Progress in the Study of C5a and Coronary Heart Disease

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Abstract: This article reviews recent research progress on C5a and coronary heart disease and discusses its potential mechanisms and clinical applications in disease onset and progression. First, C5a is a highly active complement component that plays an important role in immune and inflammatory responses. In recent years, more and more studies have focused on its role in coronary heart disease. Its mechanism consists of three main aspects: inflammatory response, thrombosis and atherosclerosis.C5a exacerbates the formation and rupture of atherosclerotic plaques by activating the inflammatory pathway, promoting cytokine secretion and inflammatory cell infiltration. It also enhances platelet aggregation and coagulation factor release, thereby promoting thrombosis. Clinical studies have further validated the importance of C5a in patients with coronary artery disease and found that it may not only serve as a biomarker for cardiovascular risk prediction, but also has potential clinical diagnostic and prognostic value. In terms of treatment, clinical intervention strategies for C5a need to be further validated for safety and efficacy. In summary, the role of C5a in the development of coronary heart disease and its potential as a therapeutic target are receiving increasing attention. Future research will focus on further revealing its specific mechanism of action and optimizing the clinical application of the blocker. This not only has the potential to improve the therapeutic efficacy of coronary artery disease, but will also promote the development of complement system-related research. With the deeper understanding of C5a function and the promotion of blockers, it is expected that this target will play an increasingly important role in coronary heart disease treatment.

Keywords: C5a; Coronary Heart Disease; Inflammatory Response; Atherosclerosis; Thrombosis

1. Preface

Coronary atherosclerotic heart disease (CHD) is one of the most lethal cardiovascular diseases globally [1],bringing a heavy burden to patients and their families. With the continuous deepening of medical research, it has been gradually recognized that inflammatory response plays a key role in the occurrence, development and prognosis of CHD[2, 3].The complement system, as an important component of innate immunity, plays an important role in the inflammatory response[4],and C5a, as an important inflammatory mediator in the process of complement activation, has received extensive attention in recent years.C5a has a potent biological activity, and is able to induce recruitment, activation, and chemotaxis of inflammatory cells and promote the release of inflammatory factors by binding to C5a receptors on the surface of a variety of cells[5],which in turn participates in the pathophysiologic process of coronary heart disease. Studies have shown that plasma concentrations of C5a can be elevated several-fold under pathophysiological conditions such as coronary artery disease, resulting in increased local blood flow, smooth muscle contraction, edema, cytokine storm, mast cell degranulation and increased vascular permeability, and endothelial dysfunction[6-9].However, studies on C5a and coronary heart disease are still in the exploratory stage, and its specific mechanism of action, potential therapeutic targets, and prospects for clinical application still need to be further studied and explored in depth. The aim of this review is to comprehensively and systematically review and summarize the

latest progress of research related to C5a and coronary heart disease in recent years, and to provide reference for in-depth research and clinical practice in this field.

2. Overview of C5a

C5a is a key component of the complement system, generated by cleavage of complement C5, a small molecule polypeptide whose primary function is to act as a mediator of inflammatory responses[10].Under physiological conditions, C5a is involved in various immune responses, including chemotaxis and activation of immune cells such as neutrophils, monocytes, eosinophils and mast cells[11].In addition to this, C5a promotes cell degranulation and release of reactive oxygen species, actions that help the body defend itself against pathogens[12, 13].However, excess C5a may trigger an excessive inflammatory response, leading to tissue damage and disease development[14].C5a achieves its biological effects by binding to its specific receptor, C5aR1, a G-protein-coupled receptor that is expressed on a variety of cell types, including immune and endothelial cells, among others[15].The binding of C5a to C5aR1 activates multiple signaling pathways, leading to changes in cellular function. For example, C5a can prolong the lifespan of neutrophils by inhibiting their apoptosis, thereby enhancing the duration of the immune response[16].This mechanism plays a key role in many inflammatory diseases.C5a has also been found to be associated with a variety of diseases, such as cardiovascular, infectious, autoimmune, and neurological disorders[7, 17, 18].In coronary artery disease, the activation of the complement system and the role of C5a have received increasing attention, especially its role in atherosclerotic plaque formation[19-21].These properties make C5a a potential therapeutic target, and by interfering with C5a production or blocking its receptor C5aR, it may help to control the inflammatory response and slow down the disease process.

3. Possible Mechanisms of c5a and the Development of Coronary Heart Disease

3.1 C5a and the Inflammatory Response

As a key active component of the complement system, C5a plays an important role in mediating the inflammatory response. It accelerates the unfolding of the inflammatory response by binding to the C5a receptor (C5aR), which rapidly triggers the recruitment and activation of a range of immune cells, such as neutrophils and monocytes [11, 22, 23].In the context of coronary artery disease, C5a has been implicated as an important contributor to the escalation of inflammatory responses at the site of atherosclerotic lesions, and elevated levels may correlate with the severity of coronary lesions[19, 24].Specifically, the interaction of C5a with its receptor promotes the release of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, and enhances the infiltrative capacity of leukocytes through the upregulation of adhesion molecules, such as VCAM-1 and ICAM-1. This leukocyte infiltration and adhesion exacerbates vascular endothelial damage, leading to more subendothelial accumulation of lipids and inflammatory cells, which in turn drives atherosclerotic plaque formation and destabilization[25].These complex signals and intercellular responses ultimately cause increased instability of atherosclerotic plaques, which has a significant impact on the development and progression of coronary heart disease.

3.2 C5a and Thrombosis

C5a not only plays an important role in the inflammatory response, but also directly promotes thrombosis through several mechanisms. In patients with coronary artery disease, the instability of atherosclerotic plaques is closely related to the risk of thrombosis[26].C5a promotes thrombosis and accelerates the progression of coronary artery disease through multiple pathways. In vitro experiments have shown that C5a induces neutrophils to produce neutrophil extracellular traps (NETs), an effect that is dependent on mitochondrial reactive oxygen species (ROS) production, and that C5a induces mitochondrial ROS production by inhibiting mitochondrial STAT3 activity, thereby triggering the production of NETs and promoting arterial thrombosis[27].It has been shown that C5a also enhances platelet

activation and aggregation and promotes their adhesion to endothelial cells, thereby accelerating thrombus formation[28].In addition, C5a can stimulate monocytes and endothelial cells to release pro-inflammatory factors, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), by binding to its receptor C5aR1, which can further induce the expression of tissue factor (TF), increase coagulation activity, and promote the process of thrombosis[29].C5a plays a crucial role in coronary artery disease-associated thrombosis. plays a crucial role, and its targeted intervention may provide a new strategy for the prevention and treatment of coronary heart disease.

3.3 C5a Atherosclerosis

C5a, as a core effector molecule of complement system activation, has a multidimensional regulatory role in the pathological process of atherosclerosis. Studies have shown that overexpression of C5a significantly aggravates atherosclerotic lesions in ApoE knockout mice, suggesting its pathogenic role in disease progression[21].In addition, C5a enhances the activation of NLRP3 inflammatory vesicles through interaction with cholesterol crystals, which amplifies inflammatory signaling pathways and exacerbates atherosclerosis in coronary and carotid arteries[30].In terms of vascular calcification, the C5a-C5aR1 axis has been shown to induce endoplasmic reticulum stress and promote vascular calcification through the PERK-eIF2α-ATF4-CREB3L1 signaling pathway, which further accelerates atherosclerosis progression[31].Clinical studies have also found that elevated C5a levels are closely associated with asymptomatic carotid atherosclerosis in patients with rheumatoid arthritis, suggesting that complement activation may be one of the important mechanisms of atherosclerotic lesion formation [32].In addition, targeted interventions against C5a receptors showed some protective effects in neointimal formation after arterial injury, suggesting that the C5a-C5aR axis may be an important target for future atherosclerosis therapy [33].

4. Summary and Outlook

As a key mediator of the complement system, C5a plays an important role in the occurrence and development of coronary heart disease. Existing studies have shown that C5a not only accelerates the process of atherosclerosis by inducing inflammatory responses, but also exacerbates coronary artery disease by promoting thrombosis, affecting vascular endothelial function, and various other mechanisms. However, relevant clinical studies in the field of coronary heart disease are still at an early stage, and further validation of their efficacy and safety in practical clinical applications is needed. Future studies should continue to explore the C5a-mediated signaling pathway and its interactions with other complement components to reveal its specific mechanism of action in different stages of coronary heart disease. Moreover, large-scale, long-term follow-up clinical studies are essential to assess the value of C5a-targeted therapy in patients with coronary artery disease. With the deepening understanding of the complement system in cardiovascular disease, C5a inhibition strategies are expected to provide new directions and means for the precise treatment of coronary heart disease.

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