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## **СОВРЕМЕННЫЕ МОЛЕКУЛЯРНО-ПАТОГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ ПРОГРЕССИРОВАНИЯ ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ У ПАЦИЕНТОВ С ИБС**

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### **АННОТАЦИЯ**

Коронарный атеросклероз представляет собой хроническое прогрессирующее заболевание артериальной стенки, патогенез которого определяется сложным взаимодействием нарушений липидного обмена, эндотелиальной дисфункции, хронического воспаления, иммунных реакций, окислительного стресса, клеточной пластичности и ремоделирования внеклеточного матрикса. Современная концепция атерогенеза существенно расширяет классическое представление о накоплении липидов в сосудистой стенке. Показано, что прогрессирование атеросклеротической бляшки является результатом динамического взаимодействия эндотелиальных клеток, моноцитов/макрофагов, лимфоцитов, гладкомышечных клеток сосудов, тромбоцитов и клеток врожденного иммунитета. Ключевое значение в инициации и прогрессировании атеросклероза имеет ретенция атерогенных липопротеинов в интиме, их модификация, активация эндотелия и рекрутирование воспалительных клеток. Окисленные липопротеины низкой плотности и кристаллы холестерина способны активировать NLRP3-инфламмасому с последующей продукцией интерлейкина-1 $\beta$  и интерлейкина-18. Существенную роль играют нарушение эффероцитоза, формирование некротического ядра, фенотипическое переключение гладкомышечных клеток сосудов, кальцификация, неоваскуляризация и образование внеклеточных ловушек нейтрофилов. Новые данные свидетельствуют также о значении клонального гемопоэза неопределенного потенциала, эпигенетических механизмов и некодирующих РНК в формировании воспалительного фенотипа клеток сосудистой стенки. Развитие технологий одноклеточного секвенирования и пространственной транскриптомики позволило выявить выраженную клеточную и молекулярную гетерогенность атеросклеротической бляшки и перейти от упрощенной модели M1/M2-поляризации макрофагов к представлению о множестве функционально различных клеточных состояний. Понимание указанных механизмов открывает возможности для разработки новых подходов к персонализированной оценке риска прогрессирования коронарного атеросклероза и созданию таргетных терапевтических стратегий.

**Ключевые слова:** коронарный атеросклероз, атеросклеротическая бляшка, эндотелиальная дисфункция, LDL, воспаление, NLRP3-инфламмаза, макрофаги, гладкомышечные клетки, эпигенетика, некодирующие РНК, клональный гемопоэз, кальцификация.

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Samarkand, Uzbekistan**MODERN MOLECULAR AND PATHOGENETIC MECHANISMS OF ENDOTHELIAL DYSFUNCTION PROGRESSION IN PATIENTS WITH CORONARY ARTERY DISEASE****ANNOTATION**

Coronary atherosclerosis is a chronic progressive disease of the arterial wall, the pathogenesis of which is determined by a complex interplay of lipid metabolism disorders, endothelial dysfunction, chronic inflammation, immune responses, oxidative stress, cellular plasticity, and extracellular matrix remodeling. The modern concept of atherogenesis substantially expands the classical view of lipid accumulation within the vascular wall. It has been demonstrated that the progression of atherosclerotic plaques results from dynamic interactions among endothelial cells, monocytes/macrophages, lymphocytes, vascular smooth muscle cells, platelets, and cells of the innate immune system. The retention of atherogenic lipoproteins within the intima, their subsequent modification, endothelial activation, and recruitment of inflammatory cells play a key role in the initiation and progression of atherosclerosis. Oxidized low-density lipoproteins and cholesterol crystals are capable of activating the NLRP3 inflammasome, followed by the production of interleukin-1 $\beta$  and interleukin-18. Impaired efferocytosis, formation of the necrotic core, phenotypic switching of vascular smooth muscle cells, calcification, neovascularization, and the formation of neutrophil extracellular traps also play important roles in disease progression. Emerging evidence also highlights the significance of clonal hematopoiesis of indeterminate potential, epigenetic mechanisms, and non-coding RNAs in the development of the pro-inflammatory phenotype of vascular wall cells. The development of single-cell sequencing and spatial transcriptomics technologies has revealed substantial cellular and molecular heterogeneity within atherosclerotic plaques and has led to a shift from the simplified M1/M2 macrophage polarization model toward a concept encompassing multiple functionally distinct cellular states. Understanding these mechanisms opens new opportunities for personalized assessment of the risk of coronary atherosclerosis progression and for the development of targeted therapeutic strategies.

**Keywords:** coronary atherosclerosis, atherosclerotic plaque, endothelial dysfunction, LDL, inflammation, NLRP3 inflammasome, macrophages, vascular smooth muscle cells, epigenetics, non-coding RNAs, clonal hematopoiesis, calcification.

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Xalqaro fakultet 5-kurs talabasi  
Samarqand, O'zbekiston**YURAK ISHEMIK KASALLIGI BO'LGAN BEMORLARDA ENDOTELIAL DISFUNKSIYA AVJ OLIB BORISHINING ZAMONAVIY MOLEKULAR-PATOGENETIK MEKANIZMLARI****ANNOTATSIYA**

Koronar ateroskleroz arterial devorning surunkali progressiv kasalligi bo'lib, uning patogenezini lipid almashinuvi buzilishlari, endotelial disfunktsiya, surunkali yallig'lanish, immun reaksiyalar, oksidlovchi stress, hujayraviy plastiklik va hujayralararo matriksning qayta tuzilishi kabi jarayonlarning murakkab o'zaro ta'siri bilan belgilanadi. Aterogenezning zamonaviy konsepsiyasi qon tomir devorida lipidlarning to'planishi haqidagi klassik tasavvurni sezilarli darajada kengaytiradi. Aterosklerotik blyashkaning progressiyalanishi endotelial hujayralar, monotsitlar/makrofaglar, limfotsitlar, qon tomirlarining silliq mushak hujayralari, trombotsitlar va tug'ma immunitet hujayralari o'rtasidagi dinamik o'zaro ta'sir natijasi ekanligi aniqlangan.

Aterogen lipoproteinlarning intima qavatida retensiyasi, ularning keyinchalik modifikatsiyalanishi, endoteliy faollashuvi va yallig'lanish hujayralarining rekrutatsiyasi aterosklerozning boshlanishi va progressiyalanishida muhim ahamiyatga ega. Oksidlangan past zichlikdagi lipoproteinlar va xolesterin kristallari NLRP3-inflammasomasi faollashtirish qobiliyatiga ega bo'lib, buning natijasida interleykin-1 $\beta$  va interleykin-18 ishlab chiqarilishi kuchayadi. Efferotsitozning buzilishi, nekrotik o'zakning shakllanishi, qon tomirlarining silliq mushak

hujayralarining fenotipik almashinuvi, kalsifikatsiya, neovaskulyarizatsiya va neytrofillarning hujayradan tashqari tuzoqlari hosil bo'lishi ham kasallikning progressiyalanishida muhim rol o'ynaydi.

Yangi tadqiqotlar, shuningdek, aniqlanmagan potentsialdagi klonal gemopoez, epigenetik mexanizmlar va kodlamaydigan RNKlarning qon tomir devori hujayralarida yallig'lanishga moyil fenotip shakllanishidagi ahamiyatini ko'rsatmoqda. Bir hujayrali sekvenslash va fazoviy transkriptomika texnologiyalarining rivojlanishi aterosklerotik blyashkaning sezilarli hujayravii va molekulyar geterogenligini aniqlash imkonini berdi hamda makrofaglarining soddalashtirilgan M1/M2 qutblanish modelidan funksional jihatdan farq qiluvchi ko'plab hujayravii holatlarni o'z ichiga olgan yangi konsepsiyaga o'tishga olib keldi. Ushbu mexanizmlarni chuqur o'rganish koronar aterosklerozning progressiyalanish xavfini individual baholash hamda maqsadli terapevtik strategiyalarni ishlab chiqish uchun yangi imkoniyatlarni ochib beradi.

**Kalit so'zlar:** koronar ateroskleroz, aterosklerotik blyashka, endotelial disfunktsiya, LDL, yallig'lanish, NLRP3-inflammasomasi, makrofaglar, qon tomirlarining silliq mushak hujayralari, epigenetika, kodlamaydigan RNKlar, klonal gemopoez, kalsifikatsiya.

## Introduction

Atherosclerosis remains the principal morphological basis of ischemic heart disease and is now understood as a chronic, complex inflammatory process affecting the intima of large and medium-sized arteries. Although major advances have been made in cardiovascular prevention and lipid-lowering therapy, a substantial residual risk of coronary events remains. This observation suggests that circulating lipid levels, while fundamental to atherogenesis, represent only one part of a much broader pathogenic process [1,2].

The current view of atherosclerosis emphasizes the close interaction between three major processes: the accumulation and modification of atherogenic lipoproteins, persistent immunoinflammatory activation, and structural remodeling of the vascular wall [1,3]. Inflammation is therefore not simply a consequence of lipid deposition. It is involved throughout the entire course of atherogenesis, beginning with endothelial activation and continuing through plaque growth, remodeling, and, ultimately, plaque destabilization [1,4]. Importantly, the clinical significance of coronary atherosclerosis cannot be determined solely by the degree of luminal stenosis. A plaque producing only modest stenosis may nevertheless contain a large lipid-necrotic core, a thin fibrous cap, and substantial inflammatory activity, all of which may increase its susceptibility to rupture or erosion and subsequent thrombosis [5]. For this reason, increasing attention is being directed toward the molecular processes that govern not only plaque formation but also its progression and stability.

Retention of Atherogenic Lipoproteins as the Initiating Event in Atherogenesis

The development of atherosclerosis begins, in large part, with the retention of apolipoprotein B-containing lipoproteins within the intima. These particles include low-density lipoprotein (LDL), very-low-density lipoprotein and its remnants, as well as lipoprotein(a) [6]. Their retention is facilitated by interactions between apolipoprotein B and proteoglycans within the extracellular matrix. Once trapped in the arterial wall, these lipoproteins undergo a range of chemical and enzymatic modifications, including oxidation and aggregation, which further increase their atherogenic potential [6,7]. Among these modified particles, oxidized low-density lipoprotein (oxLDL) has a particularly important role. Unlike native LDL, oxLDL can be readily recognized by scavenger receptors such as CD36 and scavenger receptor class A1 (SR-A1) on macrophages. Its uptake promotes intracellular cholesterol accumulation and ultimately leads to the formation of lipid-laden foam cells [7]. The sequence is therefore not simply one of passive lipid deposition. Rather, it can be viewed as a continuous process: retention of apolipoprotein B-containing lipoproteins → lipoprotein modification → endothelial activation → recruitment of monocytes → macrophage differentiation → lipid accumulation → foam-cell formation → chronic inflammation → plaque progression. Lipoprotein(a) [Lp(a)] deserves particular attention because its effects extend beyond its atherogenic properties. Oxidized phospholipids carried by Lp(a) can activate endothelial cells, increase the expression of adhesion molecules, and facilitate the recruitment of monocytes into the arterial wall [8]. Clinical evidence has also linked elevated Lp(a) concentrations with the progression of atherosclerotic plaque [9].

## Endothelial Dysfunction and Mechanotransduction

The vascular endothelium is not merely a physical barrier. It is a metabolically and immunologically active tissue involved in the regulation of vascular tone, permeability, inflammation, and hemostasis. Atherosclerotic lesions tend to develop at arterial bifurcations, curves, and branching points, where blood flow is

disturbed and mechanical forces acting on endothelial cells differ substantially from those encountered under stable laminar flow. These local hemodynamic conditions can promote a proinflammatory endothelial phenotype [10,11].

Endothelial cells respond to mechanical stimuli through a complex network of mechanosensors, including platelet endothelial cell adhesion molecule-1 (PECAM-1), vascular endothelial cadherin (VE-cadherin), vascular endothelial growth factor receptor 2 (VEGFR2), integrins, the endothelial glycocalyx, primary cilia, and the mechanosensitive ion channel PIEZO1 [12]. Under physiological laminar flow, transcription factors such as Krüppel-like factor 2 (KLF2) and Krüppel-like factor 4 (KLF4) are activated. This promotes endothelial nitric oxide synthase (eNOS) expression and supports an anti-inflammatory endothelial phenotype. In contrast, disturbed flow activates signaling pathways involving nuclear factor kappa B (NF-κB), activator protein 1 (AP-1), yes-associated protein/transcriptional coactivator with PDZ-binding motif (YAP/TAZ), and hypoxia-inducible factor 1-alpha (HIF-1α) [11,12]. The resulting changes include reduced nitric oxide (NO) bioavailability, increased production of reactive oxygen species (ROS), greater endothelial permeability, and increased expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and monocyte chemoattractant protein-1 (MCP-1), also known as C-C motif chemokine ligand 2 (CCL2). Together, these changes facilitate monocyte adhesion and recruitment and create a local environment that favors inflammation. In this way, mechanical forces are translated into a transcriptional response that promotes atherogenesis. Mechanotransduction may therefore represent one of the links between local coronary hemodynamics and the unequal distribution of atherosclerotic lesions along different segments of the coronary arterial tree [10–12].

## Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress is another major component of atherosclerosis progression. Excessive production of reactive oxygen species occurs in several cell types within the plaque, including endothelial cells, macrophages, and vascular smooth muscle cells. Important sources of ROS include nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, the mitochondrial electron transport chain, xanthine oxidase, and uncoupled endothelial nitric oxide synthase [7,13].

An excess of ROS promotes the oxidation of LDL, damages cellular membranes, impairs mitochondrial function, and activates proinflammatory transcriptional pathways. ROS can stimulate NF-κB and related signaling mechanisms, thereby increasing the production of interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and various chemokines [7,13]. Mitochondrial dysfunction further reinforces this process. Abnormal mitochondrial metabolism can increase the generation of mitochondrial ROS and lead to the release of mitochondrial deoxyribonucleic acid (DNA). Once released, mitochondrial DNA can act as a danger-associated molecular signal and contribute to activation of innate immune responses. A self-reinforcing cycle may therefore develop: ROS production → lipid oxidation → inflammation → mitochondrial dysfunction → further ROS generation → amplification of inflammation.

## Macrophages and Immunometabolic Remodeling of the Plaque

Macrophages occupy a central position within the atherosclerotic plaque. However, the traditional classification of macrophages into two broad phenotypes, M1 and M2, is now considered insufficient to describe the complexity of macrophage biology in atherosclerosis. Single-cell studies have identified multiple macrophage populations with distinct transcriptional profiles, metabolic characteristics, spatial

distribution, and functional properties [14,15]. Some macrophage populations show strong expression of proinflammatory genes such as interleukin 1 beta (IL1B) and tumor necrosis factor (TNF), whereas others are more closely associated with lipid uptake and processing. Additional populations appear to participate in tissue repair and maintenance of plaque architecture. Studies of human atherosclerotic lesions have therefore revealed considerable immune heterogeneity and multiple functional states of both macrophages and T lymphocytes [14]. The metabolic state of macrophages is also closely linked to their inflammatory behavior. Intracellular cholesterol accumulation and changes in fatty-acid, glucose, and amino-acid metabolism can influence inflammatory gene expression and help maintain chronic inflammation. Macrophages should consequently be viewed not simply as cells that ingest modified LDL, but as immunometabolic sensors whose phenotype and function are continuously shaped by the surrounding lipid, metabolic, and inflammatory environment [14,15].

#### NLRP3 Inflammasome and IL-1 $\beta$ -Dependent Inflammation

Activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome is one of the best-characterized molecular mechanisms contributing to the progression of atherosclerosis. The NLRP3 inflammasome is an intracellular multiprotein complex involved in innate immunity. Once activated, it promotes the activation of caspase-1, which converts pro-IL-1 $\beta$  and pro-interleukin-18 (pro-IL-18) into their biologically active forms. Caspase-1 also cleaves gasdermin D, thereby contributing to pyroptosis and the release of inflammatory mediators [16]. A variety of stimuli can activate NLRP3, including cholesterol crystals, LDL, ROS, lysosomal damage, mitochondrial DNA, and disturbances in intracellular ion balance. The experimental work of Duewell et al. demonstrated that cholesterol crystals can directly activate the NLRP3 inflammasome and promote atherosclerosis [17]. Subsequent research has provided further evidence of interactions between cholesterol crystals, the complement system, mitochondrial metabolism, and oxidative stress [18]. These findings indicate that cholesterol accumulation within the plaque is biologically active rather than simply a passive storage phenomenon. When cholesterol reaches sufficient concentrations, it may form crystals that act as potent stimuli for innate immune activation. The NLRP3  $\rightarrow$  caspase-1  $\rightarrow$  IL-1 $\beta$ /IL-18  $\rightarrow$  inflammation pathway has therefore become an important focus of research into residual inflammatory risk in atherosclerotic disease [16–19].

#### Impaired Efferocytosis and Formation of the Necrotic Core

Under physiological conditions, macrophages efficiently recognize and remove apoptotic cells through a process known as efferocytosis. This mechanism is essential for the resolution of inflammation and the maintenance of tissue homeostasis. In an actively progressing atherosclerotic plaque, however, this clearance process becomes increasingly ineffective. Several molecular mechanisms may contribute to impaired efferocytosis. These include abnormalities in the recognition and removal of apoptotic cells involving Mer receptor tyrosine kinase (MerTK), milk fat globule-EGF factor 8 protein (MFG-E8), phosphatidylserine, and other recognition signals [20,21]. The antiphagocytic molecule cluster of differentiation 47 (CD47) may also become increasingly important. By interacting with signal regulatory protein alpha (SIRP $\alpha$ ) on macrophages, CD47 can inhibit the clearance of dying cells [20]. When apoptotic cells remain uncleared, they undergo secondary necrosis, increasing the size of the necrotic core and further stimulating local inflammation. The process can therefore be summarized as follows: impaired efferocytosis  $\rightarrow$  accumulation of dying cells  $\rightarrow$  secondary necrosis  $\rightarrow$  expansion of the necrotic core  $\rightarrow$  persistent inflammation  $\rightarrow$  thinning of the fibrous cap  $\rightarrow$  plaque instability. Defective efferocytosis is consequently considered an important mechanism through which a relatively stable plaque can acquire characteristics of a vulnerable plaque [20,21].

#### Phenotypic Plasticity of Vascular Smooth Muscle Cells

Our understanding of vascular smooth muscle cells (VSMCs) in atherosclerosis has changed considerably. VSMCs were traditionally viewed mainly as structural cells responsible for producing extracellular matrix and forming the fibrous cap. More recent lineage-tracing and single-cell RNA sequencing studies, however, have demonstrated that these cells are highly plastic and can undergo substantial phenotypic

changes [22,23]. Exposure to LDL, inflammatory cytokines, platelet-derived growth factor (PDGF), transforming growth factor beta (TGF- $\beta$ ), ROS, and other signals can cause VSMCs to reduce the expression of contractile proteins and acquire alternative phenotypes. Several regulatory pathways are involved, including KLF4, transcription factor 21 (TCF21), myocardin/serum response factor (MYOCD/SRF), PDGF signaling, TGF- $\beta$ , Notch, Wnt/ $\beta$ -catenin signaling, microRNAs (miRNAs), and long non-coding RNAs (lncRNAs) [22–24]. As a result, VSMCs may acquire characteristics resembling macrophages, foam cells, myofibroblasts, or osteogenic cells. This phenotypic switching is not necessarily harmful in every context. Synthetic VSMCs can produce extracellular matrix and contribute to the formation of the fibrous cap, which may strengthen the plaque. Conversely, some VSMC-derived phenotypes may promote lipid accumulation, inflammation, extracellular-matrix degradation, and calcification [22,23].

#### Matrix Metalloproteinases and Fibrous-Cap Destabilization

The integrity of the extracellular matrix and the thickness of the fibrous cap are important determinants of plaque stability. Macrophages and other cells within the plaque produce matrix metalloproteinases (MMPs), including matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9). Increased activity of these proteolytic enzymes promotes the degradation of collagen and other extracellular-matrix components. Inflammatory cytokines and ROS can further stimulate protease production through NF- $\kappa$ B and related pathways while simultaneously impairing matrix repair. Over time, this imbalance can weaken the fibrous cap and make it more susceptible to mechanical disruption. The combination of a large lipid-necrotic core, persistent inflammation, and a thin fibrous cap therefore represents an important morphological and molecular basis of plaque vulnerability [1,5].

#### Neovascularization and Hypoxia of the Atherosclerotic Plaque

As an atherosclerotic plaque enlarges, oxygen delivery to its deeper regions may become insufficient, resulting in local hypoxia. This condition activates HIF-1 $\alpha$ , which in turn stimulates the expression of vascular endothelial growth factor (VEGF) and promotes the formation of microvessels within the plaque [25]. These newly formed vessels are often fragile and highly permeable. Their rupture can cause intraplaque hemorrhage, with the accumulation of erythrocytes and hemoglobin inside the plaque. This may enlarge the necrotic core and further intensify the inflammatory response. A self-perpetuating process can consequently develop: hypoxia  $\rightarrow$  HIF-1 $\alpha$  activation  $\rightarrow$  VEGF expression  $\rightarrow$  neovascularization  $\rightarrow$  intraplaque hemorrhage  $\rightarrow$  inflammation  $\rightarrow$  plaque expansion  $\rightarrow$  worsening hypoxia.

#### Calcification of the Atherosclerotic Plaque

Vascular calcification was historically considered a largely passive consequence of aging and mineral deposition. Current evidence, however, indicates that calcification is an actively regulated cellular process involving vascular smooth muscle cells and several signaling pathways [26,27]. Under conditions of inflammation and oxidative stress, and in response to bone morphogenetic protein (BMP) signaling and Wnt/ $\beta$ -catenin activation, VSMCs may acquire an osteogenic phenotype. The transcription factor runt-related transcription factor 2 (RUNX2) is an important regulator of this process [26]. Calcification should therefore not be considered a uniform phenomenon. Small areas of microcalcification may increase local mechanical stress within the fibrous cap and potentially contribute to plaque rupture, whereas larger areas of macrocalcification may, under certain circumstances, be associated with greater structural stability. The biological significance of calcification consequently depends on its size, distribution, and location within the plaque.

#### Neutrophil Extracellular Traps

Neutrophil extracellular traps (NETs) have emerged as another mechanism linking inflammation with thrombosis. NETs are extracellular structures composed primarily of deoxyribonucleic acid, histones, and proteins derived from neutrophil granules and are released by activated neutrophils.

Within atherosclerotic lesions, NETs may contribute to endothelial injury, activate macrophages, stimulate the NLRP3 inflammasome, interact with platelets, and amplify local inflammation. They may also increase the thrombogenic potential of the plaque surface. NET formation therefore provides a potential link between chronic vascular

inflammation and the development of an acute atherothrombotic event [28]. For this reason, NETs are being investigated as a possible therapeutic target in the prevention of plaque instability and thrombosis.

#### Clonal Hematopoiesis as a Novel Factor in Atherosclerosis Progression

Clonal hematopoiesis of indeterminate potential (CHIP) has recently attracted considerable interest in cardiovascular research. CHIP refers to the presence of somatic mutations in hematopoietic cells in individuals who do not have an overt hematological malignancy. Frequently affected genes include DNA methyltransferase 3 alpha (DNMT3A), ten-eleven translocation methylcytosine dioxygenase 2 (TET2), additional sex combs-like 1 (ASXL1), and Janus kinase 2 (JAK2). Experimental and clinical studies have reported an association between CHIP and an increased risk of coronary heart disease. In the study by Jaiswal et al., CHIP was associated with an approximately two-fold higher risk of coronary heart disease. Experimental loss of TET2 function in hematopoietic cells also accelerated atherosclerosis in mice [29]. The proposed mechanism involves altered epigenetic regulation of myeloid cells, resulting in enhanced inflammatory activity and increased production of mediators such as IL-1 $\beta$ . These findings suggest that somatic genetic changes occurring in hematopoietic cells can influence the inflammatory environment of the vascular wall and thereby affect atherosclerotic plaque development. CHIP has consequently introduced an additional dimension to the concept of residual cardiovascular risk, linking hematopoietic genetics and epigenetic regulation with chronic vascular inflammation [29,30].

#### Epigenetic Mechanisms and Non-Coding RNAs

Atherosclerosis is also influenced by mechanisms that regulate gene expression without altering the underlying DNA sequence. These epigenetic mechanisms include DNA methylation, histone modifications, and regulation by non-coding RNAs. Non-coding RNAs include microRNAs, long non-coding RNAs, and circular RNAs. These molecules can regulate genes involved in lipid metabolism, inflammation, endothelial function, and VSMC phenotypic switching [31]. For example, changes in microRNA activity may influence pathways associated with: NF- $\kappa$ B  $\rightarrow$  inflammation ATP-binding cassette transporter A1 (ABCA1)/ATP-binding cassette transporter G1 (ABCG1)  $\rightarrow$  cholesterol efflux KLF2/KLF4  $\rightarrow$  endothelial phenotype KLF4/TCF21  $\rightarrow$  VSMC phenotype. These regulatory mechanisms may create a form of molecular "memory" within vascular cells, allowing altered cellular behavior to persist even after the original stimulus has diminished. This concept may be particularly relevant to the persistence of inflammatory activity and residual cardiovascular risk despite correction of conventional risk factors.

#### Role of the Immune System in the Progression of Coronary Atherosclerosis

The immune response in atherosclerosis involves both innate and adaptive immunity. T lymphocytes, particularly T helper 1 (Th1) cells, produce interferon gamma (IFN- $\gamma$ ), which contributes to the maintenance of inflammation within the plaque. Regulatory T cells, in contrast, can limit inflammatory responses and may exert potentially atheroprotective effects.

B lymphocytes and antibodies also participate in atherogenesis, while dendritic cells, natural killer (NK) cells, and other components of innate immunity contribute to the local inflammatory environment [14,15]. Single-cell studies have shown that immune cells within atherosclerotic plaques do not exist as a single homogeneous population. Instead, they occupy multiple functional states and interact through a complex network of signaling pathways. Among the important molecular interactions are the CCL2/C-C chemokine receptor type 2 (CCR2), CCL5/C-C chemokine receptor type 5 (CCR5), IL-1 $\beta$ , TNF- $\alpha$ , IFN- $\gamma$ , IL-6, and CD40/CD40 ligand (CD40L) pathways. The atherosclerotic plaque should therefore be regarded as an immunologically active microenvironment in which lipids, immune cells, vascular cells, and extracellular-matrix components continuously influence one another.

#### Single-Cell and Multi-Omics Technologies in the Study of Atherosclerosis Progression

The introduction of single-cell RNA sequencing, single-cell assay for transposase-accessible chromatin using sequencing (single-cell

ATAC-seq), and spatial transcriptomics has significantly changed the way atherosclerotic lesions can be studied. Earlier approaches were largely based on measuring overall gene expression in tissue samples. Although useful, these methods could not reliably determine which individual cell populations were responsible for specific molecular signals. Single-cell technologies have made it possible to distinguish macrophage subpopulations, identify different states of vascular smooth muscle and endothelial cells, characterize T-lymphocyte heterogeneity, and investigate cellular interactions within the plaque. They have also helped identify transcriptional programs associated with plaque progression and vulnerability [32,33]. An integrated analysis of 22 single-cell RNA sequencing libraries containing more than 118,000 cells demonstrated substantial cellular heterogeneity in human atherosclerotic lesions and identified specific smooth muscle cell states associated with coronary heart disease, myocardial infarction, and coronary artery calcification [32]. These findings illustrate a broader shift in molecular cardiology: rather than treating the atherosclerotic plaque as a uniform tissue, researchers are increasingly examining the individual cell populations and molecular interactions that shape its behavior.

#### Molecular Basis of Coronary Plaque Instability

Progression of coronary atherosclerosis does not necessarily result in a proportional increase in luminal stenosis. From a clinical perspective, plaque vulnerability is more closely associated with a combination of structural and inflammatory features, including a large lipid-necrotic core, a thin fibrous cap, substantial macrophage infiltration, increased inflammatory signaling, enhanced matrix metalloproteinase activity, intraplaque neovascularization, microcalcification, and impaired efferocytosis. These features arise from the interaction of several interconnected molecular processes. A simplified representation of the central pathway is: Apolipoprotein B-containing lipoproteins  $\rightarrow$  intimal retention  $\rightarrow$  oxLDL formation  $\rightarrow$  endothelial activation  $\rightarrow$  monocyte recruitment  $\rightarrow$  macrophage accumulation  $\rightarrow$  lipid uptake  $\rightarrow$  cholesterol crystallization  $\rightarrow$  NLRP3 activation  $\rightarrow$  IL-1 $\beta$ /IL-18 release  $\rightarrow$  chronic inflammation  $\rightarrow$  cell death  $\rightarrow$  impaired efferocytosis  $\rightarrow$  necrotic-core formation  $\rightarrow$  fibrous-cap degradation  $\rightarrow$  plaque rupture or erosion  $\rightarrow$  thrombosis.

#### Other processes develop in parallel:

VSMCs  $\rightarrow$  phenotypic switching  $\rightarrow$  extracellular-matrix remodeling/calcification and hypoxia  $\rightarrow$  HIF-1 $\alpha$  activation  $\rightarrow$  VEGF expression  $\rightarrow$  neovascularization  $\rightarrow$  intraplaque hemorrhage. Plaque instability is therefore best understood as the cumulative consequence of several interacting biological processes rather than the result of a single molecular pathway.

#### Therapeutic Significance of Contemporary Molecular Mechanisms

A better understanding of the molecular mechanisms underlying atherosclerosis has opened several potential therapeutic directions. Lowering concentrations of atherogenic lipoproteins remains the most established strategy for reducing cardiovascular risk. At the same time, clinical studies of anti-inflammatory therapies have shown that modulation of inflammation may provide additional cardiovascular benefit that is not fully explained by changes in LDL levels [2,34]. Particular interest has focused on the NLRP3  $\rightarrow$  IL-1 $\beta$   $\rightarrow$  IL-6  $\rightarrow$  inflammation pathway.

The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) demonstrated that targeted inhibition of IL-1 $\beta$  could reduce cardiovascular events, providing important clinical support for the inflammatory component of atherosclerotic disease [34]. Several other approaches are also under investigation. These include NLRP3 inhibitors, therapies directed against IL-1 $\beta$  or IL-6, strategies designed to modify macrophage function, approaches aimed at restoring efferocytosis, modulators of VSMC phenotype, therapies targeting NET formation, interventions directed toward CHIP-associated inflammation, and epigenetic or RNA-based therapies. Most of these approaches, however, remain in experimental or early clinical stages, and their long-term clinical relevance requires further investigation.

#### Conclusion

The current understanding of coronary atherosclerosis extends well beyond the traditional concept of passive cholesterol accumulation within the arterial wall. The atherosclerotic plaque is a dynamic and

biologically active structure in which lipid metabolism, inflammation, immunity, cellular metabolism, mechanical forces, and vascular remodeling are closely interconnected.

Retention of apolipoprotein B-containing lipoproteins within the intima represents a key initiating event, but the subsequent course of disease depends on how the endothelium, immune cells, vascular smooth muscle cells, and extracellular matrix respond to the changing local environment. Modified lipoproteins promote endothelial activation and macrophage recruitment, while intracellular lipid accumulation and cholesterol crystallization further stimulate inflammatory signaling. As the lesion progresses, activation of the NLRP3 inflammasome, production of IL-1 $\beta$  and IL-18, impaired efferocytosis, expansion of the necrotic core, and degradation of the extracellular matrix contribute to plaque vulnerability. At the same time, phenotypic switching of vascular smooth muscle cells influences both plaque remodeling and calcification. Hypoxia and pathological neovascularization may further accelerate plaque growth and promote intraplaque hemorrhage. More recent findings concerning clonal hematopoiesis, epigenetic regulation, and non-coding RNAs suggest

that individual molecular characteristics may also influence the intensity and persistence of vascular inflammation. These mechanisms may help explain why cardiovascular risk can remain elevated even when conventional risk factors are adequately controlled. The development of single-cell RNA sequencing, spatial transcriptomics, single-cell ATAC-seq, and other multi-omics approaches has provided an opportunity to study these processes at an unprecedented level of cellular resolution. Such technologies can identify distinct cellular populations, define their functional states, and reveal molecular interactions associated with plaque progression and instability [32,33]. Overall, coronary atherosclerosis should be viewed as the result of a continuous interaction between atherogenic lipoproteins, endothelial dysfunction, immunoinflammatory activation, metabolic reprogramming, cellular plasticity, epigenetic regulation, and impaired resolution of inflammation. A more detailed understanding of these mechanisms may ultimately facilitate the identification of molecular biomarkers of disease progression and help define more individualized approaches to the prevention and treatment of atherosclerotic cardiovascular disease.

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