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The role of endothelial cells in the formation and progression of atherosclerosis

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Abstract
The functions of endothelial cells include physical barriers, sensory organs and endocrine organs, and all three of its functional abnormalities will lead to endothelial cell dysfunction, which will lead to the formation of atherosclerotic lesion initiation and continue to play an important role in the atherosclerotic process. Based on domestic and international research on endothelial cells and atherosclerosis, various causes of endothelial cell dysfunction and their important roles in the process of atherosclerosis will be explored, analyzed and synthesized, and finally the relationship between endothelial cell damage and the formation of atherosclerosis will be comprehensively analyzed at the molecular and individual levels, in order to provide new ideas and methods for the prevention and treatment of atherosclerosis.

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Introduction
Endothelial cells serve as a physical barrier, a sensory organ, and an endocrine organ. They are an obstruction structure linked to the inner layer of the blood artery wall. Endothelial cell dysfunction is caused by abnormalities in all three of their activities. This dysfunction results in the creation of atherosclerotic lesions and continues to play a significant part in the atherosclerotic process. A systematic summary of the relationship between the causative factors and their associated pathophysiological changes at both the molecular and individual levels is missing despite the recent abundance of reviews on the intricate relationship between endothelial cell dysfunction and atherosclerosis. In this article, we list the causes of endothelial cell dysfunction in the context of the link between endothelial cells and atherosclerosis as it is now understood, and we discretely study this relationship. This article lists the causes of endothelial cell dysfunction and examines, on a distinct level, how they relate to atherosclerosis.

Materials and methods
Endothelial cell function
The endothelium, intima, and endothelium make up the normal arterial wall, and the endothelium is further divided into endothelial cells, subendothelium, and endotoxin plate from the inner to the outer layer of the structure. As a result, the integrity of the endothelial cells is a physiological barrier between the lumen of the blood vessel and the peripheral tissues, and it can be involved in the development of diseases like heart disease [1]. When stimulated by various pathophysiological stimuli, endothelial cells can perform endocrine functions by releasing a variety of active substances, including NO, ET-1, adhesion molecules involved in inflammatory responses, PGI-2, NO, ET, TXA2, and Ang-II regulating vascular tone, platelet activating factor, fibrinolysis activator, and fibrinogen activator, as well as secreting hormones. Plasminogen activator as well as a number of other chemicals that change vascular permeability [2]. Vascular permeability can also change as a result of a variety of chemicals being secreted [2].

Factors of endothelial cell injury and their pathophysiologic alterations

Endothelial cell structural and functional abnormalities can significantly affect the internal environment's equilibrium by deregulating their endocrine and physical barrier functions. The following are common causes of endothelium injury and associated pathophysiologic changes, among other variables that are anticipated to contribute to its damage.

Metabolic disorders

High sugar

Atherosclerosis and abnormal blood glucose metabolism are closely related. By slowing down endothelial cell activity, preventing proliferation, increasing senescence, triggering apoptosis, and other methods, high hyperglycemia can impair vascular endothelial cells. A number of physiologically active chemicals that cause aberrant responses and aid in the development of atherosclerosis are secreted by the damaged endothelium. According to research by Peng Jun *et al*. [3], high glucose levels can decrease the activity of vascular endothelial cells, prevent their growth and proliferation, and harm the endothelium's integrity. This ultimately prevents the endothelium from performing its normal biological functions, which aids in the development of atherosclerosis. Meng *et al*.'s [4] research has demonstrated that higher glucose levels can cause endothelial cells to die, and the degree of this death is positively connected with the glucose level. According to Chen *et al*. [5], high glucose levels cause endothelial cells to undergo apoptosis, and changes in blood glucose speed up this process.

According to Wang *et al*. [6], on the molecular mechanisms of high glucose-induced atherosclerosis, a high glucose environment can alter the body's metabolism of glucose and lipids, cause the release of inflammatory mediators like adhesion factor, trigger the body's redox reaction, and increase the amount of reactive oxygen radicals (RORs) like superoxide anion. These RORs affect endothelial cell NO production, cause endothelial cell injury, and induce endothelial the damage-response theory of atherogenesis is said to be centered on endothelial cell injury.

High homocysteine

Homocysteine (Hcy) levels in the body can be affected by abnormalities in Hcy metabolism, cofactor deficits in Hcy formation, and epigenetics, all of which can result in hyperhomocysteinemia, which is characterized by serum Hcy levels that are greater than 15 mol/L [7]. He Lei [8] In order to create a cell injury model, human aortic endothelial cells (HAECs) were grown and exposed to various doses of Hcy (0, 0.5, 2.5, 5, 7.5, and 10 mM). Endothelial cell viability was assessed by CCK-8 after 24 hours. The findings demonstrated that, in comparison to the control group, the cell viability of HAECs treated with various doses of Hcy for 24 h reduced in a concentration-dependent way. The outcomes demonstrated a concentration-dependent decrease in the blood homocysteine level in HAECs. According to the findings, increased blood homocysteine levels can hasten the beginning and progression of atherosclerosis. It has been shown that Hcy promotes apoptosis by inducing NOX1, NOX2, IL- and IL-6 expression [9]. According to the Guo's study [10], elevated Hcy concentrations can increase the expression of inflammatory markers that are connected to coronary artery damage. Additionally, increased Hcy levels have been shown to have a concentration-dependent impact on endothelial dysfunction, inflammatory factor expression, and lipid and amino acid metabolism [11].

In conclusion, increased Hcy expression is closely associated with atherosclerotic disease, making Hcy an important target for clinical intervention in the development of atherosclerosis. Currently, the primary goal of treating hyperhomocysteinemia in clinics is to reduce the plasma Hcy level through vitamin supplementation. Future *in vitro* cell cultures, animal models, and clinical studies on humans will be able to investigate the relationship between various signaling pathways and inflammatory factors involved in the development of atherosclerosis, which will provide a solid theoretical foundation for clinical targeted intervention.

High fat

Wang *et al*. [12] by feeding control to rats in the general food group and high-fat diet group, it was found after 6 weeks that high-fat diet could inhibit the activity of eNOS of large artery vascular endothelial cells, reduce the endothelium-dependent vasodilator function and increase the arterial stiffness, which could prove that high blood lipids could reduce the function of endothelial cells by affecting the activity of eNOS, and thus affecting the process of atherosclerosis. In research conducted by *et al*., it was shown that high fat culture significantly reduced the ability of endothelial cells to secrete NO, and that high-sugar and high fat culture further decreased endothelial cell NO levels [6]. Abnormal fat is crucial in the primary prevention of atherosclerosis and has been demonstrated to be a risk factor for cardiovascular events [13]. The frequency of hyperlipidemia has been rising in recent years, however among Chinese persons over 35, only 16.1%, 7.8%, and 4.0% are aware of their condition or are actively managing it [6]. In conclusion, improving endothelial cell function and preventing atherosclerosis should be accomplished through a multifactorial combination of prevention and treatment, with the primary aims of lowering the burden of metabolic risk factors, such as high glucose, high fat, and high homocysteine, and encouraging a healthy lifestyle.

Low oxygen

According to Wang *et al*. [14], serum levels of interleukin 6 and tumor necrosis factor were measured by enzyme-linked immunosorbent assay in the study of vascular endothelial injury brought on by hypoxia (10% oxygen concentration) in mice. POSTN, intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule (VCAM-1) were also measured. The expression levels of POSTN, ICAM-1, VCAM-1, and p65 in the thoracic aortic tissues of mice in each group were determined by Western blotting. Mice in the hypoxia group displayed a considerable increase in key inflammatory and adhesion markers compared to the control group, as well as a more marked propensity for endothelial cell damage and atherosclerosis. It was important to show that endothelial-mesenchymal transition may be induced by hypoxia [15] and that endothelial function is diminished. Ji *et al*.'s experimental [16] evidence that hypoxia can promote vascular endothelial apoptosis by stimulating endoplasmic reticulum stress.

Oxidative stress

Oxidative stress can result in altered endocrine and paracrine function, increased production of adhesion molecules, and lipid peroxidation [17]. It can also upset the equilibrium

between the stability and permeability of endothelial cell membranes. The modulation of endothelial cell membrane stability and permeability homeostasis can be brought on by oxidative stress. Reactive oxygen radicals, comprising reactive nitrogen species and reactive oxygen species, should be produced in significant amounts when different oxidative enzymes are involved in linked enzymatic activities. Peroxynitrite (phosphorous nitrite) (ONOO -) and NO are examples of reactive nitrogen species, whereas hydrogen peroxide (H2 O2), hydroxyl radicals (OH -), and superoxide anion are examples of reactive oxygen species. By encouraging the body's excessive production of ROS, oxidative stress stimulates the production of inflammatory factors. Excessive oxidation also increases the production of ox-LDL, which alters endothelial cell permeability, impairs endothelium-dependent vasoconstriction and diastole, exacerbates the inflammatory response, and promotes apoptosis, resulting in endothelial dysfunction, endothelial [18].

Systemic diseases

Hypertension

In particular, atherosclerosis of the cardiovascular system is one of the numerous target organ damages that can result from hypertension, a common clinical condition. The methods by which it produces atherosclerosis have been the subject of numerous clinical research and reviews; in Chen [19], the discussion of its applicability includes the following typical pathogenic processes: increased catecholamine release, aggravating the development of atherosclerosis; hypertension to endothelial cell damage, endothelial cells synthesize nitric oxide, and endothelium between the dynamic balance is disrupted; plasma endothelium levels in hypertensive patients are significantly elevated; vascular smooth muscle diastolic disorder, vasoconstriction, and vascular smooth muscle proliferation; platelets are easily adherent to aggregation of. Atherosclerosis is aggravated by aggregation and adhesion. Additionally, nutritional deficiencies and problems with lipid metabolism are frequently present in hypertension individuals, which causes endothelium-dependent vasodilator dysfunction of the major arteries and increased central arterial stiffness [15]. The Thus, physiologic alterations brought on by hypertension can cause endothelial cell malfunction and injury through a variety of mechanisms, aggravating the onset of atherosclerosis.

Diabetes

Long-term hyperglycemia, a feature of diabetes mellitus that not only clinically manifests as elevated blood glucose levels but is also frequently accompanied by linked target organ and target tissue damage, is a feature of the disease. As previously mentioned, hyperglycemia causes abnormalities in the body's metabolism of glucose and lipids and impairs endothelial cell function through peroxidation and other mechanisms [5]. Peroxidation is one of the variables that affect endothelial cell function [5]. Vascular endothelial damage is the root cause of vascular disease, and diabetes mellitus has a number of risk factors that can either directly or indirectly damage the arterial wall and cause endothelial cell dysfunction and platelet-generating factor release. The latter results in the proliferation of vascular smooth muscle. Diabetes-related endothelial cell damage results in the development of atherosclerosis, which then progresses to acute and chronic heart, brain, and kidney complications. Pathophysiological changes associated with these complications can also worsen the endothelial cell stress injury [18].

Connective tissue diseases

Connective tissue disorders are a group of inflammatory connective tissue illnesses that affect various human organs and systems, are linked to immunological responses, and frequently affect the cardiovascular system. Sam *et al*. [20], Zhang *et al*. [21], and Sekiguchi *et al*. [22] found that there was a significant increase in the level of Hcy, which can affect the endothelial function by influencing lipid and amino acid metabolism pathways, causing the release of a variety of inflammatory factors, and exacerbating the development of atherosclerosis.

Infectious diseases

The polysaccharide envelope, a barrier component, is present on the surface of endothelial cells. By blocking adhesion molecules on the surface of endothelial cells, the polysaccharide envelope prevents leukocyte attachment, inhibits inflammatory responses, and prevents thrombosis by restricting platelet interaction with endothelial cells. Antithrombin can bind to acetylheparin sulfate in polysaccharide coating, enhancing its anticoagulant activity. When the polysaccharide envelope on the surface of endothelial cells is destroyed in sepsis, the balance between injury and defense is thrown off, an excessive inflammatory response is triggered, endothelial cells become less functional, and the morbidity and mortality rates of sepsis patients rise [23]. Ding *et al*. [24] used a non-parametric method of rank-sum test through a clinical prospective research method to compare and analyze the differences in s-CD62P levels, inflammatory factors, and coagulation indexes of sepsis groups and control groups. They came to the conclusion that the plasma s-CD62P expression of patients with sepsis is significantly increased, which is marked by is endothelial cells' early injury. Other viral disorders can cause endothelial cell function to be compromised by the accumulation of inflammatory cells like neutrophils and macrophages in localized lesions, which can all lead to the onset of atherosclerosis.

Localized blood flow shear force

According to Zhao *et al*. [25], it was shown that shear stress, as a significant mechanical stimulus, not only affects the morphology and function of endothelial cells but also controls the expression of related genes in endothelial cells, using different strengths of shear stress on human umbilical vein endothelial cell lines cultured *in vitro*. Endothelial cells can be made more resistant to damage when the shear stress is less than 15 dyne/cm^2 by promoting the expression of vasodilator factors, growth inhibitory factors, and antioxidants while simultaneously inhibiting the expression of vasoconstrictive factors, growth factors, inflammatory mediators, etc. [26]. Endothelial cells can be damaged less severely [26]. In contrast, at low shear stress (±4 dyne/cm^2), endothelial cell morphology is polygonal, irregularly arranged, and susceptible to chemical stimulation, which can secrete vasoactive substances, such as angiotensin-converting enzyme, related inflammatory mediators and growth factor adhesion molecules, inducing dysfunction of endothelial cells, further damaging the endothelial cells, and has a pro-atherosclerotic effect. A mechanosensitive cation channel is piezo1. cation-sensitive channel. A

mechanosensitive cation channel is called piezo1 [27]. Piezo1, a cation channel that is mechanosensitive and plays a significant role in vascular formation, is crucial. Endothelial cell dysfunction, endothelial damage, and the development of atherosclerosis can arise from the absence of Piezo1 in endothelial cells under laminar shear stress [28]. Atherosclerosis, endothelial damage, and dysfunctional endothelial cells are the results [28].

Other: Aging

Senescent endothelium cells experience considerable morphological and biological alterations. Large and flattened senescent endothelial cells, increased permeability to lipoproteins and other plasma components, decreased NO secretion, increased secretion of intercellular adhesion molecules and vascular cell adhesion molecules, increased expression of nuclear transcription factors, and cells in a pro-inflammatory and pro-apoptotic state are all characteristics of senescent endothelial cells [29]. There are two different aging processes. The first is chromosome telomere shortening, which is characterized by replication aging, cell aging, genetic factors, DNA damage, oxidative stress, and other factors. When telomere shortening reaches a certain point, the cell stops dividing, which results in growth stagnation, or aging by replication [30]. The other is telomere shortening brought on by stress. The other is cellular senescence brought on by stress [31]. Endothelial cells can experience stress senescence as a result of factors like oxidative stress, smoking, and hyperglycemia. Within a few hours of stimulation, changes in biological function take place, and the timing of these changes is positively correlated with the level of stress [32, 33]. Atherosclerosis may develop as a result of senescent endothelium cells becoming dysfunctional for a variety of reasons. To some extent, preventing or delaying the senescence of endothelial cells can reduce the development of atherosclerotic plaques.

Initiation and progression of atherosclerotic lesions

The term "atherosclerosis" describes the stiffening or localized thickening of the arterial trunk and bifurcation walls. This results in the creation of plaques, which in turn causes the lumen to narrow, obstructing blood flow and causing regional ischemia and hypoxia. The first indication of atherosclerosis is the thickening of the artery lining. There are numerous theories regarding the pathogenesis of atherosclerosis, including the lipid infiltration theory, the endothelial damage-response theory, the platelet aggregation and thrombosis hypothesis, and the smooth muscle cell cloning theory. The endothelial damage-response theory, which is the most widely accepted, primarily entails four disease-causing steps:① Endothelial cells are damaged as a result of several risk factors acting on them. LDL-C enters the tube walls through the damaged endothelium, where it is oxidized and altered before being lowered into the lumen, where it causes local blood flow. Exacerbating endothelial damage, LDL-C enters the tubular wall through the damaged endothelium and undergoes oxidative modification to become low-density lipoprotein cholesterol (ox LDL-C). ② As endothelial cells migrate into the subendothelium to become macrophages, which then phagocytose oxidized LDL-C through scavenger receptors to convert it into foam cells, the earliest lipid streaks of atherosclerosis are formed. Monocytes and lymphocytes have altered surface properties, increased expression of adhesion factors, and increased adhesion to endothelial cells. LDL-C can be oxidized by macrophages, forming peroxides and superoxide ions. Many growth factors and pro-inflammatory mediators, such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), tumor necrosis factor (TNF-), and interleukin (IL-1), are synthesized and secreted by macrophages containing oxidatively modified lipoproteins.③ T cells that infiltrate the endothelium detect macrophages and release interferon-, TNF, and lymphotoxin, which are highly atherogenic cytokines.④ Smooth muscle cells move from the mammogram to the endothelium and multiply in the presence of PDGF and FGS. They can also phagocytose lipids to change into foam cells. Under the concentrated action of thrombin, smooth muscle may occasionally proliferate extensively, producing and secreting collagen, proteoglycans, elastin, and other substances that together make up the plaque matrix. Lipid streaks develop into adipose lesions and fibrous plaques through the numerous mechanisms mentioned above [34].

Pathologic alterations brought on by atherosclerosis largely affect the cerebral arteries (medium myoglobin), coronary arteries, and aorta (big myoglobin) [34]. It has been proposed that the primary clinical causes of acute myocardial infarction and cerebral infarction are arterial stenosis and atherosclerosis. Therefore, an effective program for early prevention and therapeutic guidance of cerebral infarction and acute heart attack can be provided by objective and accurate assessment of atherosclerotic lesions and the degree of stenosis. It can affect the course and direction of the disease's development and can successfully intervene in the onset of cardiovascular and cerebrovascular disorders if recognized early and treated appropriately. The gold standard for atherosclerosis: angiography, an intrusive procedure, is not appropriate for early diagnosis of the disease because the majority of individuals with premature atherosclerosis lack apparent clinical signs. For the purpose of early detection, early diagnosis, and the identification of precise targets for its therapy, it is imperative to investigate the various signaling pathways and inflammatory mediator release associated with endothelium damage, the primary cause of atherosclerosis.

Results

In summary, endothelial cell dysfunction is indissolubly associated with the onset of atherosclerosis, and endothelial cell injury, autophagy, apoptosis, and pyrolysis are all capable of causing atherosclerotic plaque changes in the aorta, coronary artery, and other arterial systems via specific cellular pathways.

Endothelial cell injury

By altering the structure, function, and sensitivity to inflammatory factors of the endothelial cell layer of the endothelium, the aforementioned *in vivo* and *in vitro* risk factors, such as systemic diseases, local blood flow shear force, oxidative stress, and aging, all lead to endothelial cell dysfunction and injury. Endothelial cell injury becomes the initiator of atherosclerosis, which provides the site for the oxidization of LDL. It initiates its own endocrine function [18], secreting a variety of inflammatory factors, adhesion molecules, and vasoconstrictor-diastolic factors, recruiting a large number of inflammatory cells, resulting in abnormal vasoconstrictor-diastolic function, which further exacerbates

the damage to itself, and provides a place for LDL oxidation, macrophage and smooth muscle cell proliferation and migration, various adhesion factors, and the atherosclerosis growth is encouraged [18, 35].

Endothelial cell autophagy and apoptosis

Both autophagy and apoptosis, which are often advantageous physiological patterns for cells, tissues, and humans, refer to the regulation of the cell's own metabolic demands and the renewal of damaged organelles. Endothelial cells undergo aberrant autophagy and death due to a variety of risk factors. Through a variety of signaling pathways, extracellular vesicles formed during endothelial cell apoptosis, such as exosomes, microvesicles, microparticles, and apoptosis vesicles, can either block or promote the progression of atherosclerosis [36]. By preserving NO bioavailability and destroying oxidized LDL, normal levels of cellular autophagy can prevent atherosclerosis. Autophagy Atg5 knockout mice have been demonstrated to have increased atherosclerosis formation, which is a waste of the preventive function in the progression of atherosclerosis. Decrease of preventive properties as atherosclerosis progresses [37].

Endothelial cell pyroptosis

A recently identified method of planned cell death that depends on inflammatory release is called cell pyroptosis. When a cell undergoes pyroptosis, pores in the cell membrane form, causing cell swelling and plasma membrane rupture. This causes the cell to enlarge and rupture, allowing the contents of the cell and associated pro-inflammatory chemicals to enter the interstitium, provoking an immune response and cell death. Endothelial cell death can result from a multitude of internal and external risk factors, according to Yu Chai's work on the subject of atherosclerosis [17]. Inflammatory mediators that are released into the mesenchyme during endothelial cell death can encourage the secretion of IL-1, IL-18, P-selectin, intercellular adhesion molecules, vascular cell adhesion molecules, etc. This causes the adhesion of monocytes and phagocytes to the endothelial cells, which intensifies inflammatory responses in the vascular wall and compromises the integrity of the endothelium. This worsens the progression of atherosclerotic lesions by increasing inflammatory responses in the vascular wall and destroying the integrity of the vascular endothelium.

Discussion

Throughout the entire atherosclerotic process, from lipid dots to lipid streaks to prelature to atheromatous plaque changes to fibrous atheromatous plaques causing luminal stenosis, endothelial cell damage and dysfunction play a role in the initiation and progression of atherosclerosis. When a delayed unstable plaque rupture results in an acute event, endothelial cells continue to be crucial. Endothelial cell dysfunction-endothelial cell damage, which results in the development of atherosclerosis, is the final step in the aberrant chain of events that includes endothelial cell pyrolysis, autophagy, and apoptosis.

Acute cardiovascular events under stressful situations may result from atherosclerosis that is still developing and may be fatal if left untreated. Atherosclerosis is a disease-causing process that cannot be reversed, but when identified by angiography, plaque can be surgically removed or controlled with medicine so that it doesn't rupture and cause an acute event. Plaque stabilization and surgical procedures both have negative effects, thus it is preferable to catch them early. It is evident from studying the connection between endothelial cells and atherosclerosis that practically all disease-causing agents impact the shape and function of endothelial cells. The endocrine and barrier functions of endothelial cells have been controlled by a variety of drugs, and more and more people are realizing the significance of these physiological functions and funding research on the molecular mechanisms of endothelial cells in an effort to increase future options for the prevention and treatment of atherosclerosis. Additionally, endothelial cells are abundantly found in the body's innermost layer of all arterial and venous membranes, and additional study on them may yield fresh insights and treatments for kidney and brain disorders.

Conclusion

Numerous factors can cause endothelial cell dysfunction and damage, which can both initiate and promote atherosclerosis. If atherosclerosis is allowed to progress, it can result in acute cardiovascular and cerebrovascular events, which can be fatal if not promptly treated. We can help to open up new options for the future prevention and treatment of atherosclerosis by understanding the role of endothelial cells and associated molecular pathways. Furthermore, endothelial cells are widely distributed in the lining of all arteries and veins in the body, and additional research into them may yield fresh insights and treatments for kidney and brain disorders.

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Data availability statement

Not applicable

Authors' contributions

CW performed the literature search and selection, extracted and analyzed the data, and drafted the manuscript, YS, HZ, HF and YZ revised the manuscript. JD designed and supervised the study, analyzed the data, and revised the manuscript. All authors granted the final approval for submission.

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