and lipid synthesis[98], suggesting that it may influence AS through additional biological processes. However, most of these findings are derived from non-AS models and should be considered indirect evidence.

In summary, lactylation serves as a critical molecular mechanism that bridges cellular metabolic status with epigenetic regulation, exerting cell type-specific functions in endothelial cells, macrophages, and VSMCs to collectively regulate the initiation and

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progression of AS. Current research on lactylation modifications involved in AS is summarized in Table 1, which provides detailed information on the specific modification sites, the associated enzymes mediating these modifications, and their functional roles.

We propose that lactylation should be interpreted within a spatiotemporal and microenvironment-oriented framework: early lesions may be biased toward endothelial activation and monocyte recruitment, whereas advanced plaques may shift toward VSMC senescence, calcification, and instability, while specific macrophage/endothelial reparative pathways remain active. Future studies should therefore define lactylation by integrating cell type, plaque stage, subcellular localization, modification site, and microenvironmental signals to reconcile apparent discrepancies and identify context-appropriate therapeutic targets.

Therapeutic potential of lactylation-related targets in atherosclerosis

Lactylation, as a novel PTM directly mediated by lactate, bridges cellular metabolism (particularly glycolysis) with gene expression regulation. In AS, a complex chronic inflammatory disease, elevated lactate levels and lactylation modifications have been shown to play key roles in various pathological processes. To date, several preclinical compounds have been reported to modulate lactylation-related pathways. However, most evidence comes from non-AS disease models, and many targets are multifunctional. Table 2 summarizes preclinical compounds potentially affecting lactylation-related pathways, with disease models and evidence levels indicated.

Targeting lactylation-related enzymes

Previous studies have identified several inhibitors targeting the P300 acetyltransferase, including C646[30], A485[95], and Andrographolide (AGP)[97]. Research has shown that inhibiting the lactylation "Writer" P300 with A485 reduces the lactylation of YY1, thereby inhibiting angiogenesis[95]. C646 directly inhibits the activity of P300 acetyltransferase, leading to increased expression of Klotho (an anti-aging and anti-calcification protein), which in turn suppresses Akt phosphorylation and ultimately delays the progression of valvular calcification[99]. Wang et al.[97] found that AGP, as a natural P300 inhibitor, directly binds to the bromodomain of P300, decreasing H3K18la levels and reducing the area of valvular calcification, suggesting that it

could be an effective drug for preventing calcific aortic valve disease. Given that pathological angiogenesis and vascular calcification are central pathological events in AS, targeting P300 and its mediated lactylation modifications to inhibit calcification and abnormal vessel formation holds potential as a therapeutic target for AS. However, because P300 is a multifunctional acetyltransferase with broad substrate specificity, the beneficial effects of these compounds cannot be attributed solely to lactylation. Direct AS studies are needed to determine whether P300 inhibition produces net benefit in AS and whether such effects are lactylation-dependent.

In addition to drugs targeting the lactylation "Writer" P300, interventions aimed at lactylation "Eraser" (such as SIRT1 and HDAC) are also important areas of research. For example, Chen et al.[100] found that the SIRT1 activator SRT1720 significantly alleviated angiotensin II (AngII)-induced AS in APOE−/− mice by inhibiting vascular inflammation and suppressing the activation of two pro-AS pathways, NF-κB and STAT3. Additionally, Gao et al.[101] demonstrated that the pan-HDAC inhibitor Trichostatin A (TSA) reduces foam cell formation and enhances the expression of PPARγ (peroxisome proliferator-activated receptor γ), a key mediator of the anti-AS effects of HDAC inhibition, thereby exerting protective effects in AS. Macrophage inflammatory responses, endothelial dysfunction, VSMCs phenotypic transformation, and foam cell formation are all critical pathological events in AS, and interventions targeting these processes provide new therapeutic approaches for alleviating AS. However, the specificity of these compounds for lactylation-related pathways requires further investigation.

Targeting lactate production and transport

Lactate dehydrogenase (LDH), as the terminal enzyme of glycolysis, directly determines the rate of lactate production. Inhibiting LDH activity can reduce the glycolytic rate, decrease lactate production, and lower blood lactate levels. Wu et al.[102] found that the combination of the LDH inhibitor oxamate and metformin treatment significantly reduced serum lactate levels and pro-inflammatory cytokine expression in diabetic mice, while also improving insulin sensitivity and blood glucose control. Given that diabetes is a major independent risk factor for the onset and progression of AS, targeting lactate production may provide a potential

therapeutic strategy for diabetes-related AS. Lactate is primarily transported in the body through MCT. The team led by Fan[74] found that the MCT inhibitor CHC can alleviate lactate-induced EndMT and Snail1 lactylation modifications. Additionally, two studies have provided evidence for MCT4 inhibition: the MCT4 inhibitor VB124 promotes a reparative macrophage phenotype[79], and Qinggan Jianpi formula attenuates AS by suppressing the HIF-1α/MCT4 axis and activating H3K18la-mediated reparative gene programs in macrophages[103]. LDH and MCT influence the local microenvironment by regulating lactate production and transport, respectively. Their coordinated intervention may more efficiently regulate lactylation modifications. The apparently opposite effects of LDH inhibition (reducing lactate production) and MCT4 inhibition (increasing intracellular lactate retention) are not necessarily contradictory. LDH inhibition reduces systemic and intracellular lactate production, thereby lowering the availability of lactate as a substrate for lactylation. In contrast, MCT4 inhibition blocks lactate efflux, leading to intracellular lactate accumulation and, in specific macrophage contexts, increased H3K18la-mediated reparative gene programs. This difference reflects cell-type-specific transporter expression, intracellular versus extracellular lactate gradients, and context-dependent downstream effects. Therefore, these interventions are not interchangeable and require careful cell-specific evaluation. Thus, targeting lactate production and transport should be considered a context-dependent strategy. These findings suggest that targeting lactate production and transport, thereby affecting its concentration in the local microenvironment and accumulation within cells, could be a potential strategy for regulating lactylation modifications and delaying the progression of AS.

In summary, pharmacological interventions targeting lactylation-related enzymes and regulating lactate production and transport can effectively modulate the core pathological processes of AS, including inflammation, angiogenesis, calcification, VSMCs phenotypic transformation, foam cell formation, endothelial dysfunction, and EndMT. Such intervention strategies, which address the intersection of metabolism and epigenetics, may provide a complementary perspective for future AS research and drug development. However, current evidence is largely preclinical, and clinical validation is still lacking. While several findings discussed above were obtained in non-AS models, they provide indirect insights and potential clues for AS research, especially where shared pathological mechanisms exist. Notably, MCT4 inhibition

and QGJP have been directly investigated in AS and offer more robust evidence. Although specific therapies directly targeting lactylation modifications in AS remain underdeveloped, these compounds serve as useful pharmacological tools for target validation and may guide future therapeutic development. Future research should therefore focus on lactate production, lactylation-related enzymes, lactylation-specific sites, and associated signaling pathways, with validation in AS-specific models, thereby offering more innovative therapeutic strategies for the treatment of AS.

CONCLUSION AND PERSPECTIVES

Although the role of lactylation modifications in AS is gradually being revealed, several challenges remain: (1) Developing high-specificity, high-throughput, and low-cost lactylation modification detection technologies to promote their clinical application; (2) Establishing gene-edited animal models (such as lactylation enzyme knockout mice) to clarify the causal relationship between lactylation modifications and AS; (3) The interactions between lactylation and other post-translational modifications (such as acetylation and ubiquitination) are still unclear, requiring the use of multi-omics technologies to analyze dynamic regulatory networks. In particular, the crosstalk between lactylation and other acylation modifications such as crotonylation and succinylation, which have been implicated in cardiovascular disease[104], remains to be explored in AS; (4) Developing small molecule inhibitors or activators targeting lactylation modifications and evaluating their therapeutic potential in AS; (5) Investigating the shared mechanisms of lactylation in metabolic diseases (such as diabetes, obesity, and other diseases comorbid with AS) to identify broad-spectrum therapeutic targets; (6) Exploring the cell specificity of lactylation modifications (such as endothelial cells, macrophages, VSMCs) and their interactions; (7) Assessing the long-term safety and clinical feasibility of drugs targeting lactylation modifications.

Lactylation modifications, as a key hub in metabolism and epigenetic regulation, play a crucial role in AS, offering a novel perspective for its intervention. Future research should integrate multi-omics analysis and spatial transcriptomics technologies to further elucidate the spatiotemporal specificity of the lactylation modification regulatory network. The context-dependent duality of lactylation poses a central challenge for therapy: the same modification site can be protective in one cell type but

detrimental in another. Therefore, therapeutic strategies should be cell type-, stage-, and site-specific. However, current evidence is largely preclinical, and no clinical data yet support lactylation-targeted therapy for AS.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Lactylation sites and their roles in atherosclerosis and related vascular pathologies

Protein/site	Enzyme	Cell type	Model/disease	Evidence level	AS relevance	Function	Reference
H3K9	HDAC2	Endothelial cells	VEGF-induced angiogenesis	Animal model	Indirect	Promoting angiogenesis	PMID: 38918851
H3K14la / H3K9la	—	VICs	CAVD (ApoE−/−/LUM−/− mice)	Cell culture + Animal model + Human tissue	Related	Promoting valve calcification	PMID: 38976370
H3K18	P300	Macrophages	AS (ApoE−/−)	Animal model	Direct	Promoting anti-inflammatory gene transcription and delaying AS (protective)	PMID: 38733581
H3K18la	P300/ASF1A	Endothelial cells	AS (ApoE KO / Asf1a ECKO)	Animal model + Human tissue	Direct	Promoting EndMT and AS (detrimental)	PMID: 39027248

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H4K12	HDAC3	VSMCs	AS (VSMC Trap1 KO / ApoE KO)	Animal model	Direct	Promoting VSMC senescence and exacerbating AS	PMID: 39088352
MeCP2 K271	P300	Endothelial cells	AS (HFD ApoE−/− + exercise)	Animal model	Direct	Suppressing inflammatory response and slowing down AS	PMID: 37245426
FASN	—	3T3-L1 cells	HIIT mice / 3T3-L1 adipocytes	Cell culture + Animal model	Indirect	Inhibiting fat synthesis	PMID: 37726733
Sox10	—	VSMCs	Neointimal hyperplasia	Animal model	Related	Promoting vascular inflammatory response	PMID: 37481722
Snail1	P300/CBP	Endothelial cells	Post-MI EndMT	Animal model	Indirect	Promoting EndMT	PMID: 36735787

Model/disease: The experimental model or disease context of each study. Evidence level: Cell culture (*in vitro* cell experiments); Animal model (*in vivo* animal experiments); Human tissue (human specimens). No clinical trial data are currently available for lactylation-targeted therapy in AS. AS relevance: Direct (direct AS model evidence); Related (related vascular pathology, e.g., CAVD, neointimal hyperplasia); Indirect (evidence extrapolated from non-AS models). P300/CBP act as lactylation writers, whereas HDAC2 and HDAC3 act as lactylation erasers; their roles are context- and cell type-dependent. ASF1A functions as a histone chaperone cooperating with P300. **Abbreviations**: ApoE,

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apolipoprotein E; AS, atherosclerosis; ASF1A, anti-silencing function 1A histone chaperone; CAVD, calcific aortic valve disease; CBP, cyclic adenosine monophosphate response element-binding protein-binding protein; ECKO, endothelial cell-specific knockout; EndMT, endothelial-to-mesenchymal transition; FASN, fatty acid synthase; H3K14la, histone H3 lysine 14 lactylation; H3K18, histone H3 lysine 18; H3K18la, histone H3 lysine 18 lactylation; H3K9, histone H3 lysine 9; H3K9la, histone H3 lysine 9 lactylation; H4K12, histone H4 lysine 12; HDAC2, histone deacetylase 2; HDAC3, histone deacetylase 3; HFD, high-fat diet; HIIT, high-intensity interval training; K271, lysine 271; KO, knockout; LUM, lumican; MeCP2, methyl-CpG-binding protein 2; MI, myocardial infarction; P300, histone acetyltransferase p300; PMID, PubMed identifier; Snail1, snail family transcriptional repressor 1; Sox10, sex-determining region Y-box transcription factor 10; Trap1, tumor necrosis factor receptor-associated protein 1; VEGF, vascular endothelial growth factor; VICs, valvular interstitial cells; VSMCs, vascular smooth muscle cells.

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Table 2. Preclinical compounds with potential effects on lactylation-related pathways in atherosclerosis and related conditions

Target	Compound	Relationship	Model/disease	Evidence level	AS relevance	Reported setting	Reference
P300	C646	Inhibition	Aortic valvular calcification (in vitro osteogenic differentiation of VICs)	Cell culture	Indirect	Aortic valvular calcification	PMID: 28111052
P300	A485	Inhibition	Retinal neovascularization (oxygen-induced retinopathy)	Cell culture + Animal model	Indirect	Retinal neovascularization	PMID: 37085894
P300	AGP	Inhibition	CAVD (HF-fed ApoE−/− mice; VICs)	Cell culture + Animal model	Related	CAVD	PMID: 38378175
SIRT1	SRT1720	Promotion	AS (Ang II-induced ApoE−/− mice)	Animal model	Direct	AS	PMID: 26296466
HDAC	TSA	Inhibition	AS (ApoE-deficient mice)	Animal model	Direct	AS	PMID: 32621955
LDH	Oxamate	Inhibition	Type 2 diabetes (db/db	Animal model	Indirect	Diabetic mice	PMID: 28728159

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			mice)				
MCT	CHC	Inhibition	post-MI EndMT model	Animal model	Indirect	Myocardial infarction	PMID: 36735787
MCT4	VB124	Inhibition	AS (ApoE−/− mice)	Animal model	Direct	AS	PMID: 38733581
MCT4/ HIF-1α	QGJP	Inhibition	AS (ApoE−/− mice; ox-LDL-induced THP-1 macrophage injury)	Cell culture + Animal model	Direct	AS	PMID: 42032694

Model/disease: The experimental model or disease context of each study. Evidence level and AS relevance are defined in Table 1. Compounds with "Indirect" or "Related" AS relevance were tested in non-AS models. Most of these compounds target multifunctional enzymes or lactate metabolism, so their beneficial effects cannot be attributed solely to lactylation modulation. **Abbreviations**: AGP, andrographolide; Ang II, angiotensin II; ApoE, apolipoprotein E; AS, atherosclerosis; CAVD, calcific aortic valve disease; CHC, α-cyano-4-hydroxycinnamate; db/db, mice homozygous for the leptin receptor diabetes mutation; EndMT, endothelial-to-mesenchymal transition; HDAC, histone deacetylase; HF, high-fat; HIF-1α, hypoxia-inducible factor 1-alpha; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; MCT4, monocarboxylate transporter 4; MI, myocardial infarction; ox-LDL, oxidized low-density lipoprotein; P300, histone acetyltransferase p300; PMID, PubMed identifier; QGJP, Qinggan Jianpi formula; SIRT1, sirtuin 1; THP-1, human acute monocytic leukemia cell line; TSA, trichostatin A; VICs, valvular interstitial cells.

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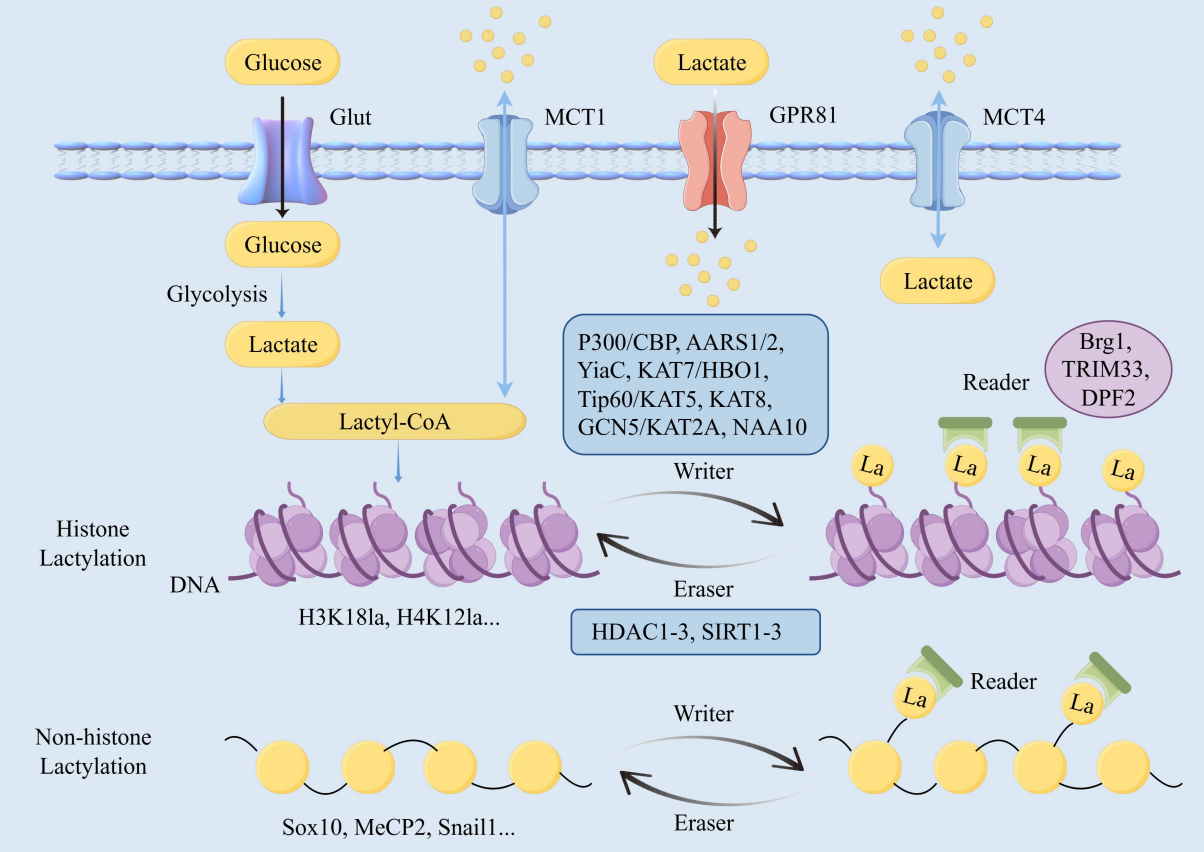


Figure 1. Metabolic and enzymatic regulation of histone and non-histone lactylation. Glucose uptake through Glut supplies glycolysis for intracellular lactate production. MCT1 and MCT4 mediate bidirectional lactate transport governed by proton and lactate concentration gradients, and extracellular lactate activates GPR81-mediated signaling. Lactylation writers catalyze the addition of lactyl groups to lysine residues on histones and non-histone proteins. Reported writers include P300/CBP, AARS1/2, Tip60/KAT5, KAT7/HBO1, KAT8, GCN5/KAT2A, NAA10, and the bacterial enzyme YiaC. The illustrated lactyl-CoA pathway represents one route of enzymatic lactylation; AARS1/2 catalyze a distinct ATP-dependent, lactyl-CoA-independent reaction. HDAC1–3, which belong to class I histone deacetylases, and SIRT1–3 act as lactylation erasers. Brg1, DPF2, and TRIM33 have been reported as readers of histone lactylation in specific experimental settings. Representative modifications shown include H3K18la and H4K12la, together with lactylation of the non-histone proteins Sox10, MeCP2, and Snail1. The schematic summarizes mechanisms reported across different biological systems. **Abbreviations**: AARS1/2, alanyl-transfer ribonucleic acid synthetases 1 and 2; ATP, adenosine triphosphate;

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Brg1, Brahma-related gene 1; CBP, cyclic adenosine monophosphate response element-binding protein–binding protein; CoA, coenzyme A; DNA, deoxyribonucleic acid; DPF2, double plant homeodomain fingers 2; GCN5, general control nonderepressible 5; Glut, glucose transporter; GPR81, G protein-coupled receptor 81; H3K18la, histone H3 lysine 18 lactylation; H4K12la, histone H4 lysine 12 lactylation; HBO1, histone acetyltransferase binding to origin recognition complex subunit 1; HDAC1–3, histone deacetylases 1–3; KAT2A, lysine acetyltransferase 2A; KAT5, lysine acetyltransferase 5; KAT7, lysine acetyltransferase 7; KAT8, lysine acetyltransferase 8; La, lactyl group; MCT1/4, monocarboxylate transporters 1 and 4; MeCP2, methyl-CpG-binding protein 2; NAA10, N-alpha-acetyltransferase 10; P300, histone acetyltransferase p300; SIRT1–3, sirtuins 1–3; Snail1, snail family transcriptional repressor 1; Sox10, sex-determining region Y-box transcription factor 10; Tip60, 60-kilodalton Tat-interactive protein; TRIM33, tripartite motif-containing protein 33; YiaC, bacterial acetyltransferase YiaC.

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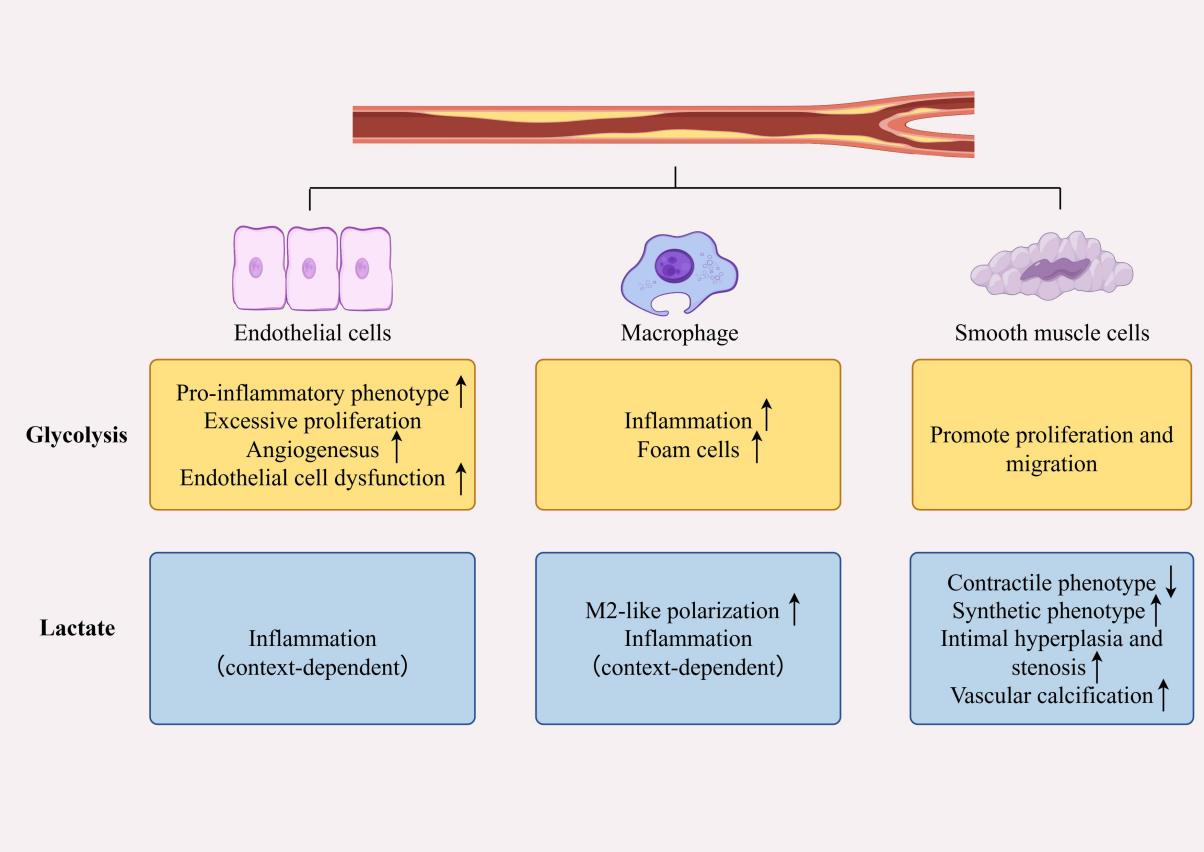


Figure 2. Effects of enhanced glycolysis and lactate on cellular processes relevant to atherosclerosis. Yellow boxes summarize the effects of enhanced glycolysis, and blue boxes summarize the effects of lactate in endothelial cells, macrophages, and vascular smooth muscle cells. Excessive endothelial glycolysis promotes a pro-inflammatory phenotype, abnormal proliferation, angiogenesis, and endothelial dysfunction. In macrophages, enhanced glycolysis supports inflammatory activation and foam cell formation, while in vascular smooth muscle cells, it promotes proliferation and migration. Lactate has context-dependent effects on endothelial and macrophage inflammation and can favor M2-like macrophage polarization in specific experimental settings. In vascular smooth muscle cells, lactate can promote a shift from a contractile to a synthetic phenotype, contributing to intimal hyperplasia and stenosis, as well as osteogenic differentiation and vascular calcification. The schematic integrates findings from different experimental models and summarizes metabolic and signaling effects that should be distinguished from effects specifically mediated by protein lactylation. Upward and downward arrows indicate increases and decreases, respectively. **Abbreviation**: M2, alternatively activated macrophages.

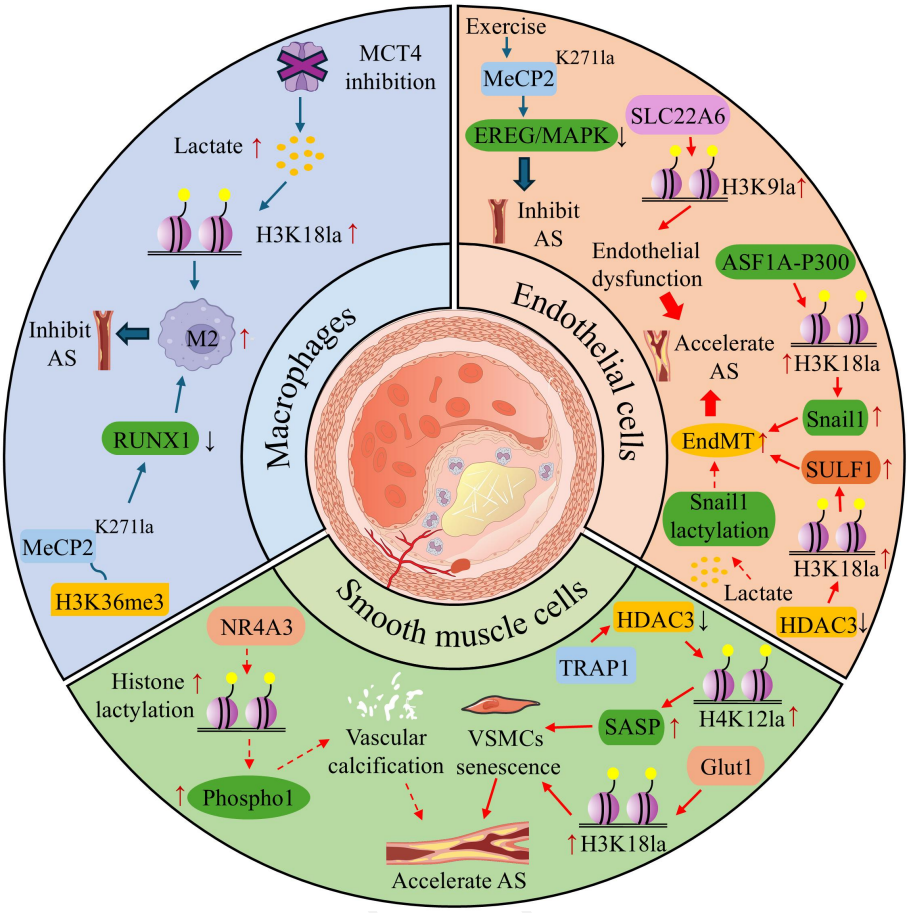


Figure 3. Selected cell-specific lactylation pathways in atherosclerosis and related vascular models. In macrophages, MCT4 inhibition increases intracellular lactate and H3K18la, promoting reparative M2-like polarization. MeCP2 K271la interacts with H3K36me3 to suppress RUNX1 expression and favor M2-like polarization, contributing to atheroprotection. In endothelial cells, exercise-induced MeCP2 K271la suppresses EREG/MAPK signaling and attenuates AS. SLC22A6-dependent H3K9la promotes endothelial dysfunction, whereas ASF1A-dependent P300-mediated H3K18la increases Snail1 expression and promotes EndMT. HDAC3 downregulation increases H3K18la enrichment at the *SULF1* promoter, activating SULF1 expression and EndMT. Lactate-induced Snail1 lactylation also promotes EndMT in myocardial infarction models. In VSMCs, TRAP1-associated HDAC3 downregulation enhances H4K12la and SASP gene expression, promoting senescence and AS. Glut1-dependent H3K18la promotes VSMC senescence in vitro, while NR4A3-driven histone lactylation increases Phospho1 expression and promotes medial arterial calcification in non-AS models. Solid arrows indicate findings from AS

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studies and AS-related cellular models; dashed arrows indicate mechanisms identified in other disease models whose relevance to AS is extrapolated. Blue and red connecting arrows indicate protective and pathogenic pathways, respectively. Upward and downward arrows indicate increases and decreases in the corresponding molecules or cellular processes. **Abbreviations**: AS, atherosclerosis; ASF1A, anti-silencing function 1A histone chaperone; EndMT, endothelial-to-mesenchymal transition; EREG, epiregulin; Glut1, glucose transporter 1; H3K18la, histone H3 lysine 18 lactylation; H3K36me3, histone H3 lysine 36 trimethylation; H3K9la, histone H3 lysine 9 lactylation; H4K12la, histone H4 lysine 12 lactylation; HDAC3, histone deacetylase 3; K271la, lysine 271 lactylation; M2, alternatively activated macrophages; MAPK, mitogen-activated protein kinase; MCT4, monocarboxylate transporter 4; MeCP2, methyl-CpG-binding protein 2; NR4A3, nuclear receptor subfamily 4 group A member 3; P300, histone acetyltransferase p300; Phospho1, phosphatase orphan 1; RUNX1, runt-related transcription factor 1; SASP, senescence-associated secretory phenotype; SLC22A6, solute carrier family 22 member 6; Snail1, snail family transcriptional repressor 1; SULF1, sulfatase 1; TRAP1, tumor necrosis factor receptor-associated protein 1; VSMCs, vascular smooth muscle cells.

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