

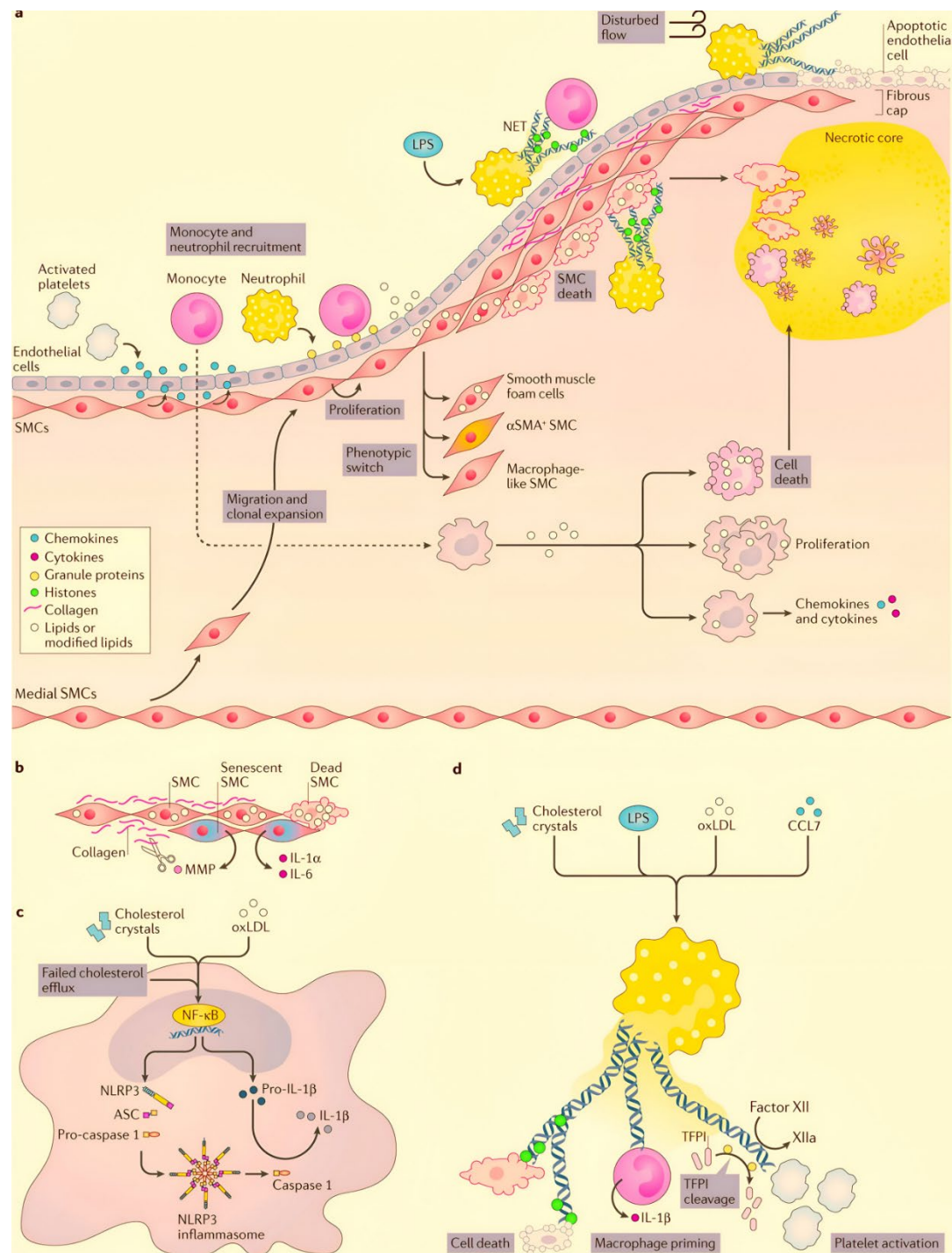


Fig. S1. The overview of inflammatory mechanisms involved in AS plaque formation can be summarized as follows: **a.** The process begins with chemokines, particularly C-C motif chemokine 5 (CCL5), produced by activated platelets, which trigger the migration of monocytes and neutrophils. Neutrophils contribute to this inflammatory environment by releasing chemotactic granule proteins, such as cathelicidin and cathepsin G, which facilitate monocyte infiltration. Activated smooth muscle cells (SMCs) further reinforce this inflammatory milieu through the production of additional chemokines like CCL2 and CCL5. The development of atherosclerotic lesions is characterized by the migration of medial SMCs toward the advanced fibrous cap, where they undergo clonal expansion, lipid accumulation, and transformation into foam cells. These changes lead to SMC apoptosis and subsequent necrosis, exacerbated by histone H4 binding from neutrophil extracellular traps (NETs). Infections with Lipopolysaccharides (LPS)-containing bacteria can also promote plaque growth **b.** Cholesterol accumulations triggers apoptosis in SMCs which in turn, diminishes the contents of extracellular matrix and causes more SMC death. Damaged SMCs secrete pro-inflammatory cytokines and matrix-degrading enzymes, including matrix metalloproteinases (MMPs). **c** Cholesterol accumulation triggers apoptosis in SMCs, reducing the extracellular matrix content and leading to further SMC death. Damaged SMCs secrete pro-inflammatory cytokines and matrix-degrading enzymes, including MMPs. Altered lipids, such as Oxidized Low-density Lipoprotein (oxLDL), activate the nuclear factor- κ B (NF- κ B) signaling pathway, stimulating the transcription of NLR Family Pyrin Domain Containing 3 (NLRP3) and pro-IL-1 β . The formation of the NLRP3 inflammasome results in the cleavage of pro-IL-1 β into its mature form. **d.** NETs exert cytotoxic effects through NET-resident histones, enhance NLRP3 inflammasome activation in macrophages, and promote coagulation by cleaving factor XII and tissue factor pathway inhibitor (TFPI), leading to direct platelet activation. This intricate interplay of cellular interactions and inflammatory mediators underscores the complexity of AS progression. The figure was designed by biorender software (www.biorender.com).

Table S1. The most important genes (genomics profile) involved in the atherosclerosis development.

No.	Genes or signaling pathways involved in atherosclerosis	Function	Effect on AS Treatment
1	Signal Transducer and Activator of Transcription 3 (STAT3)	Signal transducer involved in inflammation and cell survival	promotes atherogenesis [1]
2	IL1B	Pro-inflammatory cytokine, induces cytokine generation	promotes plaque instability [2, 3]
3	Tumor Necrosis Factor (TNF)	Cytokine involved in systemic inflammation.	enhances AS [4]
4	Toll-Like Receptor 2 (TLR2)	Receptor that recognizes pathogens, involved in inflammatory response	enhances AS [5]
5	CXCL16	Chemokine involved in immune cell recruitment	associated with atheroprotection [6]
6	IL1RN	Antagonist of IL1, regulates inflammation	reduces AS progression [7]
7	Complement Component 5a Receptor 1 (C5AR1)	Receptor for complement component C5a, involved in inflammatory response	promotes inflammation in plaques [8]
8	Proto-Oncogene, Src Family Tyrosine Kinase (LYN)	Src family kinase, involved in signaling pathways related to inflammation.	enhances AS via CD36 activation [9].
9	Interleukin-17 Receptor A (IL17RA)	Receptor for IL-17, mediates pro-inflammatory responses.	associated with increased AS risk [10].
10	Integrin Subunit Alpha M (CD11b) (ITGAM)	Integrin alpha M, involved in leukocyte adhesion and migration.	promotes inflammatory cell recruitment to plaques [11].
11	S100 Calcium-Binding Protein A8 (S100A8)	Calcium-binding protein involved in inflammatory responses and cell signaling.	associated with increased inflammation in plaques [12].
12	C-C Motif Chemokine Ligand 13 (CCL13)	Chemokine that recruits monocytes to sites of inflammation.	enhances inflammatory processes linked to plaque development [13].
13	IL-6	Pro-inflammatory cytokine involved in immune response.	targeting IL-6 signaling may reduce inflammation and improve AS outcomes [14].
14	RING Finger Protein 13 (RNF13)	E3 ubiquitin ligase involved in protein degradation.	modulation may impact inflammatory pathways related to AS [15].
15	Complement Component 3a Receptor 1 (C3AR1)	Involved in inflammatory responses.	modulation could help control inflammation linked to disease progression [16].
16	C-C Chemokine Receptor Type 1 (CCR1)	Involved in monocyte recruitment during inflammation.	targeting may reduce inflammatory cell infiltration into arterial walls, potentially mitigating plaque formation [17].
17	Anti-inflammatory Heme Oxygenase-1 (HO-1)	Enzyme providing cytoprotection through heme degradation.	induction has anti-inflammatory effects beneficial for AS treatment [18].
18	Immune Response Solute Carrier Family 11 Member 1 (SLC11A1)	Transports divalent metal ions, involved in macrophage function.	may have protective effects against AS [19].
19	Protein Tyrosine Phosphatase Receptor Type C (CD45) (PTPRC)	Protein tyrosine phosphatase involved in immune cell signaling.	enhances inflammatory responses linked to AS [20].
20	Colony Stimulating Factor 1 Receptor (CSF1R)	Receptor for colony-stimulating factor 1, regulates macrophage activity.	may limit inflammation and stabilize plaques [21].
21	CX3CR1	Receptor for fractalkine, mediates adhesion and migration of leukocytes.	associated with reduced plaque formation [22].
22	Formyl Peptide Receptor 2 (FPR2)	Formyl peptide receptor involved in immune response regulation.	may have protective effects against AS progression [23].
23	ArfGAP with Dual PH Domains 2 (ADAP2)	Adaptor protein involved in T-cell signaling and immune response regulation.	may enhance immune control over plaque formation [24].
24	Metabolism Deiodinase, Iodothyronine Type II (DIO2)	Deiodinase enzyme that converts thyroid hormone precursors into active forms.	may influence metabolic processes linked to cardiovascular health [24].
25	Insulin-Like Growth Factor 1 (IGF-I)	Promotes cell growth and survival; involved in metabolic regulation.	may influence vascular remodeling and inflammation, with targeting pathways to modulate AS progression [25].
26	Lipid Metabolism Fatty Acid Binding Protein 5 (FABP5)	Fatty acid-binding protein involved in lipid metabolism and inflammation.	may reduce lipid accumulation in plaques [24].

27	ApoE	Regulates lipid metabolism and clearance of lipoproteins.	variants linked to AS risk, enhancing function could improve lipid profiles and reduce plaque formation [24].
28	ABCA1	Transports cholesterol and phospholipids; critical for HDL formation.	enhancing function promotes reverse cholesterol transport, reducing plaque buildup [26].
29	Oxidized Low-Density Lipoprotein (ox-LDL)	Modified form of LDL promoting inflammation and foam cell formation.	reducing levels is crucial for preventing plaque progression in treatment strategies [27].
30	Oxidative Stress	Antioxidant that regulates redox state of cells.	may protect against oxidative stress, enhancing GLRX activity could mitigate plaque development [28].
	Glutaredoxin-1 (GLRX)		
31	Nrf2	Transcription factor regulating antioxidant responses.	activation enhances cellular defenses against oxidative stress in AS [24].
32	Vascular Remodeling	Receptor involved in angiogenesis and immune responses.	modulating NRP2 could influence vascular remodeling and inflammation related to AS [29].
	Neuropilin-2 (NRP2)		
33	Thrombosis	Protease-activated receptor involved in thrombotic and inflammatory processes.	associated with increased thrombus formation at plaques [24].
	Coagulation Factor II Thrombin Receptor Like 2(F2RL2)		
34	Endothelial Function	Guanylate cyclase receptor, involved in vasodilation and cardiovascular function.	may help improve endothelial function and reduce AS risk [24].
	Guanylate Cyclase 1 Soluble Subunit Alpha 2 (GUCY1A2)		

Table S2. Benefits and drawbacks of multi-omics technologies.

Omics Technologies	Advantages	Disadvantages	Ref.
Genomics (GWAS, PCR, microarrays)	The applications of SNPs include early diagnosis and treatment of diseases.	Factors such as post transcriptional and post translational modifications and epigenetics affect the prediction of the final biological effect of DNA and make genome analysis complex.	[30]
	Sensitivity to some drugs and different responses to drugs among different people can be evaluated by using gene polymorphism studies.		
Transcriptomics (RNA sequencing, hybridization-based sequence-base, Taq-based methods)	Identification of the major pathways involved in drug response and toxicity. Their advantages include providing new transcription views and precision at the transcription level.	Because modifications occur after translation, sufficient data are not available.	[31]
	By using them, the biological pathways involved in the response as well as the mechanism of drug toxicity can be identified.	Changes in the primary transcript are not detectable through the final products.	
Sequence based, Taq base methods (SAGE)	One of the advantages of this method is that it has a high throughput and also shows the level of gene expression with high accuracy and digitally.	Expensiveness and low quality are seen for relatively low throughput.	
		It is complicated and pricey to separate isoforms during analysis.	
Proteomics Gel based / Gel free proteomics 2D-DIGE	By using gel-based 2DGE proteomics, a small amount of a specific protein can be measured in a complex sample. Also, the use of 2D-DIGE gel-free proteomics allows for quantitative comparison, and by eliminating the fixation and decolorization steps (post-electrophoretic processing steps), it increases reproducibility and reduces costs.	The expensiveness of the techniques due to the use of special equipment and the lack of labeling of proteins without lysine can cause problems.	[32]
Metabolomics (NMR, MS)	The use of MS along with LC or GC can increase the sensitivity and enable the detection of different species in one sample.	The sample preparation method can affect the MS signal power, as well as scanning and sensitivity limitations in this technique.	[32]
Radiomics	The quantification of different tumor phenotypes was considered as the characteristics of Mitonan radiomics and used to predict clinical outcomes.	In the design of radiomics to check its prognostic power, data from several patients should be used for each feature.	[33]

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