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Research Progress on Diagnosis and Treatment of Atherosclerosis

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Abstract

The cardiovascular diseases are one of the leading causes of death worldwide. Despite preventive measures, early detection and common pathophysiological mechanisms of cardiovascular diseases remained unclear. Atherosclerosis is a major chronic progressive inflammatory cardiovascular disease caused by early endothelial dysfunction, oxidative stress, lipid deposition and monocyte recruitment leading to platelet aggregation. To eliminate the patient's conditions, researchers continue to explore effective strategies, including nano-inspired therapeutics and diagnostics. Nanoparticles represent a new strategy for the prevention, diagnosis, and treatment of atherosclerosis. Although nanotechnology has proven its effectiveness in cancer and other diseases, it is necessary to apply it to clinical practices for atherosclerosis. Here, we reviewed the available literature in an attempt to demystify drug delivery and atherosclerosis diagnosis of nanometer carriers. Based on the mechanisms of these drug delivery strategies, we further emphasized the pharmacology and characteristics of atherosclerotic plaques. In conclusion, this article provides a concise literature source for researchers working with the diagnosis and treatment of atherosclerosis.

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Introduction

Atherosclerosis is a major cardiovascular disease initially described as a chronic progressive inflammatory disease caused by early endothelial dysfunction, oxidative stress, lipid deposition and monocyte recruitment leading to platelet aggregation [1]. The arteries gradually stiffen because of dyslipidemia in this condition. Ultimately, the formation of atherosclerotic plaque leads to characteristic stenosis and sclerosis of arterial walls that limit blood flow in the vessels [2]. There is a significant interaction between different types of cells in the subepithelial layer, adhesion molecules, chemical attractants and lipoproteins associated with atherosclerosis [3]. Due to the complexity of this disease, therapeutic techniques have not been able to achieve the desired results for clinical use. Many popular conventional therapeutic techniques, which have already been approved by the US food and drug administration (FDA), continue to struggle to achieve the desired results. These include statins, which lower bad cholesterol as low-density lipoproteins [4], nicotinic acid (niacin), which improves overall cholesterol in the body [5], fibrates for the reduction of triglycerides [6], and ezetimibe for the reduction of cholesterol in the intestines [7], among others. Researchers and clinicians continue to explore other innovative therapeutic methods to help combat the condition with higher precision and effect. This article reviews the application of nano-system in the treatment and diagnosis of subclinical atherosclerosis, and the progress of nano-system as a therapeutic method.

Nanotechnology: Therapeutic opportunities in atherosclerosis

Nanoparticle therapy was originally developed to treat cancer [8]. These initial applications exploit the properties of the tumor microenvironment to promote nanoparticle extravasations by enhancing local vascular permeability and destroying lymphatic drainage. This combination of microenvironmental properties is known as enhanced permeability and retention, which is the most common passive targeting mechanism [9]. Nanomedicine-based approaches in vascular medicine are often classified as diagnostic and therapeutic devices, although multifunctional devices, such as those designed for image-guided therapy, are widely reported in the literature [10]. Nanodevices, or "nanoparticles," can be made of a variety of organic and inorganic materials. To produce contrast enhancement, the nanoimaging agent may be made of gadolinium or ferric oxide for magnetic resonance contrast, and gold colloid or radioactive tracer-based nanocomponents for x-ray contrast [11, 12]. These contrast agents may be intravenously encapsulated in an emulsion, lipid, or polymer-based biocompatible matrix, to improve the performance of the contrast agent (*i.e.*, more contrast agents per nanoparticle) or to improve the half-life and targeting effect *in vivo*. Prominent examples of nanomaterials include liposomes, micelles, and block copolymer nanoparticles [11, 13, 14]. The future of nanomedicine in vascular diseases is because of the nanoscale of biological interactions of many materials that exhibit novel properties. For example, quantum dots can be engineered on a single nanoscale to adjust their fluorescence emission spectra from UV to IR to encode the color of different cell populations within plaques [15]. Polymer-based nanospheres can be encapsulated by bioactive ligands to allow them to effectively internalize into diseased cells for specific site delivery of antithrombotic drugs [16].

Conventional therapeutic methods for atherosclerosis

Atherosclerosis remain a chronic inflammatory disease that can lead to high mortality. It is characterized by plaque in the arteries. Major risk factors for atherosclerosis include diabetes, dyslipidemia, hypertension, smoking, and genetic abnormalities. Currently, there is no cure for atherosclerosis, but treatment can slow the progression of the disease. The primary objective of treatment is to reduce arterial stenosis, thereby avoiding the signs and symptoms of atherosclerosis. Driven by this goal, patients can change their lifestyle by adopting practices such as regular physical activity, diet changes and quit smoking, thereby improving blood lipids. However, in case of lifestyle changes that cannot control the persistent accumulation of bad cholesterol in the body, the health risk profile of a particular patient, and the treatment of cardiovascular diseases (such as dyslipidemia, hypertension and diabetes) has put forward a high demand [17].

In addition to macrophages, the smooth muscle cells proliferate, migrate and synthesize different matrix proteins like collagen that form the fibrous cap around the atherosclerotic plaque. Plaque

progression through lipid accumulation, neovascularisation, smooth muscle cell and macrophage apoptosis can last from years to decades. When a plaque breaks, the protease released by apoptotic cells degrades the cap, exposing the highly coagulating lipid core and triggering another associated disease, thrombosis [18]. Due to the multifactorial and the chronic nature of atherosclerosis, plaques most prone to rupture, called vulnerable plaques, are often discovered only after a major clinical event. Below we will discuss some conventional methods used to control atherosclerosis.

Lipid-lowering agents

HMG-CoA reductase inhibitors (Statins)

Statins work by targeting and blocking enzymes called HMG-CoA reductase, which is responsible for cholesterol production. Statins mimic the successful binding of HMG-CoA with HMG-CoA reductase [19]. The competition between statins and HMG-CoA delayed the conversion of HMG-CoA into the cholesterol precursor l-methoxyvalerate, resulting in reduced cholesterol synthesis. Statins significantly inhibit cholesterol synthesis in the liver because most circulating cholesterol is produced in the body rather than consumed by food [20]. When the liver reduces cholesterol production, the plasma cholesterol level also decreases. Loop statins are also effective at reducing triglyceride levels and can improve high-density lipoprotein (HDL) levels [21].

Fibrates

Fibrates significantly reduce plasma triglyceride levels and generally decreased low-density lipoprotein (LDL) cholesterol and increase HDL cholesterol levels. The fibrates also regulate the uptake of cellular fatty acids, causing a reduction in the production of VLDL, a granule that normally circulates in the bloodstream that carries triglycerides [22].

Niacin

Niacin inhibits the enzyme diacylglycerol acyltransferase 2, which is a crucial enzyme for triglyceride production. Niacin delays mainly the hepatic catabolism of apolipoprotein A-I, the HDL precursor protein, and inhibits hepatic lipase, the major enzyme in the HDL remodeling process, leads to the increases in HDL half-life and the number of HDL particles. It significantly raises HDL cholesterol more than other lipid-lowering medicines [22].

Ezetimibe

Ezetimibe is capable of inhibiting cholesterol absorption in the intestines by selectively blocking the NPC1L1 protein in the jejunal brush border, relevant for the uptake of intestinal lumen micelles into the enterocyte. Even though the exact mechanism by which ezetimibe employs for the entry of cholesterol into the enterocytes and hepatocytes is not entirely understood, the drug can remarkably lower LDL levels. Ezetimibe does not work very well like statins, which have a well-defined mechanism of action. This medication is usually used in addition to a statin to further lower LDL levels [23].

Plant sterols and stanols (Phytosterols)

Sterols and stanols are natural compounds extracted from plants. Their structures look like cholesterol. They mimic cholesterol and are capable of competing with it in the absorption process. High consumption of these compounds impairs the uptake of cholesterol from the gut. In order to produce more bile, more cholesterol has to be eliminated from the systemic circulation, so that the levels of cholesterol in the blood could be lowered [24].

Omega-3-acid derivatives

Omega-3 fatty acids are a mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). They reduce the amount of triglycerides in the blood in people with very high triglycerides (pre-treatment triglyceride level greater than or equal to 500 mg/dL) [25].

Antihypertensive agents

Uncontrolled high blood pressure is a risk factor for heart attack and stroke, which could be caused by atherosclerosis. The risk of cardiovascular disease starts increasing when blood pressure levels are above 110/75 mm Hg. Reducing high blood pressure clearly lowers risk. 2017 guideline for the prevention, detection, evaluation, and management of high blood pressure in adults recommended blood pressure target of <130/80 mm Hg in people at risk of cardiovascular diseases, such as people with diabetes or kidney disease [26]. There are many classes of high blood pressure drugs that work in a variety of ways, such as beta-blockers,

angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, etc.

Atherosclerosis is a condition of atherosclerotic plaque (cholesterol and fatty materials) that develops in the artery walls leading to blocked blood flow. When the plaque rupture, materials induced blood clots were released into blood circulation, leads to cardiovascular events. Conventional drugs for instant, anti-hyperlipidaemic drugs, anti-inflammatory drugs, anticoagulant drugs and anti-hypertensive drugs, poorly treat the inflammatory processes during plaque formation. Statins are useful in both lipid-lowering property and anti-inflammatory potential. However, statins and other cardiovascular drugs only prolong the progression of atherosclerotic disease. This is the main reason why scientists are still studying to overcome these present treatment problems [26].

Conclusions

Atherosclerosis is still a chronic inflammatory disease that can lead to high mortality. In recent years, there have been significant changes in alternative approaches to improving cardiovascular prevention based on evolving concepts, new data and revised targets. Among those, nanotechnology can provide a major development in the treatment and diagnosis of atherosclerosis. At present, lipid-lowering drugs and antihypertensive drugs play an important role in the treatment of atherosclerosis.

Conflict of interest

The authors declare that they have no conflicts of interests

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