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REVIEW

Trained Immunity–Like Memory in Vascular Structural Cells: Metabolic–Epigenetic Reprogramming as a Driving Mechanism of Atherosclerosis and Residual Cardiovascular Risk

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Abstract: Despite major advances in lipid-lowering therapies and widespread achievement of optimal LDL-C targets, a substantial burden of residual cardiovascular risk (RCVR) persists, underscoring fundamental gaps in current preventive strategies. Existing mechanistic frameworks have largely centered on professional immune cells as the primary drivers of chronic vascular inflammation, insufficiently accounting for the durability and tissue specificity of vascular pathology after risk factor correction. Emerging evidence supports a paradigm in which vascular structural cells (VSCs), notably endothelial cells (ECs) and vascular smooth muscle cells (VSMCs), acquire a trained immunity–like state that enables them to act as a long-term reservoir of pathogenic molecular memory. Repeated metabolic, inflammatory, or mechanical priming induces persistent phenotypic switching in VSCs through a tightly coupled metabolic–epigenetic axis. This process is characterized by PFKFB3-driven glycolytic reprogramming, rewired mitochondrial metabolism with accumulation of tricarboxylic acid cycle intermediates such as succinate and fumarate, and the establishment of stable epigenetic scars, including H3K4me1, H3K27ac, and histone lactylation. These epigenetic imprints lower activation thresholds and sustain exaggerated inflammatory and proliferative responses, providing a mechanistic basis for chronic vascular remodeling in clinical entities such as in-stent restenosis and cardiac allograft vasculopathy. Targeting vascular molecular memory by erasing maladaptive epigenetic programs, using bromodomain and extraterminal domain inhibitors or metabolic modulators such as metformin, represents a promising therapeutic avenue to mitigate RCVR beyond conventional lipid-centric approaches.

Keywords: trained immunity–like response, vascular structural cells, metabolic–epigenetic axis, epigenetic scars, residual cardiovascular risk

Introduction

Atherosclerosis (AS) is a chronic inflammatory disease characterized by endothelial dysfunction, oxidative stress, and dysregulated lipid metabolism, and it constitutes the major pathological basis of cardiovascular diseases such as coronary heart disease, myocardial infarction, and stroke.[1–3] Over recent decades, lipid-lowering therapies such as statins and PCSK9 inhibitors have substantially reshaped the prevention and management of ASCVD by markedly reducing low-density lipoprotein cholesterol (LDL-C) levels.[4–7] However, extensive evidence from clinical trials indicates that even after achieving recommended LDL-C targets with statins, non-statin agents, or combination therapies, patients continue to experience recurrent cardiovascular events, a phenomenon known as "residual risk".[8–10] Accumulating evidence indicates that chronic low-grade inflammation is a key driver of residual risk and that anti-inflammatory interventions can partially reduce cardiovascular events.[11,12] The CANTOS trial provided the first proof that targeting interleukin-1β (IL-

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1β) lowers cardiovascular events independently of lipid reduction.[13] Nevertheless, broad immunosuppression increases infection risk, underscoring the need to identify upstream mechanisms sustaining vascular inflammation.[14]

Traditionally, immunological memory—defined as the ability to mount faster and stronger responses upon re-encounter with previously encountered pathogens—has been regarded as an exclusive feature of the adaptive immune system, namely T and B lymphocytes.[15,16] The concept of "trained immunity" (also referred to as innate immune memory), first proposed by Netea et al, challenged this dogma by demonstrating that innate immune cells also possess memory-like properties.[17] In contrast to adaptive immunity, which relies on antigen-specific gene rearrangements, trained immunity is mediated by metabolic reprogramming (such as enhanced glycolysis) and epigenetic remodeling (including modifications of H3K4me1 and H3K27ac), enabling innate immune cells—such as monocytes, macrophages, and natural killer cells—to mount amplified nonspecific inflammatory responses to subsequent stimuli following transient exposure to exogenous (e g., Candida albicans, BCG vaccination) or endogenous (e g., oxidized LDL, hyperglycemia) triggers.[18–20]

Current research on trained immunity in atherosclerosis has primarily focused on circulating monocytes and bone marrow progenitor cells.[21,22] However, this immune cell–centric perspective may be insufficient to fully explain the long-term persistence of vascular inflammation and lesions. Vascular structural cells (VSCs), particularly endothelial cells (ECs) and vascular smooth muscle cells (VSMCs), are not inert scaffolds but active participants in the maintenance of vascular homeostasis and pathological remodeling.[23,24] Their longevity renders them plausible candidates for sustaining long-term pathogenic imprinting. Observations of "metabolic memory" in diabetic vascular and renal complications suggest durable epigenetic imprinting within long-lived structural cells.[25–28] Consistently, single-cell transcriptomic and epigenomic analyses indicate that ECs and VSMCs undergo stable chromatin remodeling after disturbed flow or pro-atherogenic lipid exposure, adopting persistent pro-inflammatory or dedifferentiated states reminiscent of trained immunity.[29,30]

At this point, it is essential to clarify conceptual boundaries. Classical trained immunity refers to enhanced responsiveness in short-lived innate immune cells, sustained in part through progenitor reprogramming in the bone marrow. By contrast, the memory-like phenotypes observed in vascular structural cells arise in long-lived, tissue-resident cells that are not primarily specialized for pathogen defense. Rather than generating acute inflammatory amplification, these cells tend to develop persistent pro-inflammatory and pro-remodeling states under chronic metabolic or mechanical stressors.[31,32] Although such states similarly involve epigenetic stabilization and metabolic rewiring, their functional consequences are predominantly linked to structural remodeling and chronic vascular pathology. Accordingly, although mechanistically analogous to classical trained immunity, these vascular phenotypes do not fully conform to its canonical immunological definition and are therefore more appropriately designated as "trained immunity-like" responses. A conceptual comparison between classical trained immunity in professional immune cells and TI-like states in vascular structural cells is summarized in Table 1.

Importantly, analogous memory-like reprogramming has been described in other long-lived structural cells beyond the vasculature. Cardiac fibroblasts exposed to transient stress can develop sustained pro-fibrotic programs, while renal mesangial cells demonstrate persistent epigenetic alterations following hyperglycemic exposure.[33,34] Comparable findings in epithelial and stromal compartments suggest that durable chromatin imprinting after environmental stress may represent a broader feature of structural cell biology rather than a vascular-restricted phenomenon. From a comparative biological perspective, such imprinting may reflect a potentially conserved stress-adaptation program in long-lived tissue-resident cells. Under conditions of chronic metabolic or inflammatory burden, however, this adaptive imprinting may become maladaptive, promoting sustained inflammation and pathological remodeling.

This review integrates recent advances to elucidate how ECs and VSMCs establish and maintain pathological memory through metabolic-epigenetic coupling and explores the implications of these "epigenetic scars" in in-stent restenosis, transplant vasculopathy, and progressive atherosclerosis.

Vascular Structural Cells: Experimental Evidence and Phenotypic Heterogeneity of Non-Professional Immune Memory

The vascular wall is not merely a passive victim of atherogenic stress but rather an active, highly plastic responsive unit. Emerging evidence indicates that vascular endothelial cells (ECs) and vascular smooth muscle cells (VSMCs), following

Table 1 Trained Immunity in Immune and Vascular Cells This Table Illustrates a Comparative Overview of Trained Immunity in Professional Immune Cells and Trained Immunity–Like States in Vascular Structural Cells. In Both Cell Types, Transient Inflammatory or Metabolic Stimuli Induce Metabolic Rewiring and Epigenetic Remodeling That Lower Activation Thresholds Upon Restimulation. While Immune Cells Exhibit Enhanced Glycolysis and Transient Epigenetic Changes Limited by Cellular Turnover, Endothelial Cells and Vascular Smooth Muscle Cells Develop More Stable Chromatin Reprogramming Due to Their Long-Lived, Tissue-Resident Nature. These Persistent Molecular Imprints Sustain Exaggerated Inflammatory and Phenotypic Responses, Providing a Mechanistic Basis for Chronic Vascular Inflammation and Residual Cardiovascular Risk Beyond Traditional Lipid-Centered Paradigms

Comparison Dimension	Trained Immunity (Professional Immune Cells)	Vascular Structural Cells (TI-like State)
Representative Cells	Monocytes, Macrophages, and NK cells.	Endothelial Cells (ECs) and Vascular Smooth Muscle Cells (VSMCs).
Primary Stimuli	Microbial components, BCG, oxLDL, and high glucose.	Disturbed flow (d-flow), high glucose, oxLDL, and mechanical injury.
Sensing Mechanisms	Pattern Recognition Receptors (PRRs, e. g. TLRs).	Mechanoreceptors (e. g. Piezo1) and PRRs
Metabolic Reprogramming	Enhanced glycolysis; mTOR/HIF-1α activation.	PFKFB3-dependent glycolytic enhancement; impaired mitochondrial function.
Epigenetic Features	H3K4me1, H3K27ac, and latent enhancers.	Stable enhancer remodeling and alterations in chromatin accessibility.
Functional Consequences	Enhanced non-specific inflammatory response upon restimulation.	Low-threshold, hyper-responsive pro-inflammatory or dedifferentiated state.
Persistence	Short-to-medium term (limited by circulatory turnover).	Long-term and stable (due to the resident, long-lived nature of VSCs).
Pathological Significance	Amplification of innate immune-mediated inflammation.	Maintenance of chronic vascular inflammation and residual cardiovascular risk.

transient pathological insults, can convert short-lived stimuli into durable functional alterations through molecular-level "imprints," a process that closely mirrors trained immunity in innate immune cells in both functional characteristics and molecular underpinnings.

Endothelial Cells: Metabolic Memory and the Hemodynamic "Legacy Effect"

Endothelial cells (ECs), serving as the physical interface between circulating blood and underlying tissues, are the primary sensors of systemic metabolic disturbances. In diabetic vascular complications, this early stress sensing is frequently translated into persistent functional dysfunction, a phenomenon termed "metabolic memory" or the "legacy effect".[35,36] The landmark UK Prospective Diabetes Study (UKPDS) demonstrated that early intensive glycemic control confers cardiovascular protection lasting for decades, with benefits persisting even after subsequent normalization of blood glucose levels, suggesting the existence of a pathogenic "record" within the vascular wall that is independent of contemporaneous glycemic status.[37] In a seminal study, El-Osta et al uncovered an epigenetic mechanism underlying hyperglycemia-induced metabolic memory: following transient high-glucose exposure, human aortic endothelial cells maintain sustained transcriptional activation of NF-κB p65 even after restoration of normoglycemia, resulting in prolonged upregulation of downstream inflammatory genes such as MCP-1 and VCAM-1.[38] Overall, the core mechanism involves a hyperglycemia-induced burst of reactive oxygen species (ROS), which activates the methyltransferase Set7 to promote epigenetic modification of NF-κB p65 and induces stable enrichment of H3K4me1 at the promoters of inflammation-related genes (e g., VCAM1 and MCP1), thereby sustaining chronic activation of inflammatory transcriptional programs.[38–40] These epigenetic modifications function like "bookmarks" imprinted on the genome, enabling

endothelial cells to retain a heightened pro-inflammatory phenotype even after metabolic stress is relieved, thereby continuously promoting monocyte adhesion and early plaque formation.

Beyond metabolic stress, endothelial cells also exhibit a pronounced feature of "mechanical priming," whereby endothelial cells exposed to disturbed flow (d-flow) retain pro-inflammatory properties long after flow patterns are normalized, resulting in sustained leukocyte adhesion and increased susceptibility to atherosclerosis.[41,42] Evidence indicates that disturbed flow activates the downstream transcription factors ETS1 and c-JUN via the mechanosensitive ion channel Piezo1, leading to specific upregulation of the histone demethylase KDM5B, which remodels the endothelial epigenetic landscape by reducing H3K4me3 levels and ultimately drives endothelial inflammation and accelerates atherosclerotic plaque formation.[43] In addition, at arterial branches and curvatures, disturbed flow can trigger Piezo1-mediated calcium influx, subsequently activating the Ca^{2+}/calmodulin (CaM)/CaMKII signaling pathway, thereby promoting endothelial pro-inflammatory responses and dysfunction.[44] At the metabolic level, disturbed flow induces metabolic reprogramming in endothelial cells characterized by enhanced glycolysis and impaired mitochondrial oxidative capacity, a process dependent on the stabilization and activity of hypoxia-inducible factor-1α (HIF-1α).[45] At the epigenetic level, disturbed flow alters chromatin accessibility and regulatory element utilization, accompanied by remodeling of transcription factor regulatory networks, including reduced activity of homeostasis-associated transcription factors such as KLF4 and KLF2 and suppression of their protective gene programs.[46,47] This endothelial "susceptible phenotype" shaped by local hemodynamic features explains why, under identical lipid conditions, endothelial cells located at flow-disturbed regions such as arterial branches and curvatures exhibit exaggerated pro-inflammatory responses to mild inflammatory stimuli, thereby contributing—under the combined influence of multiple risk factors—to the characteristic spatial distribution of atherosclerotic lesions at these anatomical sites.[48,49] (Figure 1).

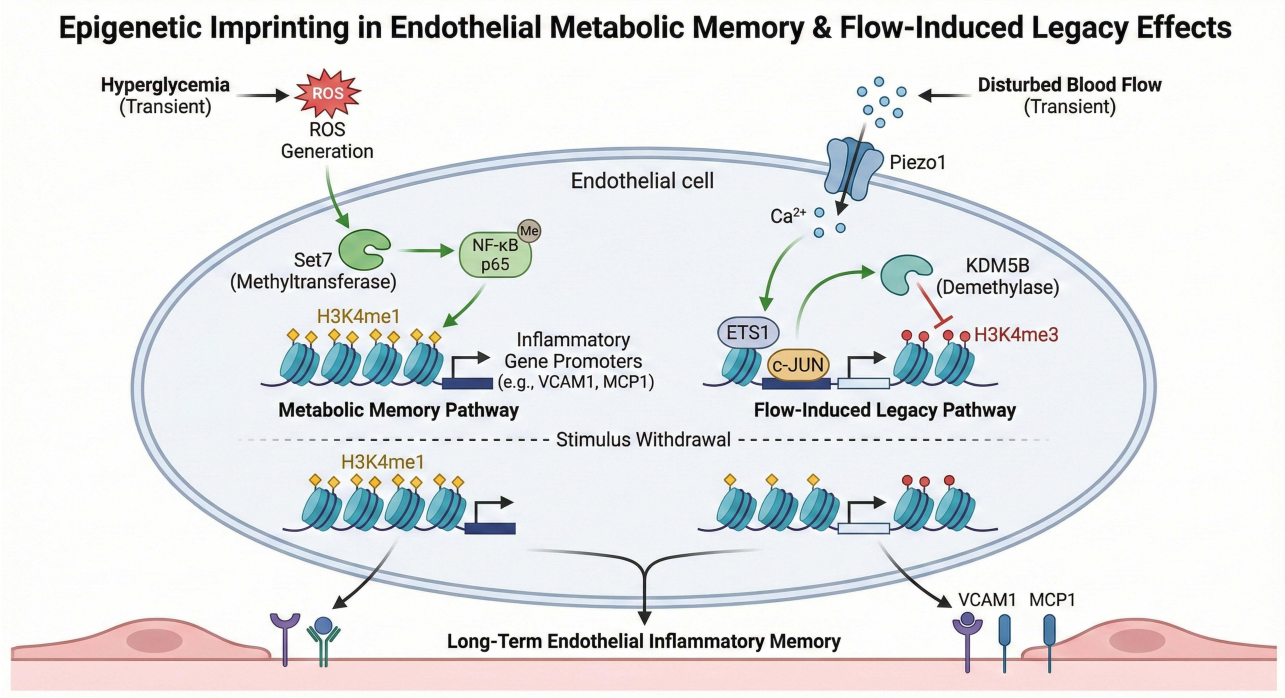

Figure 1 Endothelial Metabolic Memory and Flow Legacy This figure illustrates how endothelial cells convert transient metabolic and hemodynamic stress into persistent dysfunction through trained immunity–like mechanisms. Short-term hyperglycemia and disturbed flow are sensed via reactive oxygen species–dependent pathways and mechanosensitive channels, leading to glycolytic reprogramming and mitochondrial impairment. These changes drive stable epigenetic remodeling at promoters and enhancers of inflammatory genes, including sustained enrichment of H3K4me1 and H3K27ac. Notably, these epigenetic imprints persist after normalization of metabolic or flow conditions, maintaining a pro-inflammatory endothelial phenotype that promotes leukocyte adhesion and regional susceptibility to atherosclerosis.

Vascular Smooth Muscle Cells: Epigenetic Scars During Phenotypic Switching

In vascular smooth muscle cells (VSMCs), phenomena resembling the functional features of "trained immunity" are primarily manifested by their pronounced and persistent phenotypic plasticity. Under physiological conditions, VSMCs maintain a highly differentiated contractile phenotype, characterized by expression of contractile genes such as MYH11 and ACTA2, thereby preserving vascular tone and structural integrity. However, under pathological conditions such as inflammatory stimulation, oxidized lipid accumulation, or vascular injury, VSMCs can undergo dedifferentiation and transition toward synthetic or macrophage-like phenotypes, marked by downregulation of contractile genes and upregulation of genes associated with inflammation, phagocytosis, and migration, a phenomenon particularly prominent in atherosclerotic lesions.[50,51] In recent years, lineage tracing and single-cell transcriptomic studies have demonstrated that, in multiple experimental models and in human atherosclerotic lesions, a substantial proportion of foam cells do not originate from the classical monocyte–macrophage lineage but instead arise from VSMCs through phenotypic switching.[52,53] These VSMC-derived foam cells play critical roles in plaque formation, stability regulation, and disease progression.

Notably, phenotypic switching of VSMCs is not a simple or readily reversible functional adjustment but is accompanied by relatively stable epigenetic regulatory alterations, including remodeling of transcription factor regulatory networks and systematic changes in chromatin accessibility and histone modification states. These epigenetic alterations provide a molecular basis for the establishment and maintenance of specific gene expression programs.[54–56] For example, atherosclerosis-related stimuli such as oxidized low-density lipoprotein (oxLDL) induce upregulation of the transcription factor KLF4, which represses contractile phenotype genes including MYH11 and ACTA2 while activating gene programs associated with dedifferentiation and inflammation, thereby driving VSMCs toward synthetic or macrophage-like states.[57,58] Meanwhile, alterations in the expression of epigenetic regulators such as TET2 are closely associated with VSMC phenotypic states, with TET2 downregulation correlating with changes in DNA hydroxymethylation and reduced expression of contractile genes, suggesting that TET2 may participate in the long-term stabilization of these gene expression programs.[59] Even when subsequent pathological stimuli are attenuated or removed, these epigenetically mediated changes may keep VSMCs locked in a persistent pro-inflammatory and synthetic state, characterized by elevated cytokine expression and enhanced migratory and proliferative capacities.[60,61] On this basis, VSMC phenotypic switching and its potential "memory-like" features provide a novel conceptual framework for understanding the sustained aberrant reactivity of VSMCs in in-stent restenosis following percutaneous coronary intervention (PCI). (Figure 2).

Molecular Cascades of Trained Immunity in the Vascular Wall: From Stress Sensing to Epigenetic Imprinting

The "trained immunity–like responses" observed in vascular structural cells (VSCs) are not driven by a single signaling event but instead represent a multilevel regulatory process operating across temporal and spatial scales.[19] Accumulating evidence suggests that this process can be conceptually abstracted as a regulatory axis comprising stress sensing, metabolic reprogramming, and epigenetic remodeling, whereby external physical or chemical stresses are first sensed and transduced into intracellular signals, subsequently induce rewiring of metabolic pathways, and ultimately establish relatively stable transcriptional regulatory states at the chromatin level through epigenetic mechanisms, thereby shaping responses to subsequent stimuli.[62,63] Thus, trained immunity is not simply a consequence of sustained signaling pathway activation but more likely reflects long-term remodeling of chromatin regulatory states. A summary of the major stimuli, sensing pathways, metabolic rewiring, epigenetic remodeling, and functional consequences associated with trained immunity–like responses in vascular structural cells is presented in Table 2.

Stress Sensing and Signal Initiation: Integration of Mechanical and Metabolic Stimuli

Vascular wall cells are chronically exposed to complex mechanical and chemical stressors, and endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) transduce these external cues into intracellular signals through multiple sensing mechanisms. Disturbed flow (d-flow) represents one of the most characteristic mechanical stimuli in vascular pathological conditions. Studies have shown that the mechanosensitive ion channel Piezo1 senses fluid shear stress and

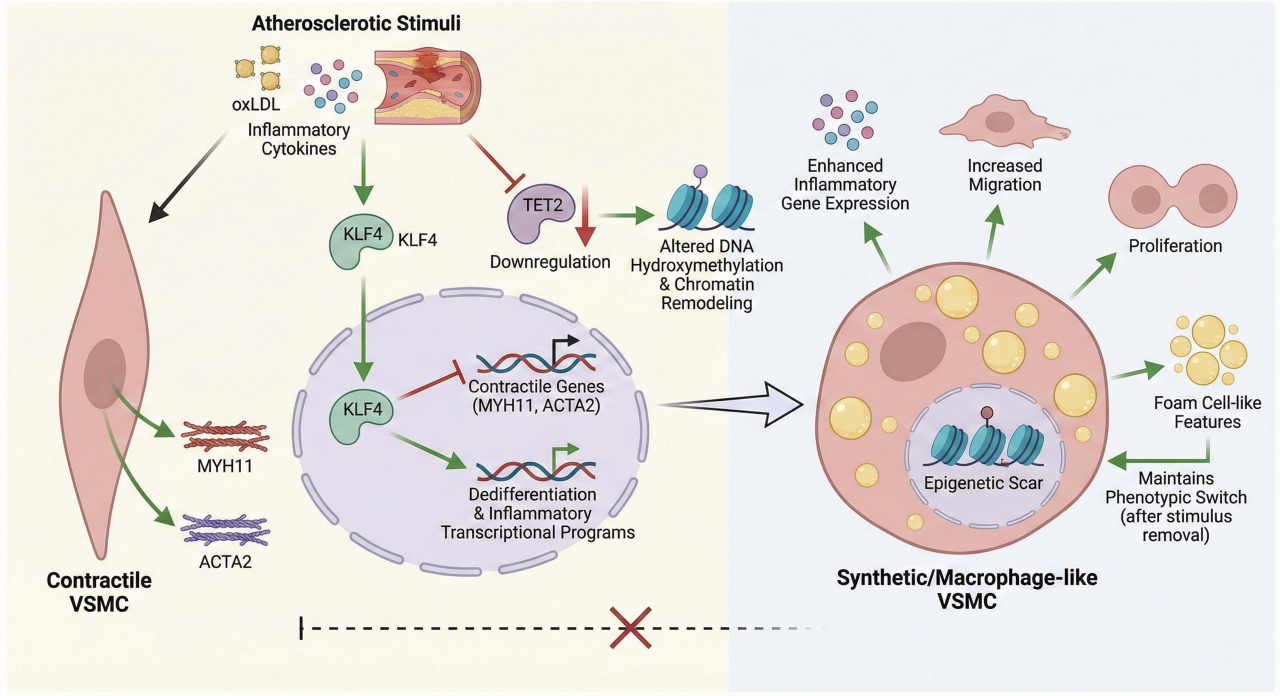

Figure 2 Epigenetic Scars in VSMC Phenotypic Switching This figure illustrates the establishment of long-lasting epigenetic scars during phenotypic switching of vascular smooth muscle cells. Transient exposure to inflammatory cytokines, oxidized lipids, hypoxia, or vascular injury induces metabolic rewiring and activation of transcriptional regulators such as KLF4, resulting in repression of contractile gene programs and induction of synthetic or macrophage-like phenotypes. These transitions are accompanied by stable changes in chromatin accessibility and DNA hydroxymethylation, often associated with TET2 downregulation. Even after stimulus withdrawal, these epigenetic alterations persist, locking smooth muscle cells in a hyper-responsive state that contributes to plaque progression and restenosis.

mediates calcium (Ca^{2+}) influx into endothelial cells.[64] Under disturbed flow or mechanical stress, activation of this channel induces intracellular Ca^{2+} accumulation, which subsequently activates calcium/calmodulin-dependent kinase signaling (including CaMKII) and other downstream pathways, thereby contributing to endothelial inflammatory responses and metabolic adaptation processes.[44,65] In addition, at endothelial cell–cell junctions, a mechanosensory complex composed of PECAM-1, VE-cadherin, and VEGFR2 is considered a central structure for shear stress signal transduction.[66] Upon shear stress stimulation, this complex cooperatively transmits mechanical signals and activates multiple downstream pathways, including NF-κB and Akt/eNOS, thereby influencing endothelial homeostasis and inflammation-related gene expression.[67,68]

In addition to mechanical stimuli, vascular wall cells also sense metabolic and inflammatory signals through pattern recognition receptors. Oxidized low-density lipoprotein (oxLDL) activates NF-κB–dependent inflammatory responses via the TLR4–MyD88 pathway,[69,70] while the gut microbiota–derived metabolite trimethylamine N-oxide (TMAO) has also been shown to amplify endothelial inflammatory signaling and promote atherosclerosis progression.[71,72] Together, these physical and chemical stimuli constitute a "first-hit" signal in the vascular wall, providing the initial conditions for subsequent metabolic state alterations and epigenetic remodeling. Available evidence suggests that these changes preferentially accumulate at key regulatory elements such as enhancers and promoters and are accompanied by alterations in chromatin accessibility, rendering subsequent transcriptional responses more readily reactivated and potentially giving rise to self-reinforcing regulatory architectures. (Figure 3).

Metabolic Reprogramming: An "Amplifier" Linking Transient Stimuli to Persistent Memory

Sustained stress signals do not need to persist over long periods to induce profound alterations in vascular wall cells; rather, the metabolic state itself serves as a central amplification and transduction hub that links transient stimuli to long-term phenotypic memory. Under pathological conditions such as inflammation, hyperglycemia, or disturbed flow, both

Table 2 Molecular Features of Vascular Trained Immunity This Table Summarizes the Defining Molecular Features and Pathological Consequences of Trained Immunity–Like States in Vascular Structural Cells. In Endothelial Cells, Mechanical and Metabolic Stress Induces PFKFB3-Dependent Glycolytic Enhancement, Mitochondrial Dysfunction, and Enrichment of H3K4me1 and H3K27ac, Sustaining Endothelial Activation. In Vascular Smooth Muscle Cells, Inflammatory and Lipid Stimuli Promote Metabolic Bias and Stable Epigenetic Remodeling Associated with Altered Chromatin Accessibility and TET2 Downregulation. Together, These Persistent Cellular Programs Maintain Chronic Vascular Inflammation and Contribute to Residual Cardiovascular Risk

Dimension	Endothelial Cells (ECs)	Vascular Smooth Muscle Cells (VSMCs)	Vascular Wall (Overall Perspective)
Priming Stimuli	Disturbed flow (d-flow), hyperglycemia, oxLDL, and TMAO	Oxldl, inflammatory cytokines (e. g., IL-1β), vascular injury, and hypoxia.	Systemic inflammation or metabolic stress (e. g., infection, chronic inflammation).
Primary Sensors	Piezo1; PECAM-1;VE-cadherin;VEGFR2 complex; TLR4.	TLR4;CD36	Pattern Recognition Receptors (PRRs) and cytokine receptors.
Metabolic Rewiring	Enhanced glycolysis (PFKFB3 upregulation); decreased mitochondrial oxidative capacity; lactate accumulation.	Glycolytic bias; mitochondrial dynamics remodeling; altered TCA cycle flux.	Accumulation of metabolic intermediates (succinate, fumarate); metabolic-epigenetic coupling amplification.
Key Epigenetic Markers	H3K4me1 (Set7-mediated); H3K27ac (Acetyl-CoA driven); chromatin accessibility remodeling.	Decreased DNA hydroxymethylation (TET2 downregulation); altered chromatin accessibility; histone lactylation.	Latent enhancer activation; H3K4me1/H3K27ac enrichment.
Pathological Outcomes	Persistent endothelial activation, impaired barrier function, increased leukocyte adhesion, and pro-thrombotic phenotype	Phenotypic dedifferentiation, synthetic/macrophage-like transdifferentiation, enhanced migration and proliferation.	Maintenance of chronic vascular inflammation, plaque progression, and instability.
Potential Interventions	Metformin; PFKFB3 inhibitors; BET inhibitors.	BET inhibitors (e. g., Apabetalone); metabolic modulators; statins.	Anti-inflammatory therapy (e. g., IL-1β pathway inhibition); metabolic-epigenetic targeting strategies

ECs and VSMCs commonly exhibit a glycolysis-biased metabolic profile, with 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) recognized as a key rate-limiting node driving glycolytic flux reprogramming.[73,74] Enhanced glycolysis not only fulfills cellular energy demands but also markedly reshapes the intracellular landscape of metabolic intermediates. The resulting increase in acetyl–coenzyme A provides a direct substrate for histone acetyltransferases (HATs), preferentially targeting promoters and enhancers of inflammation-related genes, thereby amplifying and stabilizing the transcriptional programs induced by the initial stimulus at the chromatin level.[75–77]

Meanwhile, mitochondrial metabolism and dynamics are also profoundly remodeled. Under chronic stress or pathological stimuli—such as oxidative stress, inflammation, or metabolic reprogramming—mitochondria tend to shift from a fused toward a fragmented state, accompanied by alterations in tricarboxylic acid (TCA) cycle flux and accumulation of intermediates such as succinate and fumarate.[78,79] Extensive experimental evidence indicates that these TCA intermediates act as competitive inhibitors of α-ketoglutarate (α-KG), thereby suppressing the activity of α-KG–dependent dioxygenases—including histone and DNA demethylases—disrupting demethylation processes and favoring the maintenance of a pro-inflammatory chromatin state.[80,81] In addition, lactate produced under hypoxic or hyperglycemic conditions can induce histone lactylation, providing a novel mechanism by which metabolic states directly reshape chromatin architecture, and has been implicated in the stabilization of synthetic or fibrotic phenotypes in VSMCs.[82–84] (Figure 4).

Epigenetic Engraving: Locking Mechanisms of Trained-Like Memory

Metabolism-driven chromatin modifications are ultimately "engraved" at enhancer and promoter regions as relatively stable epigenetic states, thereby endowing vascular wall cells with a transcriptional potential characterized by a lowered activation threshold and heightened responsiveness. Classic studies have demonstrated that under hyperglycemic or

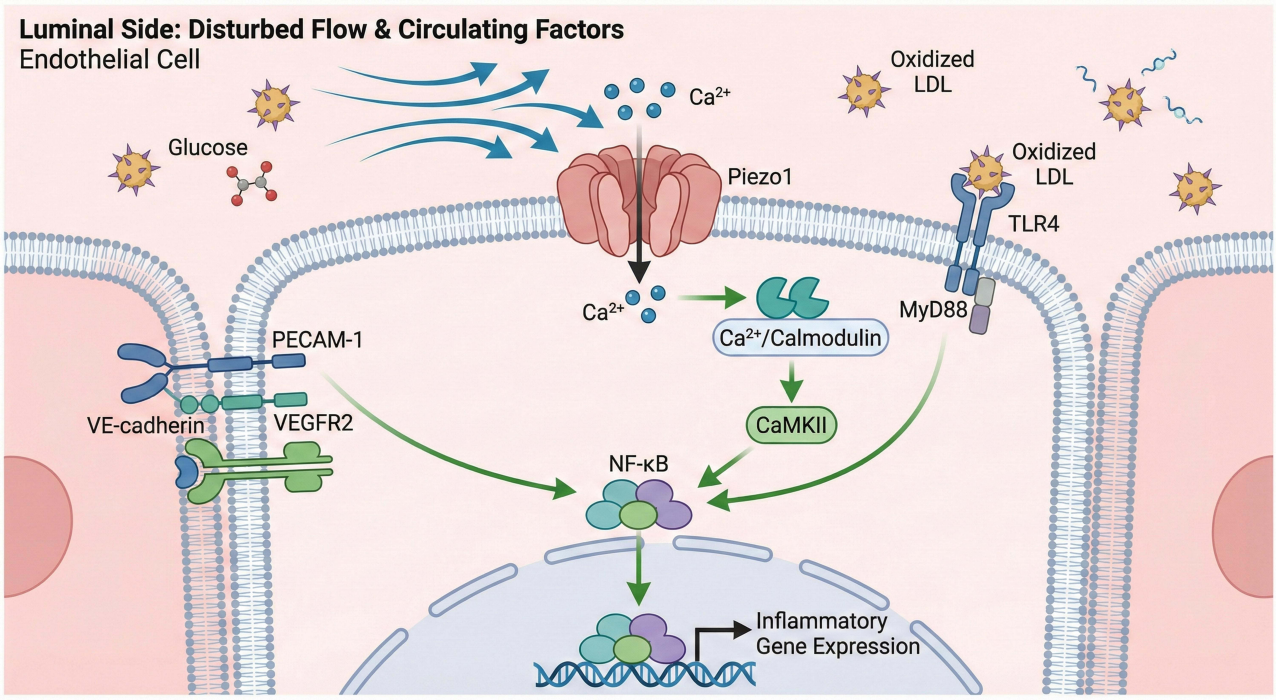

Figure 3 Integration of Mechanical and Metabolic Stress Sensing This figure illustrates how vascular structural cells integrate mechanical and metabolic stimuli to initiate trained immunity–like responses. Endothelial cells and vascular smooth muscle cells sense disturbed flow, shear stress, and vascular injury through mechanosensitive structures, including Piezo1 and junctional complexes, leading to Ca^{2+}-dependent inflammatory signaling. In parallel, metabolic and inflammatory cues such as oxidized LDL and hyperglycemia activate pattern recognition receptors, including TLR4. The convergence of these signals constitutes a critical priming phase that establishes permissive conditions for downstream metabolic reprogramming and epigenetic imprinting.

lipotoxic conditions, the histone methyltransferase Set7/9 mediates the deposition of H3K4me at promoters of inflammatory genes such as CCL2. Notably, this modification can persist after stimulus withdrawal, giving rise to the so-called "metabolic memory" or "legacy effect".[38,85] More recently, chromatin accessibility profiling and single-cell omics studies have revealed the existence of so-called "latent enhancers" in models of trained immunity and chronic stimulation.[86] These regulatory elements acquire enhancer-associated marks following an initial stimulus and remain partially accessible during the resting state, enabling cells to rapidly and robustly activate associated gene expression upon subsequent mild stimulation.[87] Although this mechanism was originally described in innate immune cells, the fundamental principle of "enhancer preprogramming and reactivation" provides an important conceptual framework for understanding how vascular structural cells acquire trained-like memory under chronic or repetitive stimuli. In VSMCs, the transcription factor KLF4 is considered a key molecular link between phenotypic dedifferentiation and epigenetic remodeling. By repressing contractile gene expression and reshaping epigenetic regulatory networks, KLF4 drives the transition toward synthetic or pro-inflammatory states. Concurrently, alterations in DNA demethylation–related regulators, such as TET2, may contribute to the long-term maintenance of these states by modulating the global DNA methylation landscape.[56,88]

Taken together, these studies indicate that trained immunity–like responses in the vascular wall do not rely on sustained signaling inputs, but are more likely maintained by transcriptional programs "locked in" through metabolism-driven epigenetic remodeling.

Clinical Implications and Therapeutic Strategies: Erasing Epigenetic Scars in the Vascular Wall

The recognition that vascular structural cells (VSCs) can acquire trained immunity–like properties provides a unified and mechanistically informative pathophysiological framework to explain multiple long-standing "failure modes" in cardiovascular interventions, particularly adverse outcomes that persist despite adequate lipid control. Among these, in-stent restenosis (ISR) and neointimal hyperplasia represent some of the most clinically relevant manifestations. Although drug-

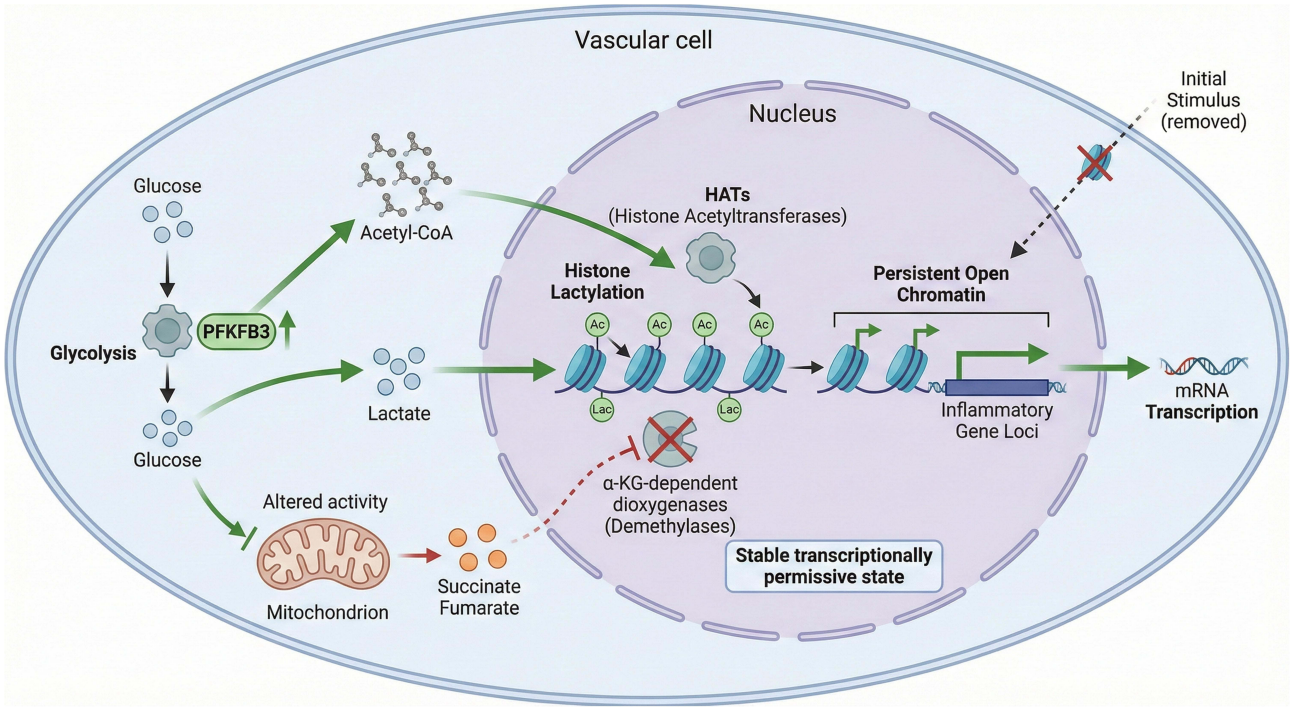

Figure 4 Metabolic Reprogramming as a Memory Amplifier This figure illustrates metabolic reprogramming as a central amplifier linking transient stimuli to persistent cellular memory in the vascular wall. Pathological stressors induce a glycolysis-biased metabolic shift driven by PFKFB3 upregulation, accompanied by impaired mitochondrial oxidative metabolism. Increased production of metabolites such as acetyl–coenzyme A, lactate, succinate, and fumarate directly influences chromatin-modifying enzymes, promoting histone acetylation, lactylation, and impaired demethylation. Through these mechanisms, metabolic rewiring stabilizes pro-inflammatory epigenetic states and sustains trained immunity–like phenotypes in vascular structural cells.

eluting stents (DES) have markedly reduced the incidence of early luminal loss, the mechanical overexpansion imposed on the vascular wall during stent deployment constitutes a potent "first hit," which may induce durable epigenetic reprogramming in residual vascular smooth muscle cells (VSMCs).[89,90] Studies have shown that the epigenetic regulator TET2, which is critical for maintaining the contractile phenotype of VSMCs, is downregulated under multiple pathological conditions and is strongly associated with the transition of VSMCs from a contractile phenotype toward synthetic or dedifferentiated states—a phenotypic switch considered a key epigenetic hallmark of pro-inflammatory and proliferative VSMC activation.[91–93] Consequently, even when intensive postoperative statin therapy reduces low-density lipoprotein cholesterol (LDL-C) to very low levels, these epigenetically "primed" smooth muscle cells may still exhibit exaggerated proliferative and migratory responses upon subsequent exposure to mild systemic inflammatory stimuli (a "second hit"), thereby providing a biologically plausible explanation for restenosis beyond lipid burden alone.[94,95]

Similar pathological memory–like phenomena are also observed in cardiac allograft vasculopathy (CAV), a leading cause of long-term graft failure after heart transplantation. During donor organ procurement and implantation, the vasculature inevitably undergoes ischemia–reperfusion injury (IRI), a process that induces mitochondrial reactive oxygen species (ROS) production and leads to sustained endothelial activation.[96,97] Injured endothelial cells can release extracellular vesicles enriched in miR-155, paracrinally promoting monocyte polarization toward a pro-inflammatory M1 phenotype, thereby propagating inflammatory signaling within the vascular microenvironment and accelerating atherosclerotic progression.[98,99] Importantly, this non-coding RNA–mediated epigenetic remodeling may establish a trained immunity–like sensitized state in endothelial cells, predisposing graft vessels to amplified inflammatory responses upon subsequent immune stress from the host and thereby markedly accelerating the development of occlusive vasculopathy.

Based on these findings, targeting and "erasing" or remodeling epigenetic memory in the vascular wall has emerged as a novel direction in cardiovascular pharmacology. Bromodomain and extraterminal domain (BET) inhibitors, such as apabetalone (RVX-208), suppress inflammatory transcriptional programs driven by epigenetically primed vascular

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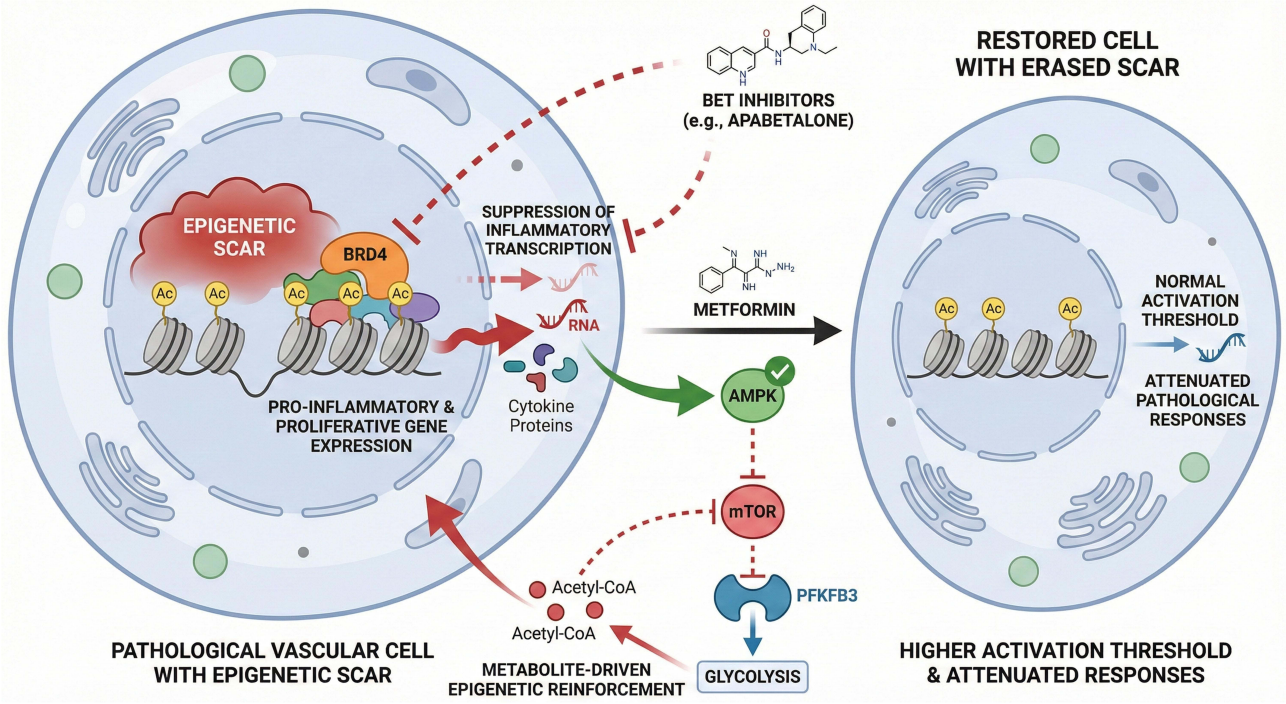

Figure 5 Epigenetic Targeting of Vascular Memory This figure illustrates therapeutic targeting of trained immunity–like vascular memory through inhibition of bromodomain and extraterminal proteins. In epigenetically primed endothelial cells and vascular smooth muscle cells, sustained histone acetylation supports BRD4-dependent transcription of pathogenic gene programs. BET inhibitors, such as apabetalone, disrupt the interaction between acetylated histones and BET proteins, thereby suppressing enhancer-driven transcription. By modulating epigenetically locked transcriptional states rather than acute inflammatory signaling, BET inhibition attenuates chronic vascular inflammation and cellular hyper-responsiveness.

structural cells (VSCs) by blocking the recognition of acetylated histones by reader proteins including BRD4[100–102] (Figure 5). In the Phase III BETonMACE trial, although apabetalone did not significantly reduce major adverse cardiovascular events (MACE) in the overall population, a clear benefit signal was observed in the subgroup of patients with type 2 diabetes and concomitant chronic kidney disease.[103] These findings suggest that pharmacological interventions targeting metabolic–epigenetic regulation may offer clinical benefits in selected high-risk populations. Beyond dedicated epigenetic therapies, conventional metabolic modulators may also indirectly influence the establishment and maintenance of trained immunity–like states. Metformin, by activating AMP-activated protein kinase (AMPK) and inhibiting mTOR signaling, limits sustained glycolytic flux and reshapes cellular metabolism,[104,105] potentially modulating acetyl-CoA availability and associated epigenetic modifications, thereby providing a molecular basis for its anti-inflammatory and vasculoprotective effects beyond glucose lowering.[106–108] (Figure 6)

At the therapeutic level, local delivery strategies offer new opportunities to selectively remodel vascular memory while minimizing systemic adverse effects. Functionalized nanoparticle platforms targeting endothelial adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), have been developed to deliver pharmacological agents or epigenetic modulators directly to atherosclerotic lesions. Multiple studies in experimental models of atherosclerosis have demonstrated that VCAM-1–targeted nanotherapeutic approaches achieve enhanced lesion accumulation and exhibit anti-inflammatory potential, thereby providing experimental support for precision interventions based on epigenetic regulation[109–111] (Figure 7). In parallel, endogenous anti-inflammatory metabolites and their derivatives, including 4-octyl itaconate (4-OI), have been shown to activate the Nrf2 antioxidant pathway via KEAP1 alkylation, while suppressing NLRP3 inflammasome–driven inflammatory responses and cellular pro-inflammatory capacity.[112–115] (Figure 8)

Looking ahead, cardiovascular risk assessment is expected to evolve from reliance on single circulating biochemical markers toward multidimensional evaluation of vascular epigenomic features. The integration of single-cell assay for transposase-accessible chromatin sequencing (scATAC-seq) with spatial transcriptomic technologies enables the

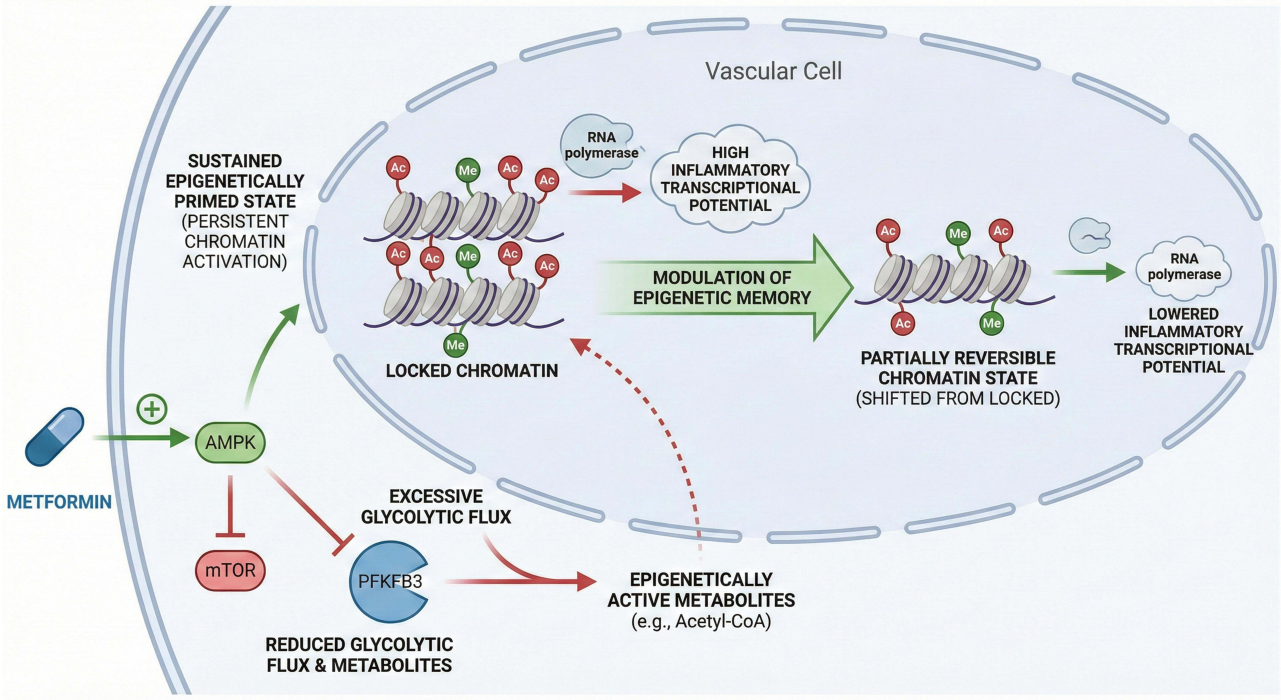

Figure 6 Metabolic Modulation of Vascular Memory This figure illustrates how metabolic intervention reshapes trained immunity–like responses in vascular structural cells. Metformin activates AMP-activated protein kinase and inhibits mTOR signaling, suppressing excessive glycolytic flux and PFKFB3-driven metabolic reprogramming. These effects limit the availability of key epigenetic substrates, including acetyl–coenzyme A, thereby attenuating histone acetylation and pro-inflammatory transcriptional programs. Through modulation of metabolism–epigenetic coupling, metabolic therapy reduces vascular cell hyper-responsiveness beyond glucose and lipid lowering.

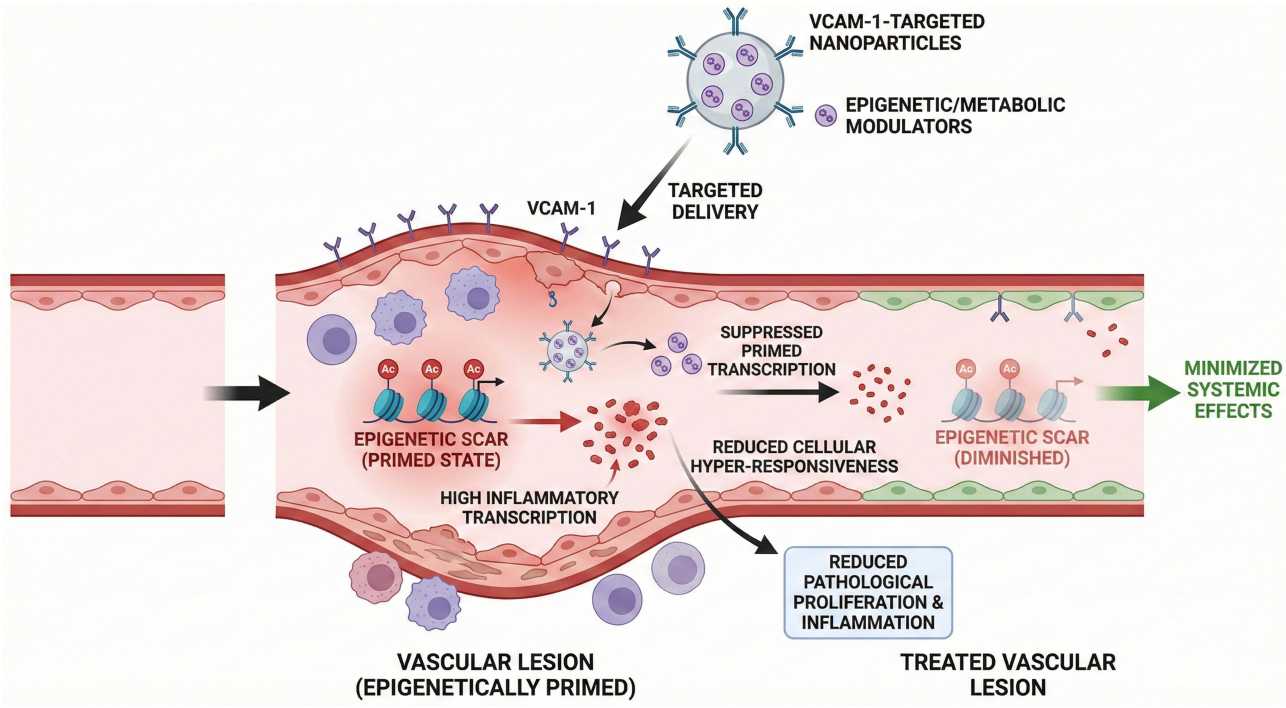

Figure 7 Targeted Nanotherapy for Memory Remodeling This figure illustrates nanoparticle-based strategies for selectively targeting trained immunity–like states within the vascular wall. Nanoparticles functionalized with endothelial adhesion molecules, such as VCAM-1, preferentially accumulate at sites of endothelial activation and atherosclerotic lesions. Localized delivery of metabolic or epigenetic modulators attenuates inflammatory signaling and epigenetically primed transcriptional programs in vascular structural cells while minimizing systemic exposure. This precision approach offers a strategy to remodel pathological vascular memory.

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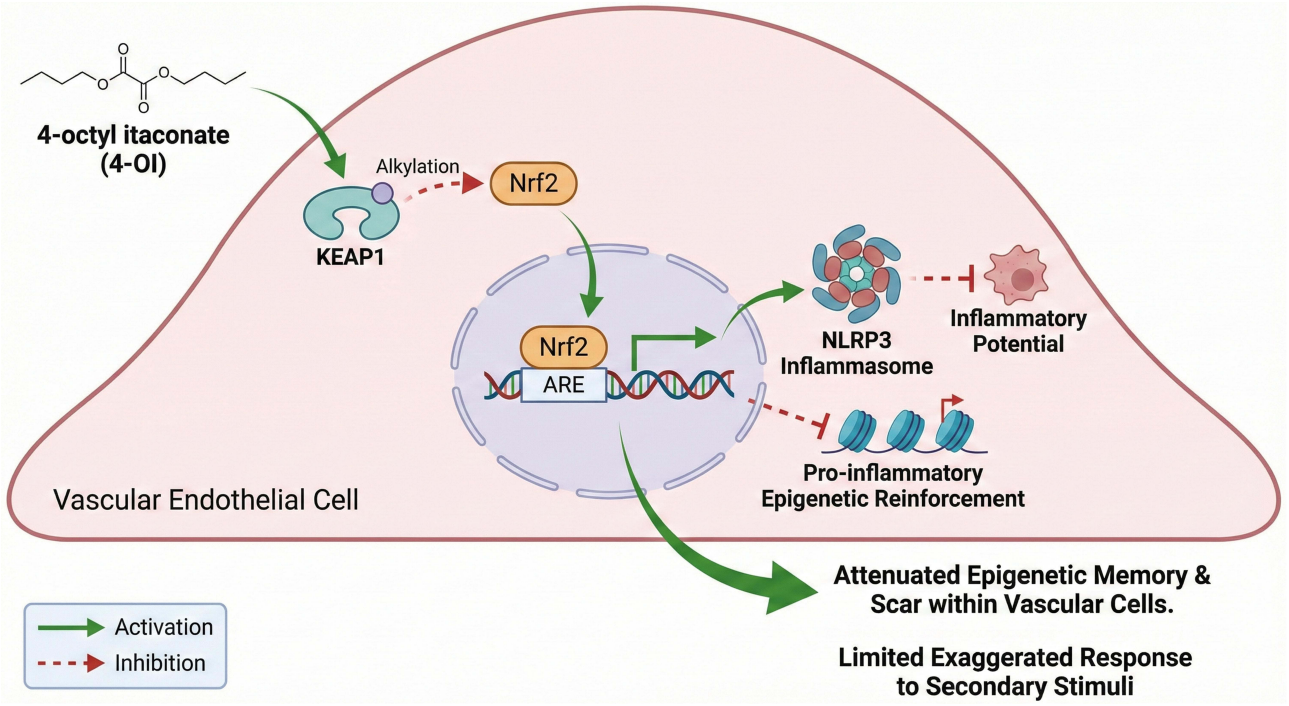

Figure 8 Endogenous Metabolites Limiting Inflammatory Memory This figure illustrates the role of endogenous immunometabolic regulators in suppressing trained immunity–like vascular inflammation. Itaconate and its derivative 4-octyl itaconate activate the Nrf2 antioxidant pathway via KEAP1 alkylation while inhibiting NLRP3 inflammasome activation and downstream cytokine production. By integrating redox regulation with inflammatory control, these metabolites reduce inflammatory responsiveness of vascular structural cells, highlighting a physiological mechanism to attenuate vascular inflammatory memory.

identification of key cellular subpopulations within atherosclerotic plaques that reside in a "primed" or hyper-responsive state. Enrichment patterns of enhancer-associated epigenetic marks, such as H3K4me1 and H3K27ac, may aid in predicting plaque stability and therapeutic responsiveness, thereby advancing a new paradigm of precision cardiovascular medicine that targets molecular memory rather than terminal clinical events.

Knowledge Gaps and Conceptual Challenges

Despite growing mechanistic support for trained immunity-like phenotypes in vascular structural cells, important conceptual and translational uncertainties remain. A key question is whether these vascular adaptations fulfill the strict definition of memory. Classical immunological memory implies a return to baseline followed by an augmented response upon re-exposure. By contrast, vascular structural cells often display sustained activation without a clearly defined resting phase, suggesting that these states may represent persistent maladaptive reprogramming rather than inducible memory in the traditional sense.

In addition, longitudinal human evidence is limited. Much of the current support derives from in vitro systems, animal models, or cross-sectional observations. Direct proof of durable epigenetic imprinting within human vascular tissues over time-particularly in response to defined metabolic or mechanical stressors-remains scarce, leaving the temporal stability and clinical relevance of these phenotypes incompletely established.

The issue of reversibility further complicates this framework. Although epigenetic modifications are theoretically dynamic, it remains unclear whether established vascular reprogramming can be therapeutically reversed or whether prolonged disease exposure results in progressively fixed chromatin states. Clarifying this point is crucial for determining whether vascular memory constitutes a modifiable driver of pathology or merely a biomarker of irreversible damage.

Moreover, causal relationships are not yet fully resolved. While metabolic-epigenetic remodeling strongly associates with endothelial dysfunction and smooth muscle phenotypic switching, definitive evidence demonstrating that such reprogramming is necessary and sufficient to drive atherosclerotic progression remains limited. Addressing this gap will require temporally controlled interventions and more precise mechanistic models.

Finally, distinguishing adaptive from maladaptive forms of vascular memory is essential. Transient priming responses may serve protective functions, whereas chronic epigenetic stabilization may promote sustained inflammation and structural remodeling. Resolving these conceptual challenges will be critical for refining the trained immunity-like framework and for translating it into effective strategies to reduce residual cardiovascular risk.

Conclusion

Despite substantial advances in lipid-lowering and blood pressure–controlling therapies, a considerable residual cardiovascular risk persists even when traditional risk factors are optimally managed. This clinical reality underscores the need to move beyond trigger-centered strategies and to address the intrinsic cellular programs that sustain vascular inflammation and remodeling. Vascular structural cells, endowed with remarkable metabolic and epigenetic plasticity, emerge as central orchestrators of this persistent pathological state.

Accumulating evidence suggests that endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) can acquire stable metabolic–epigenetic reprogramming in response to transient mechanical, metabolic, or inflammatory stressors, thereby adopting trained immunity–like phenotypes.[116,117] These adaptations may provide a mechanistic explanation for sustained inflammatory activation, plaque progression, in-stent restenosis, and transplant vasculopathy despite apparent risk factor control. Targeting the metabolic and epigenetic circuits underlying these memory-like states therefore represents a promising therapeutic direction.

Looking forward, several key areas warrant focused investigation. High-resolution single-cell multi-omics approaches integrating transcriptomic, epigenomic, and metabolic profiling will be essential to delineate cell-type–specific memory landscapes within the vascular wall. Lineage-tracing strategies are needed to determine the durability and clonal propagation of reprogrammed vascular cells over time, thereby clarifying whether these phenotypes represent transient activation or stable heritable states. In parallel, emerging epigenome-editing technologies offer the possibility of directly testing causality and selectively reversing pathogenic chromatin configurations.

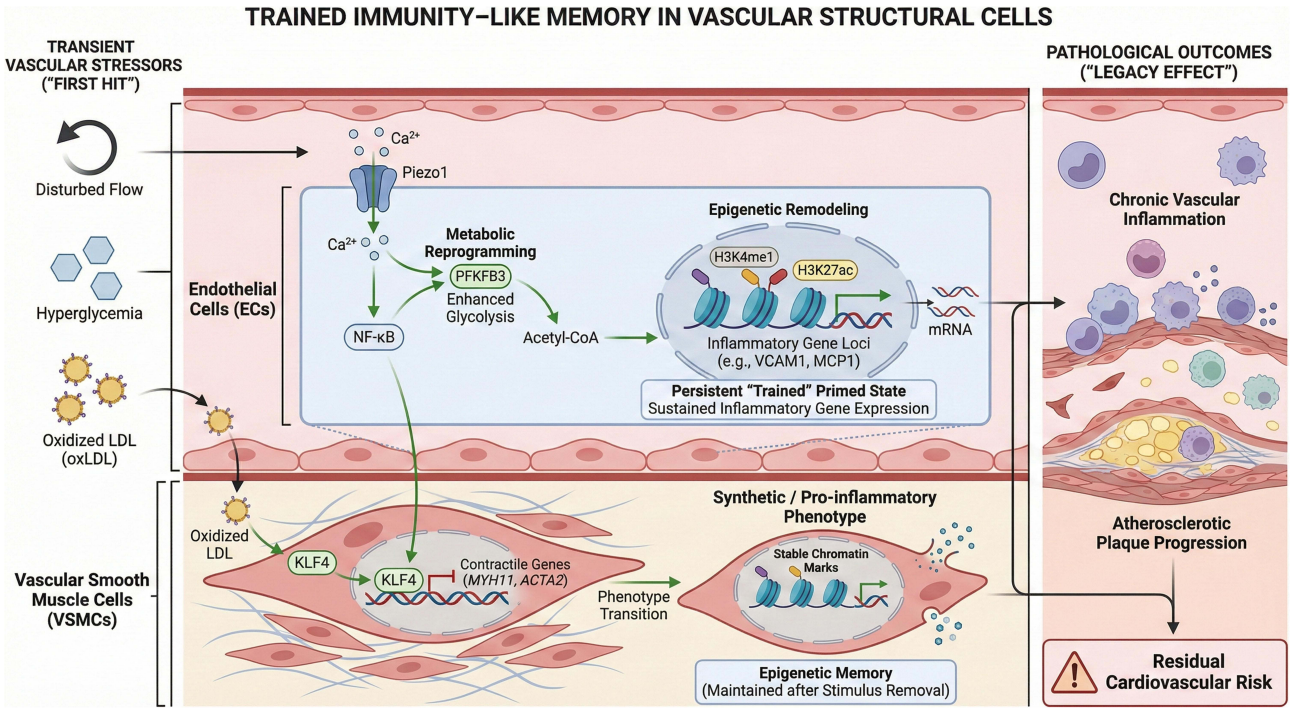

Figure 9 Vascular Trained Immunity and Residual Risk This figure summarizes the central concept of the review, positioning trained immunity–like memory in vascular structural cells as a unifying mechanism underlying residual cardiovascular risk. Transient metabolic, inflammatory, or mechanical stimuli induce durable metabolic and epigenetic reprogramming in endothelial cells and vascular smooth muscle cells, maintaining a hyper-responsive phenotype despite risk factor control. Targeting these maladaptive memory programs represents a conceptual shift toward restoring vascular cellular homeostasis.

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From a translational perspective, the identification of reliable clinical biomarkers reflecting vascular trained immunity–like activity will be critical for patient stratification and therapeutic monitoring. Furthermore, the development of cell-specific targeting strategies—including nanoparticle-based delivery systems and precision epigenetic modulators—may enable selective modulation of pathological memory without compromising systemic immune function.

In summary, the vascular wall should be viewed not merely as a passive structural barrier but as a dynamic tissue capable of molecular memory imprinting. Elucidating, monitoring, and selectively reshaping pathological trained immunity–like programs may represent a transformative frontier in cardiovascular prevention, with the potential to meaningfully reduce residual cardiovascular risk. (Figure 9).

Author Contributions

Jingxuan Dai: Conceptualization, Data curation, Validation, Visualization, Writing – original draft, Writing – review & editing. Xuancheng Zhou: Methodology, Formal analysis, Writing – original draft, Writing – review & editing. Kun Yuan: Investigation, Data curation, Writing – original draft, Writing – review & editing. Keming Huang: Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. Ying Zhang: Conceptualization, Data curation, Validation, Visualization, Writing – original draft, Writing – review & editing.All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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