IQRO JURNALI , IQRO JOURNAL, ИКРО ЖУРНАЛИ
ISSN:2181-4341| wordlyknowledge.uz/index.php/iqro
Volume 24. Issue 02. Noyabr ,2026

HISTOPATHOLOGICAL AND MOLECULAR MECHANISMS OF ATHEROSCLEROSIS DEVELOPMENT AND PROGRESSION

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https://doi.org/10.5281/zenodo.23958879

Abstract

Atherosclerosis is a chronic inflammatory disease of medium-sized and large arteries characterized by lipid accumulation, endothelial dysfunction, inflammatory cell infiltration, and progressive structural remodeling of the vascular wall. The development of atherosclerotic lesions involves complex interactions between circulating lipoproteins, vascular endothelial cells, smooth muscle cells, macrophages, and extracellular matrix components. This article examines the histopathological and molecular mechanisms underlying the initiation, progression, and complications of atherosclerosis. Particular attention is devoted to endothelial dysfunction, low-density lipoprotein retention and modification, foam cell formation, vascular smooth muscle cell phenotypic changes, and fibrous plaque development. The study is based on a narrative analysis of established scientific literature using descriptive, comparative, and morphological-functional approaches. The findings indicate that atherosclerosis is not simply a consequence of lipid deposition but represents a dynamic inflammatory and fibroproliferative process. Plaque vulnerability is influenced by the composition of the fibrous cap, inflammatory activity, lipid-rich necrotic core, and local vascular conditions. Understanding the cellular and histological mechanisms of atherosclerosis is essential for improving cardiovascular risk assessment, prevention, and therapeutic strategies.

Keywords: atherosclerosis, histopathology, endothelial dysfunction, low-density lipoproteins, foam cells, vascular inflammation, smooth muscle cells, fibrous plaque, cardiovascular disease.

Introduction

Atherosclerosis is one of the principal pathological processes underlying cardiovascular diseases, including coronary artery disease, ischemic stroke, and peripheral arterial disease. It develops predominantly in medium-sized and large arteries and is characterized by progressive changes in the intimal layer of the vascular wall. These changes include lipid accumulation, inflammatory cell recruitment, extracellular matrix remodeling, and the formation of atherosclerotic plaques.

The normal arterial wall consists of three principal histological layers: the tunica intima, tunica media, and tunica adventitia. The tunica intima contains endothelial cells and underlying connective tissue, the tunica media consists predominantly of vascular smooth muscle cells and extracellular matrix components, and the tunica adventitia contains connective tissue, nerves, and vascular structures supplying the outer arterial wall.

Under physiological conditions, vascular endothelial cells maintain vascular homeostasis by regulating permeability, vascular tone, coagulation, leukocyte adhesion, and inflammatory

signaling. Endothelial dysfunction contributes to the development of atherosclerosis by promoting the retention of atherogenic lipoproteins and facilitating inflammatory cell recruitment into the arterial intima.

The traditional interpretation of atherosclerosis as a disorder caused primarily by cholesterol accumulation has evolved considerably. Contemporary research demonstrates that lipid metabolism, innate and adaptive immunity, oxidative processes, vascular cell signaling, and tissue remodeling participate in disease development.

Atherosclerotic lesions may remain clinically silent for many years. However, progressive plaque growth can produce arterial narrowing, while plaque rupture or superficial erosion may trigger thrombosis and acute cardiovascular events.

The scientific importance of investigating atherosclerosis is associated with the need to understand how cellular and molecular abnormalities produce structural changes in the arterial wall. Histopathological analysis provides valuable information about lesion development, plaque composition, inflammatory activity, and mechanisms of vascular complications.

The aim of this article is to analyze the histopathological and molecular mechanisms of atherosclerosis development and progression, emphasizing the roles of endothelial cells, lipoproteins, macrophages, vascular smooth muscle cells, and inflammatory signaling pathways.

Materials and Methods

The present study was conducted as a narrative review of scientific literature addressing the histological, cellular, and molecular mechanisms of atherosclerosis. The theoretical framework was based on established research in cardiovascular pathology, vascular biology, lipid metabolism, and inflammatory mechanisms of arterial disease.

Descriptive histological analysis was used to characterize the structural organization of the arterial wall and the morphological changes associated with atherosclerotic lesions. Comparative analysis was employed to distinguish early fatty streaks from advanced fibroatheromatous plaques and complicated atherosclerotic lesions.

The morphological-functional approach was applied to explain the relationships between endothelial dysfunction, lipoprotein retention, macrophage activation, smooth muscle cell proliferation, and extracellular matrix remodeling. Particular attention was devoted to the pathological significance of inflammatory mediators, oxidative processes, and plaque instability.

The review also considered established histopathological classification principles and molecular mechanisms associated with lesion progression.

No original clinical observations, experimental animals, histological specimens, or laboratory measurements were obtained. Accordingly, the Results section presents a structured synthesis of previously published scientific evidence rather than original experimental findings.

Results

Histological structure of the arterial wall and early atherosclerotic changes

The arterial wall possesses a complex structural organization that supports blood circulation and maintains vascular integrity. Its inner surface is covered by a continuous layer of endothelial cells, which forms a selective barrier between circulating blood and the underlying vascular tissues.

The tunica intima is the principal site of atherosclerotic lesion development. Early pathological changes involve the retention of apolipoprotein B-containing lipoproteins within the subendothelial extracellular matrix. These retained particles may undergo biochemical modifications that promote local inflammatory responses.

Atherosclerotic lesions frequently develop in arterial regions exposed to disturbed blood flow, including vascular bifurcations and curvatures. Local hemodynamic conditions influence endothelial gene expression, inflammatory signaling, and susceptibility to lesion formation.

The earliest visible lesions may contain accumulations of lipid-laden macrophages, commonly known as foam cells. These cellular aggregates contribute to the development of fatty streaks, which represent an early morphological manifestation of atherosclerosis.

Although fatty streaks may be observed before clinically significant vascular narrowing develops, their progression is influenced by lipid exposure, inflammatory activity, genetic susceptibility, and additional cardiovascular risk factors.

Endothelial dysfunction in the initiation of atherosclerosis

Endothelial dysfunction represents an important mechanism in the initiation and progression of atherosclerosis. Healthy endothelial cells produce nitric oxide, which contributes to vascular relaxation, inhibits platelet activation, and limits excessive leukocyte adhesion.

Under pathological conditions, endothelial nitric oxide bioavailability may decrease because of oxidative stress, inflammatory signaling, and disturbances in endothelial nitric oxide synthase activity.

Major cardiovascular risk factors, including elevated concentrations of atherogenic lipoproteins, arterial hypertension, smoking, and diabetes mellitus, may contribute to endothelial dysfunction.

Endothelial activation increases the expression of adhesion molecules such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1. These molecules facilitate the attachment and migration of circulating leukocytes into the arterial intima.

Monocytes entering the vascular wall differentiate into macrophages and participate in the uptake of modified lipoproteins. This process contributes to the development of lipid-rich inflammatory lesions.

Thus, endothelial dysfunction establishes conditions that favor lipid accumulation, inflammatory cell recruitment, and progressive vascular remodeling.

Lipoprotein retention and foam cell formation

Low-density lipoprotein cholesterol is a major causal factor in atherosclerotic cardiovascular disease. The accumulation of apolipoprotein B-containing lipoproteins within the arterial intima represents a central event in lesion development.

Retained lipoproteins may undergo oxidative and enzymatic modifications that influence their interactions with vascular cells and inflammatory pathways.

Macrophages internalize modified lipoproteins through several receptors and uptake mechanisms. Excessive intracellular cholesterol accumulation promotes the formation of lipid droplets, producing the characteristic foamy appearance of macrophages observed in histological preparations.

Foam cells contribute to local inflammation through the production of cytokines, chemokines, and other biologically active mediators. They may also undergo apoptosis or other forms of cell death.

When the clearance of dead cells becomes inefficient, cellular debris and extracellular lipids accumulate within the lesion, contributing to the formation of a necrotic core.

Foam cell formation is not restricted exclusively to macrophages. Vascular smooth muscle cells can also accumulate lipids and acquire foam-cell-like characteristics during atherosclerotic progression.

Role of vascular smooth muscle cells

Vascular smooth muscle cells are essential components of the arterial media and participate in maintaining vascular tone and structural stability.During atherosclerosis, some smooth muscle cells undergo phenotypic changes that alter their contractile properties and increase their capacity for migration, proliferation, and extracellular matrix production.These cells may migrate from the tunica media into the intima, where they contribute to lesion development and fibrous cap formation.The extracellular matrix synthesized by smooth muscle cells includes collagen and other structural proteins that influence plaque stability.

However, smooth muscle cell behavior is highly heterogeneous. Depending on local signaling conditions, these cells may adopt phenotypes associated with matrix production, inflammation, lipid accumulation, or osteogenic differentiation. Therefore, vascular smooth muscle cells contribute both to the development of atherosclerotic lesions and to structural processes that may stabilize or destabilize plaques.

Inflammatory mechanisms of atherosclerotic progression

Atherosclerosis is characterized by persistent inflammatory activity involving innate and adaptive immune mechanisms.Macrophages, T lymphocytes, endothelial cells, and smooth muscle cells participate in the production and regulation of inflammatory mediators.Interleukin-1β, interleukin-6, tumor necrosis factor, and various chemokines are involved in inflammatory signaling pathways associated with vascular injury and lesion progression.Cholesterol crystals and other danger-associated signals can activate intracellular inflammatory mechanisms, including the NLRP3 inflammasome in certain cellular contexts.Activation of these pathways may promote the production of inflammatory cytokines and contribute to the persistence of vascular inflammation.Inflammatory activity also influences extracellular matrix degradation. Matrix metalloproteinases and other proteolytic enzymes can modify the structural components of the fibrous cap.Excessive degradation of extracellular matrix proteins may contribute to plaque vulnerability, particularly when combined with reduced collagen synthesis and increased cellular death.

Histopathological characteristics of advanced atherosclerotic plaques

Advanced atherosclerotic lesions contain several structurally distinct components, including a fibrous cap, lipid-rich necrotic core, inflammatory cells, smooth muscle cells, extracellular matrix, and variable calcification.The fibrous cap separates the thrombogenic contents of the plaque from circulating blood. Its structural characteristics are important determinants of plaque

stability.A relatively thick, collagen-rich fibrous cap is generally associated with greater mechanical stability, whereas thin fibrous caps overlying large necrotic cores are characteristic of many rupture-prone plaques.Plaque rupture exposes thrombogenic material to circulating blood and can initiate platelet activation and thrombus formation.

However, acute coronary thrombosis may also develop through plaque erosion without fibrous cap rupture. The mechanisms of plaque erosion differ from those of plaque rupture and involve alterations in endothelial integrity and local thromboinflammatory responses.

Calcification is another common feature of advanced atherosclerosis. Its pathological significance depends partly on the size, distribution, and location of calcium deposits within the plaque.

The principal morphological stages of atherosclerosis are summarized below.

Stage	Main histopathological characteristics	Functional significance
Early intimal lesion	Lipoprotein retention and scattered foam cells	Initiation of local inflammatory responses
Fatty streak	Accumulation of lipid-laden macrophages	Early visible atherosclerotic change
Fibroatheroma	Fibrous tissue formation and lipid-rich necrotic core	Development of an advanced plaque
Complicated plaque	Rupture, erosion, hemorrhage, or thrombosis	Increased risk of acute vascular events
Fibrocalcific lesion	Fibrosis and variable calcification	Chronic vascular remodeling and altered arterial mechanics

Atherosclerosis in diabetes mellitus and metabolic disorders

Diabetes mellitus is associated with an increased risk of atherosclerotic cardiovascular disease. Chronic hyperglycemia, insulin resistance, dyslipidemia, oxidative stress, and inflammatory abnormalities contribute to vascular dysfunction.

Advanced glycation end products and their interactions with cellular receptors may promote inflammatory signaling and vascular injury.

Insulin resistance is frequently associated with elevated triglyceride-rich lipoproteins, reduced high-density lipoprotein cholesterol, and alterations in low-density lipoprotein particle composition.These metabolic abnormalities may accelerate atherogenic lipoprotein accumulation and impair vascular homeostasis.In addition, diabetes-related endothelial dysfunction and changes in inflammatory cell activity can contribute to the development and progression of atherosclerotic lesions.The relationship between diabetes and atherosclerosis is therefore multifactorial, involving interconnected disturbances in glucose metabolism, lipid metabolism, endothelial function, and immune regulation.

Discussion

The reviewed evidence demonstrates that atherosclerosis represents a complex interaction between lipid accumulation, vascular inflammation, cellular phenotypic changes, and structural remodeling of the arterial wall.The retention of atherogenic lipoproteins within the arterial intima

provides an important initiating stimulus, while endothelial activation and inflammatory cell recruitment contribute to lesion development. Macrophage lipid accumulation, foam cell formation, and impaired clearance of dead cells promote the development of necrotic cores.The role of vascular smooth muscle cells is particularly significant because these cells participate in both pathological lesion growth and the formation of protective fibrous structures. Their phenotypic plasticity demonstrates that atherosclerosis cannot be adequately explained through a simple distinction between inflammatory and structural cellular populations.The inflammatory hypothesis of atherosclerosis is supported by extensive experimental and clinical evidence. Nevertheless, inflammation should not be considered independently of lipid metabolism. Atherogenic lipoprotein retention and inflammatory activation interact throughout lesion development.

From a clinical perspective, these mechanisms provide a biological foundation for interventions aimed at reducing cardiovascular risk. Lowering low-density lipoprotein cholesterol reduces exposure to a causal driver of atherosclerosis, while appropriate management of hypertension, diabetes, and smoking-related risks contributes to vascular protection.Clinical trials have also demonstrated that selected anti-inflammatory interventions can reduce cardiovascular events in specific high-risk populations. However, the benefits and risks of such treatments depend on the intervention and clinical context.Histopathological analysis remains important for understanding plaque vulnerability. The risk associated with atherosclerotic lesions depends not only on the degree of arterial narrowing but also on plaque composition, inflammatory activity, fibrous cap integrity, and thrombogenic potential.The present study is limited by its narrative design and the absence of original histological or molecular investigations. Future research combining advanced vascular imaging, spatial transcriptomics, single-cell analysis, and histopathological assessment may further clarify the relationships between cellular heterogeneity and plaque instability.

Conclusion

Atherosclerosis is a chronic inflammatory and fibroproliferative disease characterized by progressive changes in the structure and function of the arterial wall.The initiation of atherosclerotic lesions involves the retention of atherogenic lipoproteins, endothelial activation, and recruitment of inflammatory cells into the vascular intima. Subsequent foam cell formation, smooth muscle cell phenotypic changes, extracellular matrix remodeling, and necrotic core development contribute to plaque progression.The histopathological characteristics of advanced plaques, particularly fibrous cap integrity, inflammatory activity, and necrotic core composition, influence the likelihood of vascular complications.Metabolic disorders such as diabetes mellitus and insulin resistance may accelerate atherosclerotic progression through disturbances in lipid metabolism, endothelial function, and inflammatory signaling.Understanding the molecular and histological mechanisms of atherosclerosis is essential for improving cardiovascular prevention, identifying mechanisms of plaque instability, and developing targeted therapeutic approaches.

Further investigation of vascular cell interactions and inflammatory pathways may contribute to more effective strategies for reducing the burden of atherosclerotic cardiovascular disease.

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