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Unravelling the multi-omics interplay in atherosclerosis development: Their integration for diagnostic and therapeutic strategies of the disease

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Abstract

Atherosclerosis (AS) is a leading cause of coronary artery disease (CAD), characterized by the gradual accumulation of plaques within arterial walls, resulting in severe health complications such as myocardial infarctions and strokes. Recent advancements in multi-omics technologies including genomics, transcriptomics, proteomics, and metabolomics have significantly enhanced our understanding of the complex molecular mechanisms underlying atherosclerosis. These technologies provide a comprehensive view of the disease by integrating diverse biological data that extend beyond traditional risk factors. The integration of network medicine with multi-omics approaches further enhances our ability to elucidate the intricate interactions among biological components in both health and disease states related to atherosclerosis. This interdisciplinary framework not only facilitates the identification of novel diagnostic biomarkers and therapeutic targets but also improves patient stratification for personalized interventions. By employing machine learning (ML) techniques, we can combine multiple omics and clinical datasets into innovative tools that support the development of tailored diagnostic and therapeutic strategies. However, challenges such as data quality, integration, and privacy remain significant barriers to progress. This review offers a comprehensive overview of various multi-omics technologies and their contributions to precision medicine in managing atherosclerotic cardiovascular disease (ASCVD). Additionally, we address current challenges and limitations while outlining future research directions aimed at improving patient outcomes through innovative methodologies. The convergence of multi-omics data with network medicine signifies a critical shift toward more effective and individualized treatment paradigms in combating ASCVD, presenting substantial opportunities for advancements in clinical practice and patient management.

Keywords: Atherosclerosis; Coronary Artery Disease; Plaque Formation; Network Medicine; Precision Medicine; Single-Cell Multi-Omics

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Introduction

Atherosclerosis (AS) is a complex chronic inflammatory disease marked by lipid, immune cell, and smooth muscle accumulation in arterial walls, causing plaque formation and arterial stiffening. It underlies atherosclerotic cardiovascular diseases (ASCVD) such as coronary artery disease and stroke as major global causes of morbidity and mortality. Thus, identifying new inflammatory mechanisms, therapeutic targets, and biomarkers is essential for advancing ASCVD management[1]. Atherosclerotic plaques with thin, collagen-poor fibrous caps and dense macrophage and lymphocyte infiltration are considered highly unstable and prone to rupture, leading to acute clinical events. Plaque erosion, an increasingly recognized cause of arterial thrombosis, further complicates disease pathology. Focusing on the molecular signatures of vulnerable plaques may uncover novel therapeutic targets and help address residual ASCVD risk beyond conventional risk-factor control. Consequently, there is a critical need for advanced strategies to identify high-risk plaques and patients before symptom onset or atherothrombotic events[2]. Over the past two decades, omics technologies including genomics, epigenomics, transcriptomics, proteomics, metabolomics, and lipidomics have significantly advanced our understanding of plaque biology (Fig. S1). These approaches have characterized molecular pathways, cellular functions, and systemic responses involved in disease progression. Recent technological advances have also uncovered cellular heterogeneity and spatial organization within plaques. Genomic studies have identified susceptibility loci, while transcriptomic and proteomic profiling have refined molecular signatures specific to plaques. Integrating multi-omics data with network medicine is paving the way for more precise diagnostics, targeted therapies, and improved risk prediction (Fig. 1).

Genomics

Genomics has become central to understanding cardiovascular disease (CVD), particularly ASCVD, which arises from complex interactions between genetic, environmental, and lifestyle factors. Whole-exome sequencing (WES) and whole-genome sequencing (WGS) have been instrumental in identifying pathogenic variants associated with diverse CVD phenotypes, thereby clarifying disease pathobiology[3]. Genetic susceptibility to ASCVD is largely driven by genes regulating lipid metabolism, inflammation, endothelial function, and vascular remodeling. The apolipoprotein E (ApoE) gene plays a key role in cholesterol transport, with specific variants associated with altered lipid profiles and increased coronary artery disease (CAD) risk. Mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9) cause familial hypercholesterolemia, leading to elevated low-density lipoprotein (LDL) cholesterol and increased ASCVD risk[4]. Likewise, ATP-binding cassette transporter A1 (ABCA1), essential for cellular cholesterol efflux, is implicated in Tangier disease, characterized by high-density lipoprotein (HDL) deficiency and premature atherosclerosis[5]. Inflammation is a hallmark of atherosclerosis. Genes involved in chemokine signaling, such as C-X-C motif chemokine receptor 4 (CXCR4) and C-X-C motif chemokine ligand 2 (CXCL2), are upregulated during plaque progression and represent potential therapeutic targets[6]. The 5-lipoxygenase (5-LO) pathway further contributes to chronic inflammation and plaque growth. Endothelial dysfunction acts as a critical mechanistic bridge linking inflammatory and lipid-driven pathways in ASCVD progression[7]. Krüppel-like factor 2 (KLF2) and endothelial nitric oxide synthase (eNOS) regulate nitric oxide bioavailability and vascular tone, and their dysregulation predisposes to atherosclerosis. In addition, endothelin receptor type A (EDNRA), a mediator of vasoconstriction, has been linked to increased cardiovascular risk[8]. Genes involved in lipid homeostasis extend beyond classical pathways. Sortilin 1 (SORT1) influences very-low-density lipoprotein (VLDL) production and lipid trafficking, with genetic variation at this locus associated with CAD risk[9]. ATP-binding cassette subfamily G members 5 and

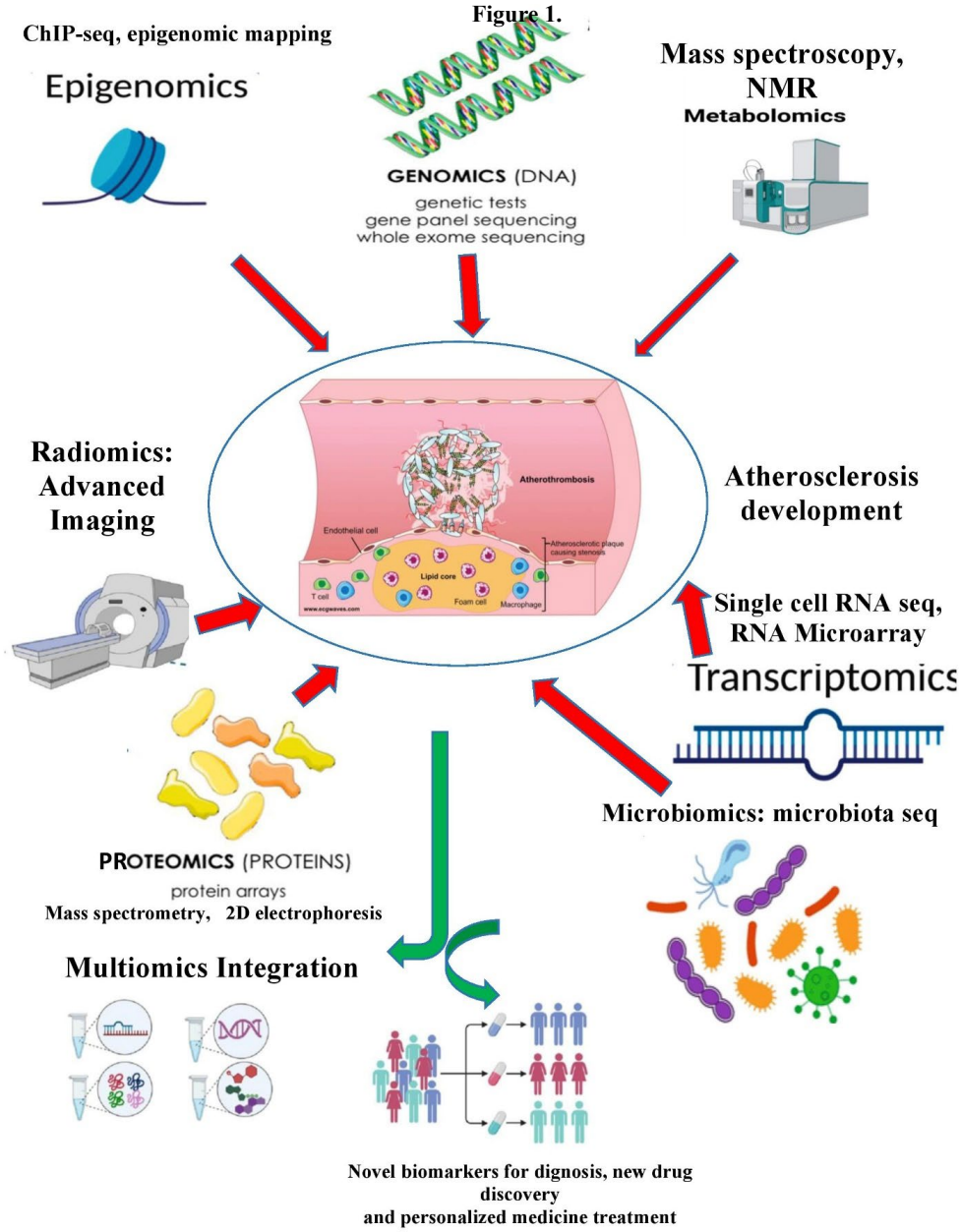


Figure 1. Changes at different omics levels leading to change in cellular and molecular components of affected tissue involved in AS development. The figure was designed by biorender software (www.biorender.com).

8 (ABCG5/ABCG8) regulate intestinal cholesterol absorption, and pathogenic variants cause sitosterolemia[10]. Genome-wide association studies (GWAS) have substantially expanded the catalog of CAD-associated loci. A large meta-analysis of 48 GWAS confirmed known loci and identified novel genetic determinants of CAD, while independent studies revealed new susceptibility genes for idiopathic and familial PAH. However, population-scale association signals alone often lack cellular and mechanistic resolution. Single-cell genomics has further advanced the field by enabling cell-specific detection of genomic variants and mosaicism, although challenges related to cost, data storage, and computational demand remain. Long-read sequencing has partially addressed limitations in resolving repetitive genomic regions. Despite the identification of more than 300 CAD-associated loci since the first GWAS in

2007, most variants reside in noncoding regions, complicating causal inference. Integrative pipelines combining genomic, transcriptomic, and epigenomic data are therefore essential for functional prioritization and therapeutic translation[11,12].

Beyond inherited germline variation, Population-based exome sequencing has revealed age-related clonal hematopoiesis (CH), characterized by somatic mutations in hematopoietic cells[13]. These mutations frequently affect genes such as DNA methyltransferase 3 alpha (DNMT3A), ten-eleven translocation 2 (TET2), additional sex combs-like 1 (ASXL1), Janus kinase 2 (JAK2), and tumor protein p53 (TP53), and are associated with increased ASCVD risk through inflammatory pathways involving interleukin 1 beta (IL 1β) and interleukin 6 (IL 6)[14]. Rare variant association studies have further linked loss-of-function mutations in low-density lipoprotein receptor (LDLR), PCSK9, and apolipoprotein C-III (APOC3) to CAD risk via lipid metabolism and blood pressure regulation[15]. Table S1 summarizes key genes implicated in atherosclerosis, highlighting their roles in inflammation, lipid metabolism, oxidative stress, endothelial function, and vascular remodeling.

Epigenomics

Epigenetic changes can affect gene expression without modifying the DNA sequence, and by chemical changes of DNA/histone complexes. These epigenetic changes regulate gene expression via DNA methylation, acetylation, and other epigenetic changes, which are essential in the progression of vascular atherosclerotic disease. Epigenetic changes are also caused by environmental factors such as smoking and can be inherited by the next generation and leading to early disorders of the cardiovascular system[16,17]. DNA methyltransferases1 (DNMT1)/ DNMT3a and DNMT3b are chief enzymes in DNA methylation[18]. Promoter methylation prevents gene expression[19]. In addition to the aforementioned epigenetic factors, non-coding RNA (ncRNA) also affects the regulation of gene expression[20]. AS is an inflammatory malady in which rupture of the atherosclerotic plaque can lead to dangerous consequences such as ischemic stroke and myocardial infarction[21]. Valencia-Morales et al. observed that increased DNA methylation of genes and inflammatory pathways occurs with disease progression[22]. Also, the studies of Deng et al. show that the reduced DNMT1 in blood cells is related to higher CAD risk. DNA methylation generally increases with age, and oxidative stress can affect demethylation[23]. Examination of abnormal DNA methylation in AS shows that methylation levels increase with age. The selective inhibitor drugs such as 3-deazaneplanocin A (DZNep) and BIX-01294 inhibit histone methylation via lysine methyltransferases (KMTs) and may control immune cell differentiation. Also, the relationship between the expression of some specific microRNAs including miR-26a, miR-92, miR-195-3p, miR-182, and lipid accumulation, inflammation, and plaque formation has been identified. In general, DNA hypomethylation is common in AS plaques, and hypomethylated regions of genes such as Retrotransposon Gag Like 1 (RTL1) (a gene associated with capillary formation) and several miRNAs have been identified in AS[24]. Costantino et al. showed that in AS patients, as a result of increased DNA methylation, endothelial cell damage, macrophage inflammation, and plaque rupture occur, and targeting aberrant DNA methylation can be one of the most important therapeutic strategies in the treatment and prevention of this disease[16].

Transcriptomics

The transcriptome serves as a connection between the cellular phenotype and genotype, providing insights into biological phenomena[25]. The transcriptomic profiling in human atherosclerotic vascular samples has revolutionized our understanding of the molecular characteristics of AS. Research new molecular pathways in atherosclerosis, such as microRNAs and lncRNAs offers valuable prognostic biomarkers and potential therapeutic targets. Single-cell RNA sequencing (scRNA-

seq) as a powerful tool is an emerging method that enabling efficient sequencing of individual cell transcriptomes, offering a comprehensive view of gene expression patterns[26]. It reveals disease-specific gene networks, biomarkers, and cell-to-cell interactions but lacks spatial resolution. Spatial transcriptomics (ST) overcomes this by adding spatial information, enabling precise analysis of three-dimensional tissue structures. Transcriptomic research has emerged as a potent tool for deciphering the intricate molecular pathways underlying AS[27]. Concurrent studies suggest that overexpression of CXC Motif Chemokine Ligand 3 (CXCL3), Glycerol kinase (GK), Formyl peptide receptor 1 (FPR1), and leukocyte specific transcript 1 (LST1) may serve as advanced recognition and intervention factors for unstable plaques, potentially preventing atherosclerotic rupture. Additionally, transcriptomic analysis has also revealed disparities between femoral and carotid plaques based on location[28]. By analyzing gene expression patterns within cells, transcriptomic studies have revealed crucial information about the molecular mechanisms underlying plaque formation and the role of various cell types in the disease and the role of SMCs proliferation and movement from the arterial media to the intima in plaque destabilization[27]. Utilizing single-cell RNA sequencing, researchers have identified the involvement of SMCs and endothelial cells in calcification and extracellular matrix remodeling within calcified atherosclerotic plaques. Advancements in single-cell transcriptomics, coupled with improved techniques and larger patient cohorts offer substantial promise in sex differences in plaque phenotype[29]. In summary, transcriptomics, particularly scRNA-seq, offers valuable insights into the molecular mechanisms underlying AS. It enables the identification of sex-related variances, location-based disparities, and specific cell populations involved in plaque development. These findings open avenues for personalized medicine approaches and the development of targeted therapies for AS management.

Proteomics

Proteomics addresses challenges associated with post-translational modifications using techniques such as mass spectrometry and peptide maps, enabling precise protein identification[30]. The study of proteomics entails a systematic examination of all the proteins in the body, investigating their roles in different processes and their potential as diagnostic markers. In the realm of CVDs, proteomic studies have significantly advanced our knowledge by identifying new molecular targets and biomarkers for assessing the risks and complications of these diseases. By analyzing the proteomic profile of the vascular wall in atherosclerosis, researchers can uncover protein structures that can be used for diagnosis and potential biomarkers for the disease and its complications[31]. Research on human atherosclerotic plaques has revealed notable discrepancies in protein composition between healthy and atherosclerotic tissues[32]. A key study by Theofilatos et al with focus of investigate the proteomic differences between the plaque core and periphery, as well as extracellular proteins identified a four-protein signature (calponin, protein C, serpin H1, versican) from carotid plaques predictive of future cardiovascular mortality and also highlighted sex differences in proteoglycan abundance. The study revealed that female subjects had higher abundance of the large aggregating proteoglycans versican and aggrecan compared to male subjects[33]. Studies have observed heightened levels of Cyclin-dependent kinase 9 (CDK9), CD14-like antigen, and monocytes/macrophages in patients with coronary AS, providing insights into the disease process. Additionally, Tubulin, MAGP-4, and vimentin have been linked to tages of atherosclerotic plaques, indicating their involvement in cell migration, inflammation, and tissue damage. Integrating proteomic data with genomics and protein dynamics, reveals modules linked to heart hypertrophy[34]. By examining the protein profiles of different macrophage phenotypes, proteomic analysis

provides insights into the diverse functions of macrophages in the disease, leading to the identification of novel strategies for managing the disease[35]. In predicting the risk of ASCVD, plasma proteomics and lipidomics show great potential. By combining plasma biomarkers with genetic risk scores and coronary artery imaging, a comprehensive understanding of ASCVD risk can be achieved, enabling more accurate risk assessment and personalized management strategies[36].

Metabolomics

Metabolomics is approach for understanding the metabolic processes underlying atherosclerosis. Metabolomics analysis has deepened our understanding of the specific metabolic pathways involved in cholesterol accumulation and dysregulated lipid metabolism in atherosclerosis. Additionally, metabolomics studies have highlighted changes in glucose and amino acid metabolism, showing metabolic dysregulation in the disease[37]. Metabolomics has also provided crucial insights into the role of oxidative stress pathways in AS by identifying alterations in metabolites associated with oxidative stress. This helps unravel the underlying mechanisms and potential therapeutic targets[38]. Tomas et al found that in high-risk plaques, the metabolite signature indicates elevation of glucose utilization, decreased fatty acid oxidation flux, and heightened amino acid anaplerosis. This pattern aligns with the activation of T cells and the presence of pro-inflammatory macrophages, suggesting an inflammatory and metabolically active environment[39]. Metabolomics studies have also shown that smaller LDL particles to have a higher risk of CVD and can analyze metabolites in urine or saliva[40]. Furthermore, spatial metabolomics techniques like desorption electrospray ionization mass spectrometry imaging (DESI-MSI) enable the mapping of small molecule distribution and correlation with pathology, providing insights into the metabolic mechanisms of AS. Specific lipid species, such as sphingomyelins (SMs), ceramides (Cer), and phosphatidylcholines (PC), have been implicated in inflammation and AS progression[41]. In conclusion, metabolomics plays a significant role in understanding metabolic alterations and identifying biomarkers in ASCVD and holds promise for early risk detection and primary prevention strategies.

Glycomics

Glycosaminoglycans (GAGs) and proteoglycans (PGs) are major components of the extracellular matrix (ECM) in vascular endothelial cells, smooth muscle cells (SMCs), and adventitial fibroblasts. They regulate vascular permeability and maintain homeostasis. In arteries, the main GAGs are chondroitin sulfate (CS) and dermatan sulfate (DS). Versican is the predominant CS proteoglycan (CSPG), while decorin and biglycan, members of the small leucine-rich repeat family, are key dermatan sulfate proteoglycans (DSPGs)[42]. Versican and biglycan bind strongly to native and oxidized LDL (OxLDL), while decorin enhances LDL retention by binding type I collagen, facilitating lipoprotein accumulation in arterial walls. Their elevated levels in early atherosclerosis promote lipid deposition. LDL-GAG complexes are internalized by macrophages and SMCs, promoting proliferation, migration, foam cell formation, and early lesion development[43]. CS also disrupts elastin assembly by binding elastin-binding protein, increasing vessel stiffness. Lipoprotein binding depends on CS/DS branch length, charge density, and sulfation. CS containing 4-O- or 6-O-sulfate shows stronger aortic lipoprotein binding, and atherosclerotic vessels exhibit increased CS content and a higher 6-O-/4-O-sulfate ratio[44,45]. Perlecan is the main heparan sulfate proteoglycan (HSPG) in endothelium and SMCs. HSPG levels are reduced in atherosclerosis and inversely correlate with cholesterol, suggesting a protective role. HSPG depletion at sclerotic sites increases lipoprotein A interaction with the ECM and stimulates heparanase production[46]. Heparanase degrades heparan sulfate, increasing arterial permeability, SMC migration, and macrophage recruitment and inflammatory cell infiltration. Hypoxia reduces macrophage surface heparan sulfate, promoting

migration and plaque progression. Hyaluronic acid (HA), produced by SMCs, increases during atherosclerosis and promotes SMC proliferation and migration via ERK1/2 signaling through CD44 interaction, contributing to intimal hyperplasia. HA binds LDL and is rapidly taken up by macrophages, increasing cytokine and growth factor release and altering SMC phenotype[47]. Low-molecular-weight HA (LMW-HA) is elevated in plaques and promotes inflammation, monocyte migration, and foam cell formation via CD44, whereas high-molecular-weight HA (HMW-HA) is less inflammatory[48]. Sialyltransferase activity is increased in atheromatous tissue, though its effect on circulating sialic acid and protein sialylation remains unclear. Desialylated LDL is highly immunogenic and induces proatherogenic autoantibodies. Overall, vascular GAGs and PGs drive ECM remodeling, immune cell adhesion, lipid retention, intimal hyperplasia, and thrombosis, making them potential therapeutic targets in atherosclerosis prevention[49].

Microbiomics

Today, atherosclerotic plaque rupture is a leading cause of acute cardiovascular events. In addition to atherosclerotic underlying factors, the gut microbiota also has a significant impact. Gut microbiota improves biological activities by producing metabolites derived from dietary components. Through regulatory mechanisms related to serotonin and cytokines, it has a positive effect on host metabolism[50]. Recently, an association has been established between microbiota and microbe-derived metabolites, including trimethylamine-N-oxide (TMAO), short-chain fatty acids (SCFAs), and lipopolysaccharide (LPS), and atherosclerosis. Trimethylamine-N-oxide (TMAO), derived from the bacterial conversion of nutrients like choline and carnitine, promotes atherosclerosis. Like TMAO, LPS (an endotoxin originating from the outer membrane of Gram-negative bacteria) can cause atherosclerosis. LPS is recognized by the immune system and activates multiple atherosclerotic inflammatory pathways. In contrast to TMAO and LPS, SCFAs such as acetate, butyrate, and propionate modulate the host's immune system, thereby playing a protective role against atherosclerosis[51]. A study by Koren et al. showed that oral bacteria that cause periodontal disease may be related to atherosclerosis[52]. In a metagenomic examination of patients with atherosclerosis, Liu et al. showed that intestinal microbial metabolite, nicotinic acid, was an effective lipid-lowering drug for reducing cardiovascular risk and can be used as probiotics for treating atherosclerosis[53]. Table 1 categorizes a diverse array of omics-based biomarkers employed for both diagnostic and prognostic purposes in the context of atherosclerosis.

Integrative Multi-omics Perspective on Biomarkers Discovery in Atherosclerosis

The integration of omics technologies has increased our understanding of atherosclerotic plaque biology and is helping to uncover new ways to improve risk prediction and discover novel therapeutic targets. Genes such as Apolipoprotein E (APOE), low-density lipoprotein receptor (LDLR), PCSK9, and Interleukin 6 (IL-6) contribute to AS through their effects on lipid metabolism, endothelial function, and inflammatory responses. Consequently, despite this genomic background, other omics layers are influenced by the environment and metabolism and contribute to the pathogenesis of the disease[71]. Epigenetic changes also dynamically regulate gene expression under different conditions and can reveal the relationship between fixed genomic sequences and disease phenotypes. In addition, miRNAs and lncRNAs also regulate the transcriptional and subsequent expression of proinflammatory cytokines and adhesion molecules, altering their proteomic profiles. Findings indicate that circulating inflammatory mediators and extracellular matrix remodeling proteins are associated with plaque and vulnerability[72]. Dysregulation of inflammatory proteins can lead to endothelial dysfunction, changes in lipid processing, and increased vascular dysfunction[73]. Biochemical evidence of lipid accumulation and changes in the arterial wall has also been demonstrated

Table 1. Diagnostic and prognostic biomarkers across molecular multi-omics layers in atherosclerosis.

Omics Level	Category	Biomarker	Structure	Source	Function	Pathomechanism	Context of Diagnosis	*Clinical / Translational	Reference
Genomics	Genetic Risk Loci	LDLR (Low-Density Lipoprotein Receptor)	Transmembrane glycoprotein	Hepatic cells, peripheral tissues (mainly liver)	Clears LDL cholesterol from circulation by binding and internalizing lipoproteins.	Mutations impair LDL uptake → elevated LDL → plaque formation and early atherosclerosis.	Risk stratification for familial hypercholesterolemia (FH).	Clinical	[54]
Genomics	Genetic Risk Loci	ApoE genotype (ε2/ε3/ε4)	Gene polymorphism	Liver, intestine, CNS	Regulates lipoprotein clearance and inflammation.	ApoE4 variant → lipid accumulation and inflammation → higher atherosclerosis/Alzheimer risk.	Risk stratification for lipid disorders and CVD.	Clinical	[55]
Transcriptomics	microRNA	miR-33 (MicroRNA-33)	Non-coding RNA	Endothelial cells, macrophages	Regulates cholesterol metabolism and HDL biogenesis.	Overexpression inhibits ABCA1/ABCG1 → foam cell formation → plaque progression.	Early detection of lipid dysregulation and vascular change.	Translational	[56]
Transcriptomics	microRNA	miR-92a	Non-coding RNA	Endothelial cells	Modulates endothelial cell proliferation and migration.	Upregulation suppresses KLF2/KLF4 → endothelial dysfunction → reduced NO → plaque growth.	Risk assessment for endothelial dysfunction and plaque development.	Translational	[57]
Transcriptomics	microRNA	Exosomal miR-126	Non-coding RNA	Endothelial cells, exosomes	Maintains endothelial homeostasis and vascular repair (via SPRED1/PI3K-AKT signaling).	Reduced expression impairs repair and promotes inflammation.	Early endothelial dysfunction marker before clinical disease.	Translational	[58]
Proteomics	Inflammatory Cytokine	IL-6 (Interleukin-6)	Cytokine	Macrophages, endothelial cells	Regulates immune response and inflammation.	Chronic elevation causes endothelial dysfunction and plaque instability.	Tracks disease progression and inflammatory burden.	Translational	[59]
Proteomics	Growth Factor/Cytokine	Growth Differentiation Factor 15 (GDF 15)	Protein	Macrophages, endothelial cells	Regulates cell differentiation and apoptosis.	High levels indicate endothelial injury and inflammation.	Predictive marker for plaque rupture and CVD risk.	Translational	[60]
Proteomics	Enzyme	Lipoprotein-associated phospholipase A2 (Lp-PLA2)	Enzyme	Macrophages, endothelial cells	Links lipid metabolism and inflammation.	Elevated levels destabilize plaques via inflammation.	Monitoring plaque rupture risk and systemic vascular inflammation.	Clinical	[61]
Proteomics	Enzyme	MMP9 (Matrix Metalloproteinase 9)	Enzyme (Matrix metalloproteinase family)	Leukocytes, macrophages, neutrophils, smooth muscle cells	Degrades extracellular matrix.	Overexpression weakens fibrous cap → plaque rupture and events.	Monitoring disease progression or instability.	Translational	[62]
Proteomics	Cytokine / Signaling Protein	Osteopontin	Glycoprotein	Macrophages, smooth muscle cells, T-cells within plaques	Mediates adhesion, migration, calcification.	Upregulated in plaques → chronic inflammation & calcification.	Used for risk stratification and progression monitoring (MACE).	Translational	[63]
Proteomics	Cytokine / Signaling Protein	Osteoprotegerin (OPG)	Glycoprotein	Endothelial cells, vascular smooth muscle cells	Decoy receptor for RANKL; regulates vascular calcification.	High OPG paradoxically associates with advanced calcification and mortality.	Prognostic marker for CVD severity and mortality, esp. CKD and advanced atherosclerosis.	Translational	[63]

Table 1. Diagnostic and prognostic biomarkers across molecular multi-omics layers in atherosclerosis.

Omics Level	Category	Biomarker	Structure	Source	Function	Pathomechanism	Context of Diagnosis	*Clinical / Translational	Reference
Lipidomics	Sphingolipid	Ceramide	Lipid	Macrophages, adipocytes	Regulates apoptosis and inflammation	Specific species (C16:0–C24:1) promote endothelial dysfunction & lipotoxicity.	Risk marker; ceramide score (CERT1/CERT2) predicts major CV events.	Clinical	[64]
Lipidomics / Proteomics	Genetically Determined Atherothrombotic Biomarker	Lipoprotein(a) [Lp(a)]	LDL-like particle with ApoB-100 covalently linked to apolipoprotein(a) containing kringle-IV repeats	Liver (genetically set by LPA gene; minimally affected by lifestyle)	Pro-inflammatory, pro-atherogenic, antifibrinolytic.	Induces endothelial dysfunction, calcification, and inhibits fibrinolysis via plasminogen competition.	Major inherited risk factor; single lifetime measurement recommended.	Clinical	[65]
Metabolomics	Amino Acid Metabolite	Homocysteine (Hcy)	Sulfur-containing non-protein-amino-acid (derivative of methionine)	Plasma (also in liver metabolism)	Intermediate in methionine → cysteine cycle; methylation / trans-sulphuration pathway	Elevated Hcy → oxidative stress, NO impairment, hypomethylation → thrombosis & plaque formation.	Early detection or risk stratification for ASCVD.	Clinical	[66]
Metabolomics	Gut Microbiome Metabolite	TMAO (Trimethylamine-N-Oxide)	Metabolite	Gut microbiota, liver	Modulates cholesterol and inflammation.	Elevated levels impair eNOS, activate NF-κB → inflammation & plaque development.	Risk stratification via circulating TMAO for AS severity.	Clinical	[67]
Metabolomics	Methylation Metabolite	ADMA (Asymmetric Dimethylarginine)	Amino acid derivative	Plasma (endothelial cells)	Endogenous inhibitor of nitric oxide synthase (NOS).	Reduced NO bioavailability → endothelial dysfunction.	Translational marker of endothelial dysfunction and CV risk.	Translational	[68]
Glycomics	Lectins & Glycoproteins	PSGL-1 (P-selectin Glycoprotein Ligand-1)	Glycoprotein	Endothelial cells, platelets	Mediates leukocyte adhesion through P-selectin binding.	Triggers vascular inflammation via TLR4; accelerates atherogenesis.	Marker of inflammatory plaque progression.	Translational	[69]
Glycomics	Glycoprotein Acetyls	GlycA	Glycoprotein	Composite NMR Signal	Integrates acetylated glycoproteins (α1-AGP, α1-AT, haptoglobin, etc.).	Reflects low-grade systemic inflammation → predicts plaque progression and CVD events.	Marker of chronic systemic inflammation across AS stages.	Clinical	[70]

* Clinical biomarkers are established, routine diagnostic tools approved for standard patient care (e.g., Troponin), whereas Translational biomarkers are promising candidates currently bridging the gap between research discovery and future clinical application (e.g., miRNAs).

using lipidomics. After lesion progression and macrophage foam cell formation, glycomic alterations are observed in the composition LDL, oxidized phospholipids, and proinflammatory LPCs. As a result of the integration of genomics, proteomics, lipidomics, and glycomics, genetic variants and inflammatory proteins that can affect lipid processing and exacerbate vascular injury have been proposed[45]. Post-translational glycosylation modifications (glycomics) also significantly affect leukocyte recruitment by adhesion molecules (such as VCAM-1 and Intercellular Adhesion Molecule 1 (ICAM-1), the association of proinflammatory profiles with plasma proteins (such as immunoglobulin G), and protein stability. Therefore, integrated glycoproteomics can identify disease-associated glycoforms and use them for therapeutic targeting. Metabolomics reveals the close relationship between disease mechanism and phenotype and provides more detailed information about the physiological function of living systems. For example, metabolites such as glutathione and TMAO are linked to the risk of CVD[74]. Integrating microbiomics with metabolomics reveals functional circulating metabolites resulting from microbial activity, and these specific metabolites are associated with plaque composition and calcification patterns. Microbial metabolites alter epigenetic marks and regulate systemic inflammation[75]. Overall, the crosstalk between omics layers is the main cause of the true complexity of atherosclerosis. Therefore, with integrated frameworks, causal pathways can be identified, and appropriate treatment strategies can be developed. Interplay among multi-omics levels within vascular smooth muscle cells (VSMC) in atherogenesis and its progression has been shown in Fig. 2.

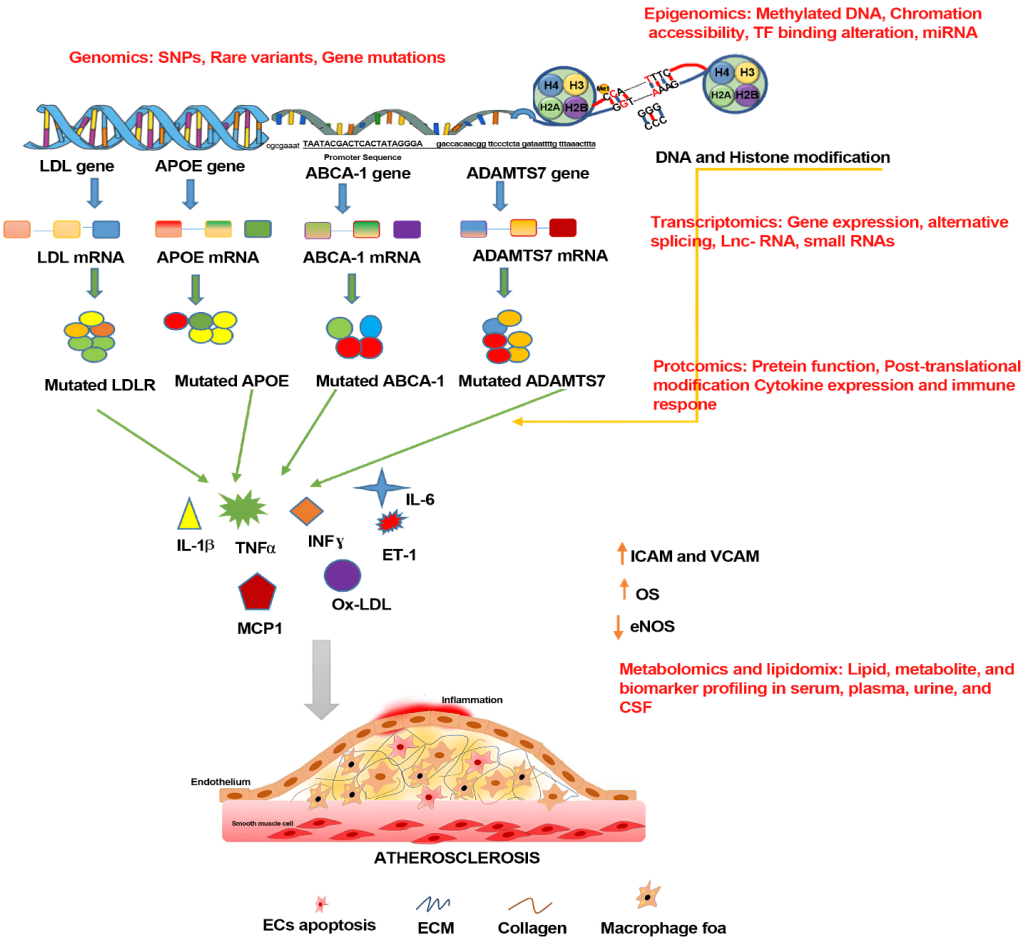


Figure 2. Interplay between different changes at multi-omicss levels within VSMC during AS development. The figure was designed by biorender software (www.biorender.com).

Integrating multi-omics and multi-organ (pancreas, liver, gut, and cardio vasculature) interactions in the pathogenesis of AS

Multi-omics approach links the relatively stable genomic pattern to the dynamic mechanisms involved in plaque formation and enables the identification of key controllers in molecular networks by tracing molecular pathways from a specific genetic variant to an altered metabolite regulated through intermediary proteins. Complicated connections between the gut, liver, pancreas, and the cardiometabolic system, play a role in the development of AS. Identification of these multi-organ interactions at multi-omics levels is essential for understanding of AS pathogenesis[50,51,76].

Mechanisms of cross-talk: the gut-liver-cardiometabolic axis (focus on microbiomics)

TMAO pathway represents a critical intersystem interaction which reflects multi-omics connections in the gut-liver-vascular axis. TMA is produced by the colonic microflora, and the process subsequently continues toward the liver, where hepatic enzymes particularly flavin-containing monooxygenase 3 (FMO3) oxidize TMA to produce TMAO. After being released into the systemic circulation, this molecule exerts its atherogenic effects on the vascular wall through multiple mechanisms, including the conversion of macrophages into foam cells, inhibition of reverse cholesterol transport (RCT), vascular endothelial dysfunction through activation of the NF-κB, mitogen-activated protein kinases (MAPK) pathways, increased oxidative stress, and reduced production of endothelial progenitor cells (EPCs)[76]. In brief, these processes contribute to the progression of AS.

Mechanisms of Cross-Talk: The Pancreas-Liver-Vascular Axis (Focus on Metabolomics/ Lipidomics)

In metabolic and lipidomics dysregulation, the interaction among the pancreas, liver, and vasculature is clearly evident. Studies indicate that fat deposition in the pancreas leads to increased carotid and aortic intima–media thickness (IMT) and ultimately vascular stiffness. This pancreatic dysregulation causes changes in systemic metabolomics, which subsequently affect hepatic lipidomics and lead to abnormal synthesis of pro-atherogenic lipids. On the other hand, AS itself impairs pancreatic function by reducing blood flow. This dysfunctional process illustrates how metabolic signals from one organ (the pancreas) are converted into inflammatory transcriptional signals in the target organ (the vessels), while vascular dysfunction simultaneously affects pancreatic function[77,78].

Data Integration Using Available Public Databases

Multi-omics network medicine platforms are very helpful in identifying key biomarkers in AS research. NeDRex integrates gene expression data to provide disease modules and support drug repurposing[79]. The OmicsNet 2.0 platform was developed to integrate multi-omics networks. It uses various omics inputs, including genes, proteins, transcription factors, and metabolites, to search compatible databases to build a heterogeneous network. For integrated analysis and visualization of multi-omics datasets, the PaintOmics 4 platform can be utilized which employs biological path maps from main path databases. The Mergeomics 2.0 platform merges multi-omics disease-related data and identifies molecular pathway controllers of diseases[80]. Another example of these databases is the human metabolome database (HMDB) (https://hmdb.ca), which has seen significant growth in the number of metabolite entries in recent years. It provides a spectral visualization tool and information on metabolite characteristics and structure[81]. The CVD database is a data source consisting of CAD data that correlates scientific information with the expression of some CVD-related factors through multi-omics[82]. Free available databases such as Encode, bioRxiv, and Snyderome contain various omics data that can be linked with genomic data. This facilitates the simultaneous analysis of molecular processes in different

human tissue studies. Unfortunately, efforts to integrate omics and non-omics data are insufficient. We hope to see an increase in these efforts with the creation of big data in medicine and biology. Recognizing a complex trait requires identifying its complex biological system and the influence of other factors, such as environmental and individual factors[34]. Integrating omics and non-omics data can help identify new disease risk factors and patients who will respond well to treatment. This will greatly impact the future of personalized medicine (Fig. 3 and Table S2).

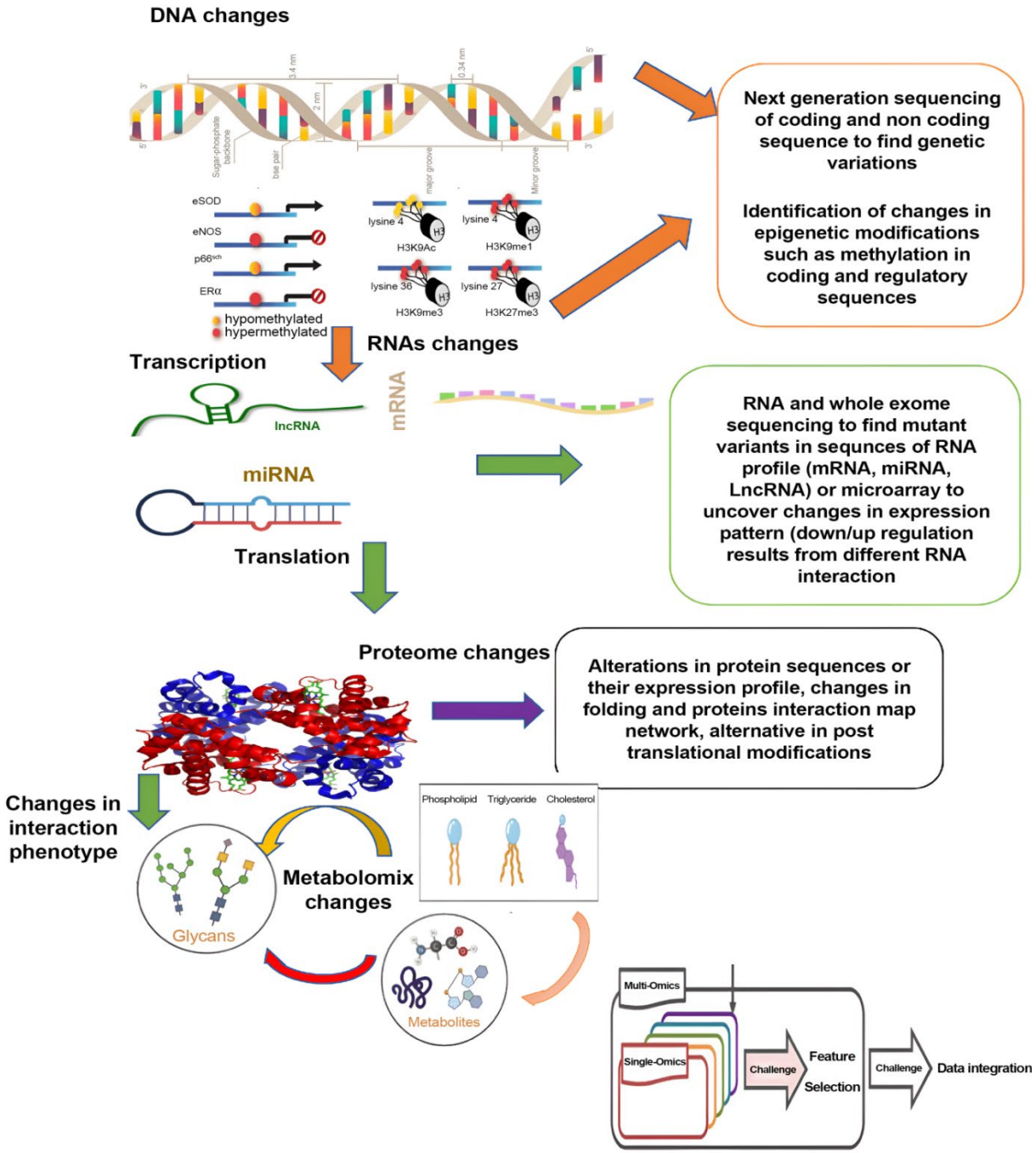


Figure 3. The integrated multi-omics approaches compared to single omic level generate a holistic view in AS management from developmental process to diagnostics and therapeutic strategies. The figure was designed by biorender software (www.biorender.com).

Future Directions and Conclusion

Multi-omics and artificial intelligence/machine learning (AI/ML) approaches are poised to transform CVD risk assessment and lifetime risk prediction by enabling deep molecular phenotyping and more personalized care. Access to multidimensional data helps identify genes and pathways involved in atherosclerosis, reveals mechanisms like exosome-mediated cell communication, and aids in discovering new drug targets. As ASCVD precision medicine evolves, the aim is to move beyond one-size-fits-all models toward data-driven, tailored therapies, with explainable AI and integrated digital biomarkers enhancing prediction and risk stratification. However, several barriers remain. Heterogeneity across omics layers, problems in analyzing multi-omics samples, and annotation/resource constraints complicate integrative analyses. High-throughput omics technologies are costly, and translating findings to large-population clinical application requires coordinated, interdisciplinary collaboration among researchers, clinicians, and data scientists. Initiatives like the CA21153 AtheroNET COST network exemplify efforts to advance multi-omics approaches in ASCVD prevention and research, promoting robust, generalizable discoveries through collaboration. Future precision cardiology will depend on explainable AI, harmonized multi-omics repositories, standardized protocols, and interdisciplinary collaboration. Multi-omics-driven deep phenotyping offers a path toward individualized risk prediction, causal target identification, and optimized therapeutic strategies in atherosclerotic cardiovascular disease.

Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: EB; SM; LA; MB
Data Acquisition: —
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