Review Article

Pathogenesis of Atherosclerosis: review

Abstract

The goal of this research was to examine the mechanisms of atherosclerosis development, such as endothelial dysfunction, fatty streak formation, fibrous plaque formation, and plaque rupture. This article takes a thorough look at the pathophysiology of atherosclerosis, addressing the pathological and biochemical mechanisms of atherosclerotic plaque development and growth.

Keywords

Atherosclerosis, endothelial dysfunction, foam cells, inflammation, LDL.

1. Introduction

Atherosclerosis is derived from the Greek term Athero, which means "gruel" (1). Marchand coined the term "atherosclerosis" to describe the relationship between fatty degeneration and arterial stiffness (2). Atherosclerosis is a systemic disease of large and medium-sized arteries characterized by the buildup of lipids and fibrous materials in the artery wall, as well as contributing immune cells, smooth muscle cells (SMC), and endothelial cells, resulting in plaques and, in some cases, stenosis. The process's beginning is unknown, although it is most likely the consequence of an interaction between multiple distinct processes, including plasma lipid levels, blood flow mechanics (shear stress and turbulent flow), and genetic predispositions. Lipoprotein retention, inflammatory cell recruitment, foam cell formation, apoptosis and necrosis, migration of smooth muscle cells (SMCs) and their proliferation and secretion of extracellular matrix (ECM) components (such as collagen, elastin, and proteoglycans), calcification, neovessel formation, arterial remodeling, fibrous cap rupture, and thrombosis (3,4).

It is the main cause of illness and death in the United States and the rest of the Western world. Cardiovascular disease (CVD) is still the leading cause of mortality in the modern age. CVD was responsible for 17 million fatalities in 2008. More than 3 million of these fatalities occurred in persons under the age of 60 and may have been avoided in major part (5). There are rising disparities across nations and socioeconomic classes in the prevalence and outcome of CVD.

2. The Origin of Atherosclerosis and the Formation of Fatty Streaks

In the past two decades, research has shown that atherosclerosis is a persistent inflammatory condition, contrary to popular belief that atherosclerosis is a degenerative illness caused by the aging process (6). Atherosclerosis begins with endothelial dysfunction, followed by LDL retention and modification in the intima (7,8). Modified LDLs, in conjunction with other atherogenic factors, stimulate EC activation, resulting in monocyte recruitment into the

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intima. Modified LDLs are rapidly captured by differentiated monocytes and VSMC, promoting foam cell production (9,10). Furthermore, various inflammatory signaling pathways are engaged, permitting the creation of fatty streaks, which is the initial symptom of atherosclerosis and is characterized by a significant buildup of lipids both inside the cells (macrophages and VSMC) and the extracellular media. Fatty streaks progress to atherosclerotic plaques, which are comprised of three components: inflammatory cells, smooth muscle cells, a fibrous component of connective tissue, and a fat component of lipids (11).

When endothelial dysfunction occurs, fatty streaks form because of matrix proteoglycan exposure and loss of the confluent elastic layer of the blood vessel lumen, which is typically detected around arterial bifurcation locations (12). Recent findings point to hypercholesterolemia as a primary cause of endothelial dysfunction by altering endothelial permeability, enabling LDL-c to migrate into the arterial wall (13). The macrophage receptor recognition shift toward LDL owing to oxidative alteration enables absorption of LDL by monocyte-derived macrophages through SR that are not controlled by cell cholesterol concentration and may bind Ox-LDL and native lipoproteins (14,15) Due to SR's action, macrophages will accumulate lipids in their cytoplasm, giving them a foamy appearance; these cells are called foam cells and are the hallmark of fatty streak (16–18).

2.1. Low-density lipoprotein cholesterol trapping and oxidation (LDL-c)

High circulating amounts of cholesterol carried by apolipoprotein B100-containing-LDL were shown to be a required step for LDL-c transport across vascular endothelium and LDL entrapment inside the blood vessel wall (19). Lipoproteins penetrate the artery wall through the defective endothelium that surrounds the vessel lumen, and this is followed by the entrance of monocytes and other inflammatory cells (20). Lipoproteins are able to pass through the endothelium barrier, which causes LDLs to accumulate and be deposited in the intima (21).

Once trapped inside the arterial wall, LDL-c undergoes lipid peroxidation because of locally released reactive oxygen species (ROS), also known as free radicals (14,22). ROS are described as oxygen molecules (O2) that take a single electron and undergo transformation into extremely reactive radicals that harm cellular lipids, proteins, and DNA (23). ROS, myeloperoxidase, lipoperoxidase, and nicotinamide adenine dinucleotide phosphate (NADH/NADPH) oxidases are all involved in the LDL peroxidation process (19,22). Oxidized LDLs include oxidized lipids and breakdown products that promote atherosclerotic plaque formation (24,25). Endothelial cells express more vasoconstricting factors (mostly endothelin-1) and less vasodilating factors (especially nitric oxide).

According to (18) and (26), trapped LDL oxidation takes place in two steps:

1. Oxidation of LDL lipids before monocyte migration to artery wall, with no change in Apo B100 protein.

2. Further oxidation of LDL lipids and modification of Apo B100 occur after monocyte recruitment to the lesion and conversion to macrophages. This is followed by the uptake of native LDL as well as Ox-LDL by macrophages via scavenger receptors (SR) and other suggested pathways such as sortilin protein receptors and fluid-phase pinocytosis.

2.3. Recruitment of Monocytes and Formation of Foam Cells

Monocytes develop into macrophages inside the intima and internalize atherogenic lipoproteins through scavenger receptors, among which SR-A and CD36 have been shown to play quantitatively important roles in experimental atherosclerosis. The formation of lipid-loaded macrophages (foam cells) containing enormous levels of cholesteryl esters is a feature of both early and late atherosclerotic lesions (27). Monocytes develop into macrophages in the

intima, where they may be polarized to the M1 (pro-inflammatory) or M2 (anti-inflammatory) phenotype (28). Nonetheless, macrophages are sensitive to changes in the inflammatory environment and may flip their phenotype from pro-inflammatory to anti-inflammatory in response to new signals.

Macrophages also express molecules that increase and amplify leukocyte adherence and migration to the artery wall, such as vascular cell adhesion molecule (VCAM), intracellular adhesion molecule (ICAM), and monocyte chemotactic protein 1 [MCP-1] (29,30). Upregulation of VCAM-1, ICAM-1, selectins and chemo-attractants such as lipids, platelets-activating factor, and chemokines such as interleukin-8 and MCP-1 are all associated with oxidized LDL (14,31). Once in the subendothelial space, monocytes develop macrophage characteristics in response to macrophage-colony stimulating factor (32) and express SR [A, B1, CD36, CD68, lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1)] that binds modified lipoproteins such as Ox-LDL, native lipoproteins, and anionic phospholipids (13,33)

2.4. Atherosclerosis endothelial dysfunction and VSMC Contribution to Foam Cell Population

Li (34) revealed that VCAM-1 expression on endothelial surfaces was a critical early stage in the etiology of atherosclerosis. Increased cellular adhesion and accompanying endothelial dysfunction subsequently "sets the scene" for inflammatory cell recruitment, cytokine release, and lipid recruitment into the atherosclerotic plaque. VCAM-1 expression increases monocyte and T-cell recruitment to sites of endothelial injury; subsequent release of MCP-1 by leukocytes magnifies the inflammatory cascade by recruiting additional leukocytes, activating leukocytes in the media, and causing recruitment and proliferation of smooth muscle cells (35). VSMCs in the intima may also ingest oxLDL in an unregulated manner through several scavenger receptors such as SR-A, CD36, and LOX-1 (36–38). At least half of the foam cells in the human coronary intima are VSMC-derived rather than monocyte-derived, demonstrating the role of VSMCs in the development of atherosclerosis (39).

Endothelial cells over-express adhesion molecules in response to turbulent flow in the presence of an unfavorable serum lipid profile, which is how atherosclerosis is likely to begin (35). Endothelial dysfunction results from disturbed vascular homeostasis (40–42). When ECs lose homeostasis, vessel walls are prone to vasoconstriction, lipid infiltration, leukocyte adhesion, platelet activation, and oxidative stress (43,44). Together, they trigger an inflammatory response that leads to the formation of fatty streaks (41,42). Endothelial dysfunction also contributes to plaque formation and rupture in later stages of atherosclerosis (42). Endothelial dysfunction is an early sign of atherogenesis (45,46).

3. Fibrous Plaque Development

A thick fibrous covering containing VSMCs covers and stabilizes the vulnerable plaque (47). The necrotic core and fibrous cap are the distinguishing features of advanced atherosclerosis (48), and atheroma plaque regression is rare at this point (49,50).

3.1. Fibrous Cap Thinning

Any action that reduces the production of fibrous cap collagen by intimal fibromyoblast-like smooth muscle cells (SMCs) and/or contributes to cap collagen breakdown would be predicted to encourage the development of plaques prone to rupture (51). Vulnerable plaques exhibit indications of SMC mortality and reduced SMC levels, and in vitro findings demonstrate that macrophages may induce SMC apoptosis by activating the Fas apoptotic pathway and secreting proapoptotic TNFa and nitric oxide (52). MMPs (matrix metalloproteinases) produced by macrophages may also be implicated in fibrous cap thinning. MMPs are a protease-activated enzyme family that may destroy diverse extracellular matrix (ECM) proteins (51).

The fibrous cap is a subendothelial barrier that separates the vascular lumen from the atherosclerotic necrotic core, which is composed of VSMCs that have migrated to the luminal side of the artery and extracellular matrix (ECM) produced from VSMCs (53,54). The fibrous cap's job is to act as a structural support to prevent the exposure of prothrombotic material from the core, which would otherwise cause thrombosis (53).

In atherosclerosis, VSMCs from the tunica media move to the intima in response to growth factors generated by foam cells (VSMC- or macrophage-derived) or intima ECs (54–57). Furthermore, IL-1 generated by macrophages increases VSMC endogenous PDGF production and, once in the intima, autocrinically leads to their proliferation (58,59). VSMCs with a synthetic phenotype boost the synthesis of ECM components such as interstitial collagen, elastin, and proteoglycans in addition to migration and subsequent proliferation (3,4,57,60) These proliferating VSMCs, in conjunction with ECM synthesis, produce a fibrous cap that surrounds and prevents the rupture of the growing atherosclerotic plaque (61).

3.2. Necrotic Core

The necrotic core is a second key characteristic of hazardous plaques that leads to inflammation, thrombosis, proteolytic plaque disintegration, and physical stress on the fibrous cap (Virmani et al., 2002). Necrotic cores form because of advanced lesional macrophage apoptosis combined with poor phagocytic clearance (or efferocytosis) of the apoptotic macrophages in advanced plaques (Tabas, 2010a). This combination is critical: although macrophage mortality occurs in early atherosclerotic lesions, efferocytic clearance is effective, resulting in reductions in lesion cellularity, inflammation, and plaque development rather than an increase in plaque necrosis.

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3.3. Plaque Calcification

Another sign of advanced atherosclerosis is calcification of atheroma plaques. It appears as a bone-like structure inside the plaque and begins in inflammatory areas with a local reduction in collagen fibers (62)(63). During the development of atherosclerosis, pericytes (64) and VSMCs (65,66) transdifferentiate into osteoblast-like phenotypes, gaining the ability to form a mineralized matrix and leading to calcium deposits, as seen in bone tissue (67–69). This all adds to microcalcifications, which are the first step of the vascular calcification cascade in both the intima and the media (62,70). Microcalcifications eventually progress to bigger calcifications that extend from the necrotic core's bottom to the surrounding matrix (66).

4. Plaque Rupture and Thrombus Formation

Plaque rupture is defined as "a plaque with profound damage with a true hole or breach in the fibrous cap that had isolated its lipid-rich atheromatous core from the flowing blood, revealing the plaque's thrombogenic core" (71). The most prevalent cause of coronary artery thrombosis is this. When the plaque fissures or ruptures, blood enters the subendothelial area, causing a coagulation process to cover the wound (4,72). Platelets first bind to subendothelial collagen and become activated, and additional platelets are then recruited and aggregated in the location to commence wound healing (73). Concurrently, prothrombotic components of the lipid core are liberated and come into touch with plasma coagulating agents. More precisely, the tissue factor of the core combines with factor VII of the plasma, triggering the coagulation cascade that results in the synthesis of thrombin, a crucial intermediary in the creation of fibrin (61,74) Fibrin is an insoluble protein that creates networks of fibrin threads and fills the lesion with platelets, providing a stable and well-organized structure. The thrombus is the name given to this structure (75,76).

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5.Conclusion

In recent years, we have seen a rise in the burden of atherosclerotic disease, which adds to CVD risk and is becoming a worldwide pandemic. The study of atherosclerosis cellular and molecular biology mechanisms has yielded significant insights into the processes that contribute to atheroma formation and clinical symptoms of the disease. In industrialized nations, atherosclerosis is the major cause of mortality. A thorough knowledge of the causes and underlying mechanisms of pathogenesis will aid in the delineation of causes and the planning of creative treatment. More therapy possibilities will emerge as our understanding of the etiology of atherosclerosis improves.

Comment [A12]: What are the main mechanisms according to the current consensus or theoretical bases regarding the subject? What are the author's considerations, based on the review carried out?

6. DISCLAIMER

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