Review Article

Pathogenesis of Atherosclerosis: review

ABSTRACT

In atherosclerosis, apolipoprotein B-lipoproteins in blood artery matrix attract monocytes, which become macrophages and dendritic cells. Macrophages generated from recruited monocytes cause a maladaptive, non-resolving inflammatory response that increases subendothelial layer. Some lesions cause myocardial infarction, stroke, and sudden cardiac death. Modern atherosclerosis research focuses on the molecular biology of atherogenesis, although the disease's complex pathophysiology is still unknown. The goal of this research is to examine the mechanisms of atherosclerosis development, such as endothelial dysfunction, fatty streak formation, fibrous plaque formation, and plaque rupture (Fig. 1.). This article takes a thorough look at the pathophysiology of atherosclerosis, addressing the pathological and biochemical mechanisms of atherosclerotic plaque development and growth. Atherosclerosis pathogenesis and disease development are the primary topics of discussion in this review, which focuses on the disease's particular targets.

Keywords

Atherosclerosis, cardiovascular diseases, *foam cells, inflammation, lipids, monocytes.*

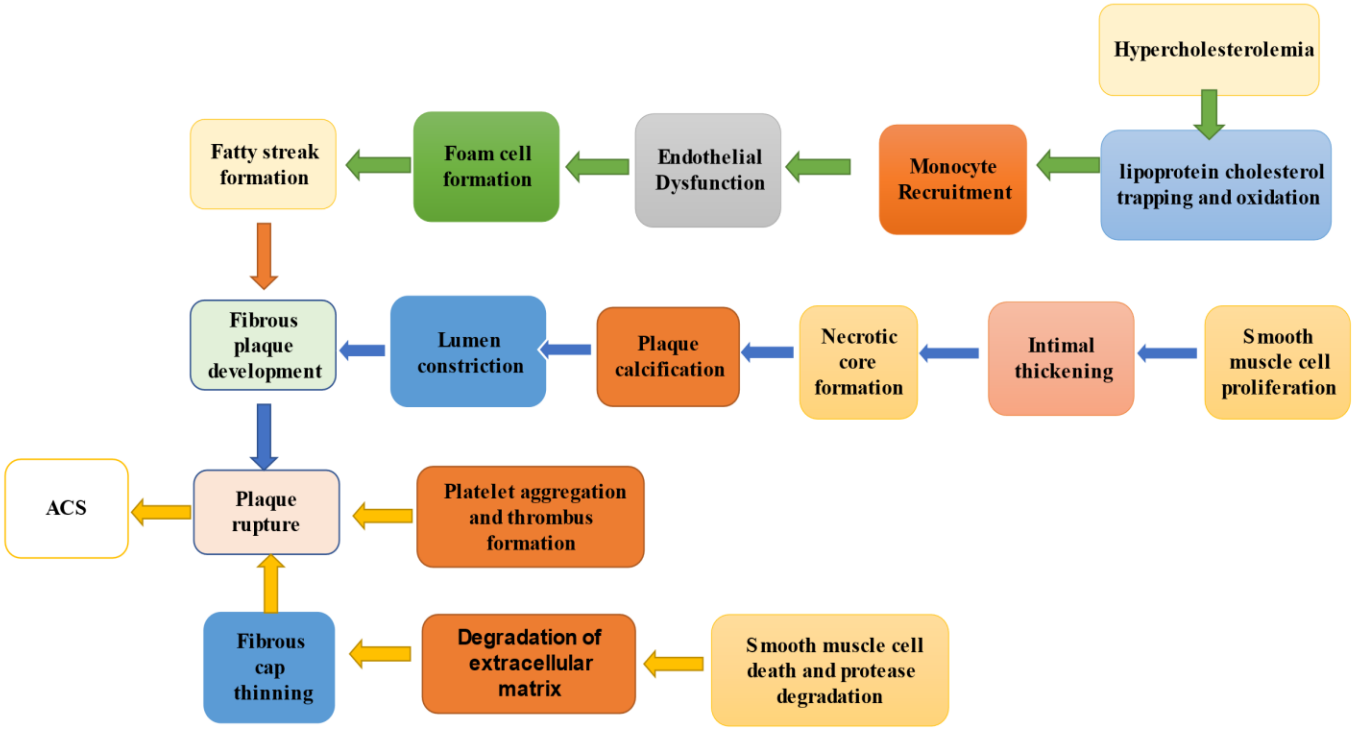

Fig. 1. Stages of atherosclerosis.

1. INTRODUCTION

Atherosclerosis comes from the Greek word "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 accumulation of lipids, fibrous materials, immune cells, smooth muscle cells (SMC), and endothelial cells, leading in plaques and stenosis. The process's origins is unclear, although it presumably results from the combination of plasma lipid levels, blood flow mechanics (shear stress and turbulent flow), and genetic predispositions. Lipoprotein retention, inflammatory cell recruitment, foam cell development, apoptosis and necrosis, smooth muscle cell migration, proliferation, and extracellular matrix (ECM) component secretion, calcification, neovessel creation, arterial remodeling, fibrous cap rupture, and thrombosis. (3).

Nearly half of all deaths in developed countries are caused by atherosclerosis, a chronic inflammatory disease of the arteries (4). Across nations and socioeconomic strata, there is an increasing disparity in the prevalence and consequences of cardiovascular disease. It is estimated that ASCVD is the leading cause of mortality and disability in the world. Caregivers are burdened to a great extent, and medical and surgical costs are incurred consequently. A more cost-effective therapy is sought by the medical community because of the high cost of treatments and the failure of most current drugs. Treatment and prevention of atherosclerosis will be made easier if the process of atherosclerosis is better understood. Endothelial dysfunction is the first step in the progression of atherosclerosis, which eventually leads to plaque rupture.

2. THE ORIGIN OF ATHEROSCLEROSIS AND THE FORMATION OF FATTY STREAKS

Endothelial dysfunction is the first step in atherosclerosis, which is then followed by LDL retention and modification in the intima (5,6). Monocytes are recruited into the intima by activated endothelial cells (ECs) and other atherosclerotic factors such as modified LDLs. Differentiated monocytes and VSMCs quickly take up modified LDLs and use them to promote foam cell formation (7,8). Fatty streaks form because of inflammatory signaling pathways being activated, which leads to an excessive accumulation of lipids in cells (macrophages and VSMC) as well as the extracellular medium, which is the first indication of atherosclerosis. There are three components to atherosclerotic plaque: inflammatory cells, smooth muscle cells, fibrous connective tissue, lipids, and a fat component of fibrous tissue (9).

Because to matrix proteoglycan exposure and loss of the blood vessel lumen's confluent elastic layer, fatty streaks are formed at arterial bifurcation points(10). 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 LDL-c may migrate into the artery wall because of hypercholesterolemia's capacity to change the arterial permeability, causing endothelial dysfunction (11). Absorption of LDL by monocyte-derived macrophages via SR that are not limited by cell cholesterol levels and can bind both Ox-LDL and native lipoproteins is facilitated by the macrophage receptor recognition shift toward LDL due to oxidative modification (12,13). Foam cells, which are characteristic of fatty streak and collect lipids in their cytoplasm as a result of SR's activity, are seen in macrophages (14–16).

2.1. LOW-DENSITY LIPOPROTEIN CHOLESTEROL TRAPPING AND OXIDATION (LDL-C)

It has been shown that high levels of cholesterol in the bloodstream are necessary for the transit of LDL-c through vascular endothelium and the trapping of LDL in the blood vessel wall (17). Inflammatory cells, including monocytes and macrophages, enter the artery lumen via the faulty endothelium that covers the arterial lumen (18). Toxic LDL particles build in the intima as a result of lipoproteins' ability to pass past the endothelial barrier (19).

Free radicals, or reactive oxygen species (ROS), are generated when LDL-c is trapped in the artery wall and subjected to lipid peroxidation(12,20). As oxygen molecules (O2), ROS are defined as taking a single electron and transforming into highly reactive radicals that damage lipids, proteins, and DNA in the body (23). A number of antioxidant enzymes and reactive oxygen species (ROS) are all involved in the oxidation of low density lipoproteins (LDL) (17,20). Lipids and breakdown products from oxidized LDLs contribute to the development of atherosclerotic plaque (21,22). Most of endothelin-1 is expressed by endothelial cells, whereas less endothelin-2 is expressed by endothelial cells (especially nitric oxide).

It seems that trapped LDL oxidation occurs in two stages, as stated by (16) and (23).

1-There was no change in Apo B100 protein after LDL had already been oxidized.

2-After macrophage recruitment to the lesion, further oxidation of LDL lipids and alteration of Apo B100 ensue. Scavenger receptors (SR), sortilin protein receptors, and fluid-phase pinocytosis all play a role in the absorption of native LDL and Ox-LDL by macrophages.

2.3. FORMATION OF FOAM CELLS AND RECRUITMENT OF MONOCYTES

Atherogenic lipoproteins enter macrophages through scavenger receptors, such as SR-A and CD36, which have been demonstrated to play quantitatively significant roles in experimental atherosclerosis. Both early and late atherosclerotic lesions are characterized by the development of lipid-loaded macrophages (foam cells) with very high levels of cholesteryl esters (24). Macrophages are formed in the intima by maturation of monocytes, and the M1 or M2 phenotypes of these macrophages may be selected (25). It's important to remember that while macrophages are normally pro-inflammatory, they may respond to novel stimuli by becoming anti-inflammatory.

To aid leukocyte adhesion and migration to the arterial wall, macrophages express molecules such vascular cell adhesion molecule (VCAM), intracellular adhesion molecule (ICAM), and monocyte chemotactic protein 1 (MCP-1) (26,27). It has been shown that oxidized LDL is related with the upregulation of a number of biomarkers including VCAM-1 and ICAM-1 as well as selectins and chemo-attractants such as lipids, platelets-activating factor, and MCP-1 (12,28). After entering the subendothelial region, macrophage-colony stimulating factor (29) induces the transformation of monocytes into macrophages, which are capable of binding modified lipoproteins, such as Ox-LDL, as well as native lipoproteins and anionic phospholipids(11,30).

2.4. ATHEROSCLEROSIS ENDOTHELIAL DYSFUNCTION AND VSMC CONTRIBUTION TO FOAM CELL POPULATION

Because VCAM-1, an adhesion molecule present on the active endothelial surface, is bound by the leucocyte, they are able to migrate across the endothelium more easily (31). Inflammatory cells, cytokines, and lipids are drawn into the atherosclerotic plaque because of increased cellular adhesion and associated endothelial dysfunction. The inflammatory cascade is amplified by the following release of MCP-1 by leukocytes, which attracts more leukocytes, activates leukocytes in the medium, and induces the recruitment and proliferation of smooth muscle cells as a result of VCAM-1 expression(32). As well as the SR-A and CD36 receptors in the intima, oxLDL may also be taken up by VSMCs via other receptors such as LOX-1 (33–35). In the human coronary intima, VSMCs are responsible for 50% of the foam cells, highlighting the importance of VSMCs in the progression of atherosclerosis (36).

Because of an unfavorable lipid composition in the blood, endothelial cells overexpress adhesion molecules in response to turbulent flow, which is how atherosclerosis develops (32). Disrupted vascular homeostasis causes endothelial dysfunction (37–39). Vascular wall vasoconstriction, lipid infiltration, leukocyte adhesion, platelet activation, and oxidative stress may all occur when ECs are out of balance (40,41). Together, they trigger an inflammatory response that leads to the formation of fatty streaks (37,39). In the latter stages of atherosclerosis, endothelial dysfunction leads to the production and rupture of plaques (37). Atherogenesis is preceded by endothelial dysfunction (45,46).

3. FIBROUS PLAQUE DEVELOPMENT

A thick fibrous covering containing VSMCs covers and stabilizes the vulnerable plaque (42). The necrotic core and fibrous cap are the distinguishing features of advanced atherosclerosis (43), and atheroma plaque regression is rare at this point (44,45).

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 (46). 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 (47). 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 (46).

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 (48).

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 (49,50). 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 (51,52). These proliferating VSMCs, in conjunction with ECM synthesis, produce a fibrous cap that surrounds and prevents the rupture of the growing atherosclerotic plaque (53).

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 (54). Necrotic cores form because of advanced lesional macrophage apoptosis combined with poor phagocytic clearance (or efferocytosis) of the apoptotic macrophages in advanced plaques (55). 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.

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 (56,57). During the development of atherosclerosis, pericytes (58) and VSMCs (59,60) transdifferentiate into osteoblast-like phenotypes, gaining the ability to form a mineralized matrix and leading to calcium deposits, as seen in bone tissue(61,62). This all adds to microcalcifications, which are the first step of the vascular calcification cascade in both the intima and the media (63). Microcalcifications eventually progress to bigger calcifications that extend from the necrotic core's bottom to the surrounding matrix (60).

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" (64). 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 (65). Platelets first bind to subendothelial collagen and become activated, and additional platelets are then recruited and aggregated in the location to commence wound healing (66). 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 (67). 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 (68,69).

The end outcome of a complicated and self-perpetuating cell reaction to mechanical stress is the development of atherosclerotic plaques, which may be caused by heart disease, cellular aging, and the vessel walls themselves. Since these changes are already in motion, investigating elements that may speed up their evolution seems sensible. As discussed in vitro and in vivo research, the mechanisms of atherosclerotic lesion development suggests that oxidized forms of cholesterol are one of the elements that accelerate growth that has already occurred in the arterial wall and have less of an influence on causing the disease's beginning (70).

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. Even though atherosclerosis in humans has drawn the attention of many experts, the underlying causes are still a mystery. Atherosclerosis is primarily caused by lipid buildup and immunological activation in the arterial wall. Inflammation and atherosclerosis development and resolution are controlled by a multitude of protein and lipid mediators with specific functions, and these mediators are either proinflammatory or antagonistic to atherosclerosis. Inhibiting proinflammatory and boosting antiinflammatory mediators and/or intracellular signaling may cure atherosclerosis. Detailed understanding of atherosclerosis' underlying mechanism is required to develop innovative treatment targets that are superior to existing secondary prevention measures. The impact of antiinflammatory medicines on preventing atherosclerosis will give insight on the future of antiinflammatory therapy as secondary cardiovascular prophylaxis. To reach this goal, experimental studies providing the rationale and proof of concept for the respective targets, observational and biomarker studies in the context of human disease, and the design of large clinical trials defining the correct target population, treatment periods, outcomes, and side effects will be crucial. Moreover, Genetics, epigenetics, inflammatory and immunological pathways may be appealing targets for illness prevention and/or therapy. 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.

6. DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors. This study has not been published before or is not under consideration for publication elsewhere. Its publication is permitted by all authors and after accepted for publication it will not be submitted for publication anywhere else, in English or in any other language, without the written approval of the copyright holder. The authors grant this journal a license to publish the article and identify itself as the original publisher.

. 7. AUTHOR CONTRIBUTION

The author confirms sole responsibility for the following: study conception and design, data collection, and manuscript preparation.

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