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The Role of the Complement System in Autoimmune Diseases and Therapeutic Targeting

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ABSTRACT

The complement system, a critical component of the innate immune system, plays a dual role in immune defense and pathogenesis, particularly in autoimmune diseases. Comprising over 30 proteins, the complement system facilitates pathogen clearance, inflammation, and immune modulation. However, its dysregulation can lead to uncontrolled activation and contribute to the development and progression of various autoimmune disorders, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), antiphospholipid syndrome (APS), and vasculitis. In these diseases, excessive complement activation triggers inflammation, immune cell recruitment, and tissue damage, exacerbating the autoimmune response. This review provides an in-depth analysis of the complement system's role in autoimmune diseases, exploring how its three activation pathways—classical, lectin, and alternative—contribute to disease pathogenesis. It also discusses key complement proteins such as C3, C5, and the membrane attack complex (MAC) in promoting inflammatory responses in these conditions. Moreover, the review highlights recent advances in therapeutic strategies targeting the complement system, including the development of C5 inhibitors like eculizumab and C3 inhibitors, which show promise in treating complement-mediated autoimmune diseases. These therapies aim to reduce inflammation and tissue destruction, offering new approaches for managing autoimmune disorders. Understanding complement dysregulation is crucial for the development of more effective treatments in the future.

Keywords: Complement system, Autoimmune diseases, Complement activation, Inflammation, Therapeutic targeting

INTRODUCTION

The complement system is a fundamental component of the innate immune system, providing a first line of defense against pathogens and playing an essential role in maintaining immune surveillance, clearing apoptotic cells, and facilitating tissue repair [1,2]. It consists of a complex network of over 30 plasma and cell membrane-associated proteins that, once activated, work in a cascade-like manner. This activation triggers a series of immune processes, including opsonization of pathogens, recruitment of inflammatory cells, and direct lysis of targeted cells through the formation of the membrane attack complex (MAC) [3]. The complement system is also closely linked to the adaptive immune system, interacting with antibodies and modulating T and B cell responses [2]. Despite its protective roles, the complement system requires tight regulation. When improperly controlled or overactivated, it can contribute to pathological inflammation and tissue damage, a feature that is particularly evident in autoimmune diseases [4]. Autoimmune diseases occur when the immune system mistakenly targets self-antigens, leading to chronic inflammation and damage to tissues and organs. Dysregulation of the complement system has been implicated in the pathogenesis of several autoimmune disorders, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), antiphospholipid syndrome (APS), and vasculitis [5]. In these diseases, complement components such as C3, C5, and MAC contribute to inflammatory processes that drive disease progression and tissue destruction. The role of the complement system in autoimmune diseases is multifaceted. It can exacerbate autoimmune pathology through the activation of inflammatory pathways, the formation of immune complexes, and the recruitment of immune cells that attack healthy tissues [4,6]. For instance, in diseases like SLE, the classical complement pathway is triggered by immune complexes containing

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autoantibodies, leading to tissue inflammation, especially in the kidneys, joints, and skin. In rheumatoid arthritis, complement activation contributes to synovial inflammation and joint destruction, while in multiple sclerosis, complement components promote demyelination and neuronal damage in the central nervous system [7].

The growing understanding of the complement system's role in autoimmune diseases has spurred interest in therapeutic strategies aimed at targeting specific components of the complement cascade [8]. By inhibiting key complement proteins, it is possible to reduce inflammation and prevent further tissue damage without completely shutting down the immune response. Therapies such as C5 inhibitors (e.g., eculizumab) and C3 inhibitors are already in clinical use or under investigation, offering new hope for patients with complement-mediated autoimmune diseases [9,10]. This review will explore the mechanisms by which the complement system contributes to autoimmune diseases, the key complement pathways involved, and current and future therapeutic strategies aimed at modulating complement activity to treat these conditions effectively.

Overview of the Complement System

The complement system operates as a series of enzymatic reactions that lead to the activation of its three main pathways: the classical, lectin, and alternative pathways. Each pathway converges at the activation of complement component C3, leading to the formation of the membrane attack complex (MAC) and subsequent cell lysis [11]. The pathways are initiated by different stimuli:

1. Classical Pathway: Triggered by antigen-antibody complexes, making it an important link between the adaptive and innate immune systems.
2. Lectin Pathway: Initiated by mannose-binding lectin (MBL) and other pattern recognition molecules binding to microbial surfaces.
3. Alternative Pathway: Constantly activated at low levels through a process known as "tick-over," where spontaneous hydrolysis of C3 leads to its activation. This pathway is self-amplifying and provides an immediate response to pathogens or damaged cells [13].

Once activated, these pathways promote opsonization, inflammation, and direct killing of pathogens through the formation of the MAC. Additionally, complement proteins such as C3b and C5a act as potent inflammatory mediators, recruiting immune cells to the site of infection or injury [14].

The regulation of the complement system is critical to prevent excessive inflammation and tissue damage. Several regulatory proteins, including complement factor H, C1 inhibitor, and decay-accelerating factor (DAF), work to control complement activation and ensure that it is directed towards pathogens rather than host tissues [15]. However, when this regulation fails, the complement system can become a driver of pathological inflammation in autoimmune diseases.

The Role of the Complement System in Autoimmune Diseases

Dysregulation of the complement system is a common feature in many autoimmune diseases. Whether through excessive activation or impaired regulation, complement proteins can exacerbate autoimmune responses by promoting inflammation, cell lysis, and the destruction of healthy tissues [16]. Below are some of the key autoimmune diseases in which complement plays a central role:

1. Systemic Lupus Erythematosus (SLE):

In SLE, the complement system is both a marker of disease activity and a contributor to its pathogenesis. SLE is characterized by the production of autoantibodies that form immune complexes, which can trigger the classical pathway of complement activation [17]. These immune complexes deposit in tissues such as the kidneys, joints, and skin, leading to inflammation and tissue damage. Reduced levels of complement proteins like C3 and C4 are often used as markers of disease flare-ups, while mutations or deficiencies in regulatory proteins (e.g., C1q, C2, C4) have been linked to a higher risk of developing SLE [14].

2. Rheumatoid Arthritis (RA):

In RA, chronic inflammation of the joints is driven by immune complex deposition and complement activation, particularly through the classical and alternative pathways [18]. The inflammatory mediator C5a, generated during complement activation, recruits neutrophils and other immune cells to the joints, exacerbating tissue damage. Complement activation products, such as C3b and MAC, contribute to synovial inflammation, cartilage degradation, and bone erosion, characteristic of advanced RA [19].

3. Multiple Sclerosis (MS):

MS is a neurodegenerative autoimmune disorder where the immune system attacks the myelin sheath of nerve cells in the central nervous system (CNS). The complement system, particularly C3 and C5 activation products, contributes to the inflammation and demyelination seen in MS [20] Myelin-reactive antibodies can trigger the classical pathway, leading to complement-mediated damage to neurons and glial cells. Complement components have been found in active MS lesions, indicating ongoing complement activation in the CNS [21].

4. Antiphospholipid Syndrome (APS):

APS is an autoimmune disorder characterized by the presence of antiphospholipid antibodies that promote thrombosis and pregnancy complications. The complement system plays a significant role in APS by enhancing

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clot formation and contributing to the inflammatory environment. C5a, for instance, recruits inflammatory cells that can damage endothelial cells, promoting thrombosis. Blocking complement activation has been shown to reduce thrombosis risk in experimental models of APS [22,23].

5. Vasculitis:

In vasculitis, inflammation of blood vessels is often driven by complement activation. The classical pathway is commonly activated by immune complexes, leading to the recruitment of neutrophils and macrophages through the release of C3a and C5a. This results in blood vessel inflammation, narrowing, and damage, with potential impacts on organs such as the kidneys, lungs, and skin [24].

Therapeutic Targeting of the Complement System in Autoimmune Diseases

Given the central role of complement activation in autoimmune diseases, targeting the complement system has emerged as a promising therapeutic strategy [25]. Several approaches have been developed to inhibit complement activation and reduce tissue damage in autoimmune diseases:

1. C5 Inhibitors:

Eculizumab, a monoclonal antibody that blocks C5, has been a revolutionary therapy for complement-mediated diseases. By preventing the cleavage of C5 into C5a and C5b, eculizumab inhibits the formation of the MAC, thus protecting cells from complement-mediated lysis [26]. It has been approved for treating paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS), and is being explored for other complement-driven autoimmune diseases [24].

2. C3 Inhibitors:

Targeting C3, a central component of the complement system, has broader effects since C3 is involved in all three activation pathways. C3 inhibitors like pegcetacoplan, a synthetic peptide, prevent C3 cleavage and have shown efficacy in diseases like PNH. C3 inhibition holds promise for a range of autoimmune diseases, including SLE and RA, where excessive complement activation is a key driver of pathology [27].

3. C1q Inhibitors:

Inhibiting C1q, which initiates the classical pathway, may be beneficial in diseases driven by immune complexes, such as SLE. Targeting C1q can reduce complement activation at its source, potentially decreasing immune complex deposition and inflammation [28].

4. Complement Regulators:

Enhancing the activity of complement regulatory proteins, such as factor H and DAF, is another potential therapeutic approach. By restoring the natural regulation of complement activation, these therapies aim to limit excessive complement activity without completely shutting down the system, maintaining the balance needed for immune defense [29].

5. Complement Blockade in Combination Therapies:

Combining complement inhibitors with other immune-modulating therapies, such as B-cell depleting agents or immune checkpoint inhibitors, may provide synergistic effects in treating autoimmune diseases. Such combination therapies could target both the cellular and humoral components of the immune response, offering more comprehensive disease control [30].

CONCLUSION

The complement system plays a dual role in immune defense and autoimmunity, acting as both a protector against pathogens and a contributor to autoimmune disease when dysregulated. In autoimmune diseases like SLE, RA, MS, and APS, complement activation drives inflammation, tissue damage, and disease progression. Understanding the intricate mechanisms by which the complement system contributes to autoimmune pathology has opened new avenues for therapeutic intervention. Targeting complement components such as C5, C3, and C1q has shown promise in reducing disease activity and preventing further damage in autoimmune patients. With ongoing advances in complement-targeted therapies and the exploration of combination approaches, the future holds significant potential for improved treatments and outcomes in patients suffering from autoimmune diseases. Continued research into the complex interplay between complement activation and immune regulation will be crucial in developing more precise and effective therapies for these chronic and often debilitating conditions.

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