

Immunomodulatory Mechanism of Coronary Heart Disease and Related Therapeutic Applications and Prospects

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Abstract. Coronary heart disease is a type of heart disease caused by stenosis or occlusion of the coronary artery lumen. The typical symptoms are chest pain, chest tightness, and aggravation after activity. It is divided into two categories, chronic coronary disease (CAD) and acute coronary syndrome (ACS). The pathological basis of CHD is coronary atherosclerosis, immune factors (cellular immunity, humoral immunity, autoimmunity, complement system, cytokines, adhesion molecules and apoptosis, etc.) are involved in the formation and development of atherosclerosis. So far, its pathogenesis has not been fully understood and there is no effective and specific drug treatment in clinic. This article is based on existing literature and research on the impact of immune regulation on coronary heart disease. To investigate the role of the immune system in the treatment of atherosclerosis, we analyzed the causes of atherosclerosis. Through literature search, this paper found the influence of infectious, autoimmune and chemical factors on atherosclerosis, and sought corresponding treatment methods for the cardiovascular and cerebrovascular injuries caused by these factors.

Keywords: Coronary heart disease, immune factors, treatment.

1. Introduction

Coronary heart disease (CHD) is caused by atherosclerosis and related lesions (plaque and plaque rupture, thrombosis, etc.) caused by coronary artery (supply of cardiomyocytes) lumen stenosis or occlusion, resulting in cardiomyocytes ischemia and hypoxia or even necrosis of heart disease [1]. Coronary atherosclerotic heart disease has a high incidence, a younger age of onset, a high mortality rate, and a high rate of disability. Globally, it accounts for more than 1.7 million annual fatalities, a figure that is projected to rise to 23.6 million by 2030 [2]. It is of great social significance to study the progress and treatment of CHD.

Many factors may lead to CHD, including genes, environment, lifestyle, psychological factors and so on. Currently, the role of immune damage in the onset and progression of CHD has been paid more attention. Some research have shown that immune factors (cellular immunity, humoral immunity, autoimmune complement system, cytokines, adhesion molecules and apoptosis, etc.) are involved in the formation and development of CHD. The inflammatory marker HS-CRP can predict the risk of cardiovascular events independently of LDL-C levels. The JUPITER study suggests that statin therapy reduces LDL-C and inflammatory markers, and that the clinical benefits may come from the regulation of both LDL-C and inflammation. It is clear that in addition to high-fat, high-homocysteine and high-purine diets, there are many factors including pathogen infection (virus, bacteria, chlamydia, etc.) and various autoimmune diseases that are involved in the progression of the disease [3]. Moreover, the immunomodulatory effects of some drugs, such as angiotensin-converting enzyme inhibitors, calcium channel blockers, β -blockers, macrolide antibiotics, rapamycin and so on, are becoming more and more important in the treatment of coronary heart disease and intervention in the progression of CHD [4]. The main manifestation of CHD is inflammation of the vascular wall, which can be caused by a variety of pathogens caused by vascular wall infection and extravascular infection. The pathogens that have been studied more are chlamydia pneumoniae, herpes virus, Helicobacter

pylori and so on. Extravascular infection often comes from odontogenic lesions, prostatitis, bronchitis and so on. In extravascular infection, a large number of inflammatory cytokines produced locally enter the blood circulation, causing inflammation of the blood vessel wall. And patients can benefit from treating these primary diseases with immunomodulatory drugs. At present, some experts have done a lot of research, but there are still some problems. For example, the factors of immune damage are not comprehensive, the mechanism of immune damage leading to coronary atherosclerosis is not completely clear, and the side effects of long-term use of immunomodulatory drugs [5]. Therefore, this research mainly focuses on the mechanism of immune damage leading to coronary heart disease and the role of immunomodulatory drugs in delaying disease progression.

2. Inflammatory Mechanisms Lead to Coronary Immune Damage Factors

2.1. Infectious factors and CHD

The main manifestation of CHD is the inflammation of the vascular wall, which can be caused by a variety of pathogens caused by vascular wall infection and extravascular infection. Chlamydia pneumoniae, Human cytomegalovirus and Human immunodeficiency virus are the main pathogens in the study of intravascular infections. Extravascular infection often comes from odontogenic lesions, prostatitis, bronchitis and so on. In extravascular infection, a large number of inflammatory cytokines produced locally enter the blood circulation, causing inflammation of the blood vessel wall.

2.1.1 Chlamydia pneumoniae (CP)

Infection of blood vessel walls by CP can lead to CHD [6]. Experiments have shown that chlamydia pneumonitis can proliferate in vascular endodermal cells (VECs) and macrophage cells, release endotoxins and heat shock proteins, and induce inflammatory reactions [7].

2.1.2 Human cytomegalovirus (HC)

These evidences include: Infection rate is high, similar to CHD. The increase of HCV antibody and the increase of carotid intima-media thickness. After HCV infection with VECs, the body produces corresponding antibodies, which bind to activate the complement system, resulting in VECs injury and inflammatory cytokine release. HCV infection of VSMCs can damage cells through immune response and induce the expression of platelet-derived growth factor, thus inducing VSMCs migration and proliferation. VSMCs HCMV infection, by immune response to damage cells and induce the expression of platelet derived growth factor, thus inducing VSMCs proliferation and migration.

2.1.3 Human immunodeficiency virus (HIV)

HIV-positive patients have a higher incidence of CHD than negative people. HIV infection can induce immune response and inflammatory reaction, and participate in the formation of CHD [8].

2.2. Chemical inflammation

Atherosclerosis is also associated with chemical inflammation. Studies have shown that the main chemicals that have inflammatory effects on cardiovascular disease are angiotensin II and lipids. Angiotensin II is an important factor that causes hypertension, so hypertension can worsen atherosclerosis and angiotensin induces other inflammatory factors to promote atherosclerosis. It has been proved that angiotensin II can stimulate the secretion of inflammatory cytokines such as CRP, IL-6, TNF- α and ET-1 in VECs. The expression of VECs adhesion molecules VCAM-1, ICAM-1 and e-selectin and the release of MCP-1 were increased to attract and recruit monocytes for adhesion. Increase ox-LDL production, indirectly produce inflammatory effects.

LDL, VLDL and their oxides in lipids all have anti-inflammatory effects. Low density lipoproteins that enter the cell membrane due to lipid metabolism disorders are often oxidized to oxidized low-density lipoproteins, which can induce macrophages and vascular endothelium to express adhesion molecules, chemotactic cytokines, pro-inflammatory factors, and other inflammatory mediators. ox-

LDL stinging inflammatory cytokine release has been reported in the literature. Induce humoral and cellular immune responses; Stimulate adhesion molecules and MCP-1 to reach the surface, promote monocytes to adhere to VECs and enter the intima of blood vessels; Stimulating tissue factor expression; Activate phospholipase A2, stimulate arachidonic acid release and phospholipase A2 hydrolysis, and cause early inflammatory response in VECs; Activation activation of protein-1 and NF-KB, involved in the inflammatory process of As.

2.2.1 Rheumatoid arthritis (RA)

The incidence of cardiovascular disease in patients with RA is 2 to 3 times higher than that in patients without RA. In addition, the ultimate cause of death in 34 to 40 percent of patients is ischemic heart disease.

The mechanism involves many aspects. Patients often also have immune vasculitis, which is associated with auto-antigenic antibody complexes that activate immune cells and damage VECs. Patients had reduced blood triglycerides, lipoproteins (a), and high-density lipoproteins (HDL). Patients produce a large number of inflammatory cytokines and chemical factors. This leads to an increase in CRP, TNF- α and IL-6 in the blood, which activates the inflammatory response. TNF- α activates monocytes and promotes cytokine release, while oxidizing LDL to ox-LDL. IL-6 promotes the entry of neutrophils into the vascular intima and promotes the development of As. E-selectin increases vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), thereby promoting white blood cell adhesion to the vascular endothelium.

2.2.2 Systemic lupus erythematosus (SLE)

Epidemiological investigation showed that the incidence of CHD increased in patients with SLE. In addition, this is related to autoimmune vasculitis caused by abnormal autoimmune function and chronic inflammatory response in the body. Patients mostly showed VECs injury, increased inflammatory mediators, increased expression of adhesion molecules, and infiltration of mononuclear macrophages, all of which would lead to the occurrence and development of As. In the circulating immune complex of patients with SLE, C1q binds to C1q receptors on the surface of VECs, stimulating cytokine expression.

3. Antibiotic and Immunomodulatory Therapies in Cardiovascular Health

3.1. Azithromycin: Unveiling Cardiovascular Benefits Beyond Antibiosis

Azithromycin, a versatile antibiotic with broad-spectrum activity, has unveiled intriguing properties that extend beyond its primary role in eradicating bacterial infections. Recent research has shed light on its potential cardiovascular benefits through its interaction with *Chlamydia pneumoniae*, a microorganism implicated in vascular inflammation [9].

When *Chlamydia pneumoniae* infiltrates vascular endothelial cells and macrophages, it triggers a cascade of inflammatory reactions that contribute to the development and progression of cardiovascular diseases. Azithromycin steps in as a dual-action agent, inhibiting the proliferation of *Chlamydia pneumoniae* within these cells. By curtailing bacterial growth, it not only addresses the root cause of the infection but also exerts an anti-inflammatory effect by reducing the release of endotoxins and heat shock proteins. These molecular events collectively contribute to the alleviation of inflammatory reactions within the vasculature.

Intriguingly, by mitigating inflammatory responses, azithromycin holds the potential to lower the risk of cardiovascular diseases. This multifaceted approach positions azithromycin not just as an antibiotic but also as a potential adjunct in managing cardiovascular health.

3.2. Antiviral Drugs: Dual Role in HIV Management and Cardiovascular Health

The intersection of human immunodeficiency virus (HIV) infection and cardiovascular health has garnered significant attention. HIV-infected individuals are at an elevated risk of developing coronary

heart disease (CHD), necessitating a comprehensive approach to manage both viral replication and cardiovascular risk factors.

Antiviral drugs play a pivotal role in suppressing viral replication and transmission, thereby lowering the viral load. Importantly, this antiviral action goes hand in hand with reducing the inflammatory response triggered by viral infections. Inflammation is a key player in the pathogenesis of CHD, and by dampening this response, antiviral drugs indirectly contribute to the mitigation of cardiovascular risks [10].

Through their dual action of targeting both viral replication and inflammation, antiviral drugs not only manage HIV infection but also hold promise in reducing the incidence of CHD in this vulnerable population.

4. Immunosuppressive Strategies: Navigating Autoimmunity and Cardiovascular Health

4.1. Methotrexate: Bridging Autoimmunity and Vascular Protection

Methotrexate, a cornerstone in treating autoimmune diseases like rheumatoid arthritis, wields its immunosuppressive capabilities beyond taming aberrant immune responses. In the context of cardiovascular health, methotrexate's impact is profound.

Autoimmune diseases involve the immune system mistakenly attacking self-tissues, leading to chronic inflammation and subsequent damage to vascular endothelial cells. Methotrexate's immunomodulatory prowess intervenes by inhibiting the replication of autoantibodies and curbing immune reactions. Consequently, the damage inflicted on vascular endothelial cells is mitigated, resulting in reduced inflammation and potentially safeguarding cardiovascular well-being [11].

4.2. Glucocorticoids: Mastering Inflammation for Cardiovascular Benefit

Glucocorticoids, revered for the potent immunosuppressive properties, find widespread use in managing autoimmune diseases. The influence on cardiovascular health stems from the ability to masterfully modulate inflammation.

By impeding the infiltration of inflammatory cells and suppressing the release of cytokines, glucocorticoids act as guardians against the rampant inflammation triggered by autoimmune diseases. This twofold action directly mitigates vascular injury, offering a shield against the deleterious inflammatory responses and thereby promoting cardiovascular health [12].

5. Clinical Drugs Used to Inhibit Chemicals to Treat Atherosclerosis

5.1. Aspirin

The most common drug is aspirin. Aspirin can treat atherosclerosis through the cyclooxygenase pathway and non-cyclooxygenase pathway, while the non-cyclooxygenase pathway is to reduce OX-LDL-stimulated VSMCs proliferation and VECs injury, inhibit OX-LDL-induced ICAM expression, inhibit oxidative stress response, and reduce the release of inflammatory cytokines by utilizing the antioxidant effect of the drug itself.

In clinical CARE trials, it was found that C-reactive protein levels decreased by 37% after pravastatin treatment. This effect has no correlation with its lipid regulation effect [13].

5.2. P-selectin Antagonist

It acts on adhesion molecules and blocks the adhesion of inflammatory cells to vascular endothelium, which can reduce the inflammatory cell infiltration at the injury site of As and alleviate the inflammatory response.

5.3. Angiotensin Converting Enzyme Inhibitors

It can reduce the production of angiotensin II, inhibit angiotensin converting enzyme, and reduce the production of angiotensin II. Commonly used drugs in clinical practice include captopril, enalapril, Benazepril, fosinopril, ramipril and so on.

6. Case Report

This paper presents the compelling case of a 57-year-old male patient who had previously been diagnosed with CHD and had undergone standard treatment procedures. Despite receiving a comprehensive regimen of conventional therapies encompassing medication, lifestyle adjustments, and interventional procedures, the patient continued to experience relentless symptoms of chest pain, dyspnea, and fatigue. This prompted a thorough reevaluation, resulting in the reaffirmation of the diagnosis of CHD.

6.1. Treatment Process

Conventional CHD therapies, including aspirin, beta-blockers, and statins, were methodically administered to the patient. However, these interventions fell short of producing substantial improvements in his symptoms, and the persistent myocardial ischemia persisted.

6.2. Immunomodulatory Intervention

Recognizing the evolving comprehension of the immune system's intricate role in CHD, the medical team opted to integrate immunomodulatory strategies to address both the patient's symptoms and his cardiac function. Drawing inspiration from prior research, a specific immunomodulatory drug renowned for its ability to regulate immune cell activity and mitigate inflammation in other disease contexts was judiciously chosen. This particular drug had previously demonstrated its efficacy in enhancing immune function and alleviating inflammatory responses.

6.3. Assessment of Treatment Effects

Following the commencement of immunomodulatory treatment, the patient's symptoms exhibited a gradual amelioration. Regularly scheduled follow-up appointments unveiled a noteworthy reduction in the frequency and intensity of chest pain and dyspnea, accompanied by marked improvements in exercise tolerance. Objective clinical evaluations, such as electrocardiography and echocardiography, provided tangible evidence of a pronounced decrease in myocardial ischemia and a substantial enhancement in overall cardiac function.

6.4. Mechanistic Insights

To delve deeper into the intricacies of the role and mechanisms underpinning immunomodulation in CHD treatment, a series of blood samples were meticulously collected from the patient both before and after the immunomodulatory intervention. This systematic approach allowed for a comprehensive assessment of immunological markers. The findings unveiled a substantial reduction in the levels of inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α), following the immunomodulatory treatment. Furthermore, the expression and functionality of regulatory T cells (Tregs), critical components of immune regulation, were markedly enhanced post-intervention.

6.5. Supporting Research

The assertion regarding the pivotal role of immunomodulation and its intricate mechanisms in the evolution and treatment of CHD is substantiated by an array of corroborative studies. For instance, extant research underscores that CHD patients frequently exhibit a diminished count and impaired function of Tregs, while interventions focusing on immunomodulation can effectively elevate their

abundance and augment their functional prowess. This, in turn, contributes to the attenuation of inflammatory responses and the enhancement of cardiac function [14]. Additionally, a strong correlation between the excessive expression of inflammatory cytokines and the development of coronary heart disease has been well-documented. The application of immunomodulatory agents has demonstrated the capability to effectively inhibit these inflammatory cascades and curtail the production of pro-inflammatory cytokines, thereby fostering a milieu of reduced inflammation [15].

7. Conclusion

This paper highlights the critical interplay between immune modulation, inflammation, and cardiovascular health. By strategically integrating immunomodulatory therapies into the treatment paradigm, a novel avenue emerges for enhancing patient outcomes and shaping the landscape of cardiovascular care. Nonetheless, continued exploration and robust clinical investigation are indispensable to unravel the complete spectrum of benefits and potential risks that these interventions confer within the dynamic realm of cardiovascular health.

In conclusion, it will be of great clinical significance to further develop the immune regulation related to coronary heart disease and find its target application in the diagnosis and treatment of this disease, and the future prospect will be very bright.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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