Perspective

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Complement-targeted therapy for autoimmune diseases

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Abstract: The success and safety seen in treating complement-mediated hemolysis conditions has sparked the development of targeted therapies for rare autoimmune diseases, with expansion to more common autoimmune conditions. Various classes of drugs, including small molecules, peptides, monoclonal antibodies, and small interfering RNA (siRNA), are undergoing development to specifically address complement activity. A dual approach targeting both complement and other immune components may be required for autoimmune diseases characterized by inflammation and complex pathogenic mechanisms. siRNA, which suppresses complement production, is emerging as a potent therapeutic tool. Combining a complement-blocking siRNA drug with a treatment that reduces autoantibodies could prove clinically feasible and impactful in managing these conditions.

Keywords: complement; autoimmune diseases; siRNA; dual target

Introduction

Complement was first discovered by Jules Bordet as heat-labile serum proteins which assist antibodies in killing bacteria and lysis of red blood cells (reviewed in Ref. [1]). Since then, our comprehension has evolved to recognize over 50 proteins within the complement system circulating in the body, encompassing effectors, receptors, amplification factors, and inhibitory factors present on cell surfaces and within intracellular compartments [2]. While renowned for its role in innate and adaptive immunity against microbes, the functions of complement system extend beyond, interacting with other systems like coagulation [3]. In a healthy state, this system is finely regulated, but its dysregulation plays a significant role in various autoimmune conditions.

The cascade activation of complement system can be initiated by any of the three pathways, namely, classical, alternative and lectin pathway. All the three pathways converge at the activation of the pivotal component, C3, and subsequently leads to activation of C5, and C6–9. The cleaved C3 and C5 components, C3a, C3b and C5a are effector molecules mediating granulocytes and dendritic cells for inflammation (Figure 1A). Consequently, complement-targeted therapies primarily focus on blocking C3 and C5 activities, although developments targeting other components such as C1 and C2 are ongoing. Approved drugs include small molecules like avacopan, peptides such as pegcetacoplan and zilucoplan, and monoclonal antibodies like eculizumab and ravulizumab, used to treat various conditions [2, 4]. Up to date, eculizumab and ravulizumab, monoclonal antibodies blocking C5, stand as the most successful complement-targeted therapies, particularly in treating paroxysmal nocturnal hemoglobinuria (PNH). However, the landscape of complement-targeted therapy for autoimmune diseases is burgeoning and promising. Current developments expand into utilizing small interfering RNA (siRNA). Additionally, research is exploring recombinant adeno-associated virus-mediated expression of complement inhibitors in preclinical models of autoimmune diseases affecting the central nervous system [5]. This essay briefly discusses approved complement-targeted therapies for autoimmune diseases and argues that concurrently targeting complement and other immune components are required to achieve impactful efficacy for autoimmune diseases with prominent inflammation.

Monoclonal antibody-based complement-targeted therapy

Both eculizumab and ravulizumab have received approval for treating myasthenia gravis (MG), with eculizumab

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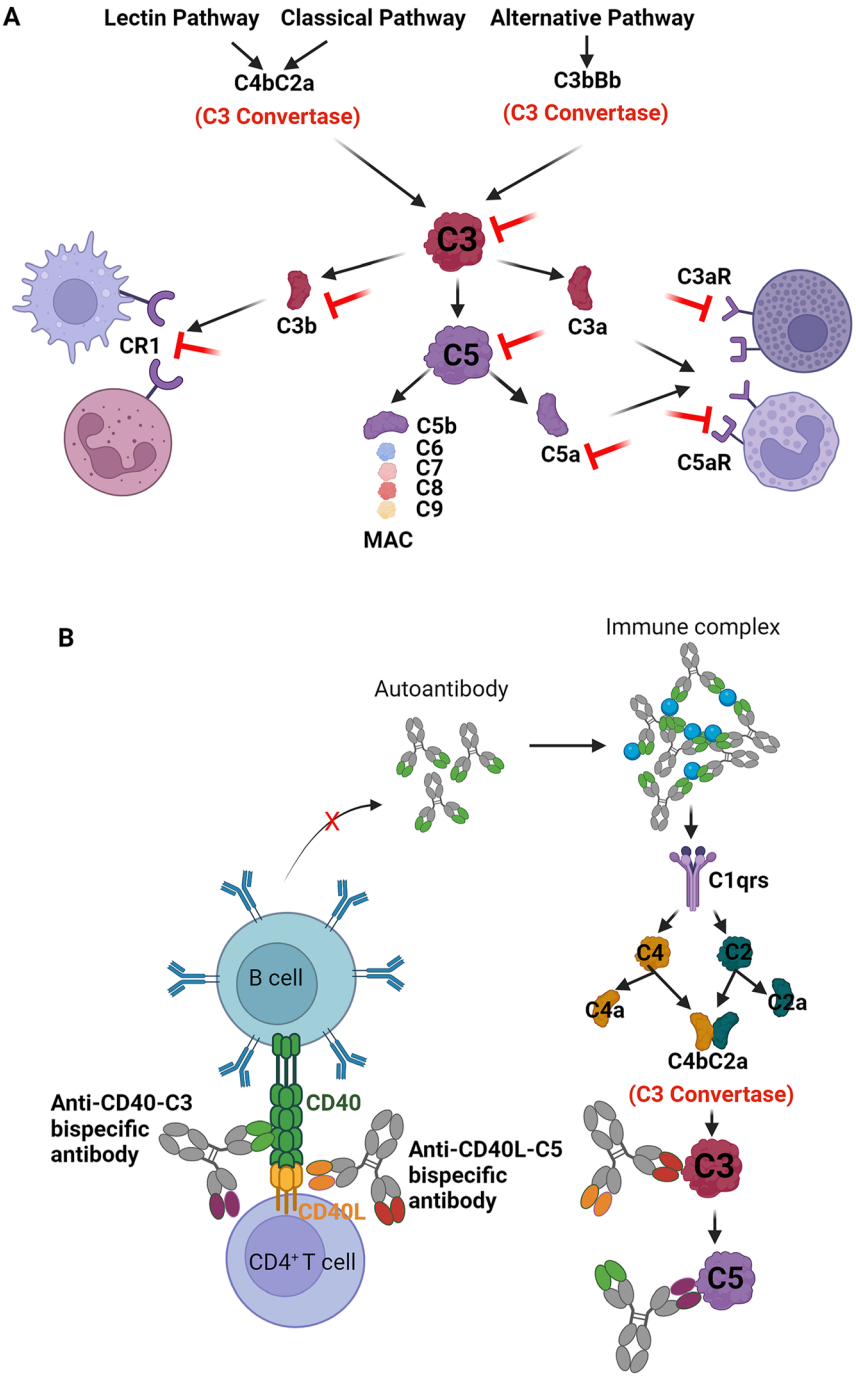

Figure 1: Complement-targeted therapy for autoimmune diseases. (A) Pathways leading to complement activation and key points (indicated by "⊥") for targeting complement activation and function. (B) Examples for dual targeting T–B cell co-stimulation and complement by bispecific antibodies.

additionally approved for managing neuromyelitis optica spectrum disorders (NMOSD). Insights from animal models and observations in MG patients underscore the pivotal role of complement in the pathogenesis of MG. In approximately 85 % of generalized MG cases with anti-acetylcholine receptor (AchR) autoantibodies, complement activation occurs due to these antibodies. This activation leads to the participation of C5b–9, the membrane attack complex, contributing to the depletion of AchR on the postsynaptic membrane, consequently compromising neuromuscular transmission [6]. Studies on C5 gene knockout mice, despite developing anti-AchR autoantibodies, demonstrated an absence of junctional injury and muscle weakness. This highlights C5 as a viable therapeutic target for MG [7]. Notably, both eculizumab and ravulizumab have demonstrated efficacy by binding to C5, inhibiting its activation, and consequently improving muscle strength and the quality of life in MG patients [8, 9]. Assessments of blocking C5 activity in MG have indicated a favorable

benefit-risk profile. Common adverse effects include pharyngitis and upper respiratory infections, mostly graded as mild to moderate. Importantly, no serious cases of meningococcal infections were reported in MG patients, despite occurrences in other indications for eculizumab and ravulizumab. Nonetheless, it is crucial to administer meningococcal vaccination at least two weeks before the initial dose of these therapeutic antibodies.

Activation of the complement system in NMOSD is instigated by the presence of anti-aquaporin 4 (AQP4) autoantibodies, leading to the cytotoxicity of astrocytes. By preventing C5 cleavage, eculizumab effectively mitigates the relapse of debilitating attacks in individuals with anti-AQP4 positive NMOSD [10]. Moreover, extended usage of eculizumab has demonstrated a favorable safety profile in the long term [11].

Indeed, while eculizumab has shown effectiveness in addressing autoimmune diseases, its impact on systemic lupus erythematosus (SLE) is confined to cases displaying thrombotic microangiopathy (TMA) features. This limited efficacy in SLE highlights the complexity of its pathogenic mechanisms. Despite substantial evidence indicating the involvement of complement in pathogenesis of SLE [12], it suggests that SLE entails more intricate underlying factors, necessitating multiple targets beyond complement for effective treatment strategies.

An anti-C5 antibody fused with factor H, known as KP-104, functions by obstructing both the upper stream of the alternative pathway and the terminal pathway of complement activation. This dual-action mechanism holds the potential for a more profound suppression of complement activity than what single inhibitors targeting either C3 or C5 alone can achieve. Early indications from the phase I trial of this anti-C5-factor H fusion protein suggest an acceptable safety profile [13]. Currently, it is being investigated in clinical trials for treating conditions such as PNH, TMA secondary to SLE (clinical trial: NCT05504187), and IgA nephropathy. To assess its therapeutic efficacy, comparative studies against either C3 or C5 monotherapy in these conditions will be essential. This approach could offer valuable insights into the potential advantages of inhibition of two complement activation pathways provided by this fusion protein in managing these complement-mediated diseases.

Peptide-based complement inhibitor

Zilucoplan, a macrocyclic peptide C5 inhibitor, has recently gained approval for the treatment of generalized MG in individuals positive for AchR antibodies [4]. This approval presents a new therapeutic option for MG patients. However, determining the comparative efficacy of this novel drug against eculizumab or ravulizumab awaits head-to-head trials for a comprehensive assessment. An aspect that might impact its practical use is the requirement for daily subcutaneous injections. This regimen could potentially pose inconvenience compared to the administration schedules of other medications used for MG. Understanding the comparative effectiveness and the potential differences in convenience and tolerability between zilucoplan and existing treatments will be crucial in shaping its role in managing MG.

Small molecule complement inhibitor

Avacopan, a small molecule that works by inhibiting the C5a receptor to prevent C5a-induced chemoattraction of neutrophils, has demonstrated promising results in combination with either cyclophosphamide or rituximab. Specifically, in anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis, avacopan combined with these therapies has shown superiority over corticosteroids in inducing remission [14]. This success suggests that avacopan holds the potential to replace corticosteroids, which often pose a significant burden on patients with ANCA associated vasculitis. Furthermore, these findings reinforce the safety and efficacy of targeting complement therapy in yet another autoimmune condition.

While the use of avacopan as a monotherapy in other autoimmune diseases may not yield similar results, its potential role in reducing or eliminating the need for corticosteroids warrants further investigation. Exploring its ability to spare patients from corticosteroid-related side effects could be a significant stride in enhancing the management of various autoimmune conditions.

siRNA therapeutics to block complement production

siRNA therapy, leveraging RNA interference mechanisms, offers precise gene knockdown capabilities [15]. Initially directed at genes considered challenging to target for rare diseases, siRNA therapeutics have advanced into a wide spectrum of genes across various conditions such as hypercholesterolemia, hypertension, cancer, infectious diseases, and autoimmune diseases [15]. Complement genes have

emerged as targets for siRNA therapeutics in complement-mediated diseases.

However, a significant hurdle in developing siRNA therapeutics is effectively delivering siRNA to specific tissues and cells. Currently, the most successful and approved siRNA drugs are tailored for delivery to hepatocytes. This approach involves conjugating siRNA to N-acetylgalactosamine (GalNAc), which binds with high affinity to the asialoglycoprotein receptor (ASGPR). ASGPR is predominantly expressed in hepatocytes rather than other cell types, making complement genes in hepatocytes ideal targets for siRNA. For instance, cemdisiran, a GalNAc-conjugated siRNA targeting C5, is under development for conditions like PNH, MG, and IgA nephropathy. A phase I clinical trial of cemdisiran in PNH demonstrated promising results by rapidly and robustly suppressing C5 production for 13 months while maintaining an acceptable safety profile [16]. Additionally, a proof-of-concept study indicated that cemdisiran achieved a clinically significant reduction in proteinuria in patients with IgA nephropathy. However, further investigations are essential to confirm its efficacy [17].

Similarly, the C3 gene is also being targeted by siRNA for developing therapies for PNH and autoimmune diseases. This approach holds substantial promise in offering highly specific and targeted treatments for complement-mediated conditions, although ongoing research is necessary to validate their efficacy across various diseases.

Dual targeting on complement and other immune components for autoimmune diseases

Absolutely, the pathogenesis of many autoimmune diseases, unlike PNH, involves a multifaceted mechanism where complement activation is just one facet among others. Diseases like SLE, anti-phospholipid antibody syndrome (APS), Sjogren syndrome, and rheumatoid arthritis are characterized by autoantibody production, with complement activation being triggered by these autoantibodies, often via the classical pathway. Moreover, the lectin and alternative pathways might also contribute to complement activation in these conditions.

Targeting both autoantibody production and complement activation concurrently holds promise for achieving more effective therapeutic outcomes. Bispecific therapeutic antibodies could potentially address this by simultaneously interfering with key pathways. For instance, CD40–CD40L interaction is vital for stimulating autoantibody production [18]. A bispecific antibody can be designed against CD40 or CD40L to disrupt the interaction between T helper cells and antibody-producing B cells, while also targeting C3 or C5 to block complement activation (Figure 1B).

This approach offers the advantage of immediate anti-inflammatory effects by acting on effector molecules like C3 or C5 while also reducing complement activation by suppressing autoantibody production. However, determining the optimal format of such bispecific antibodies will require careful consideration of pharmacokinetics and pharmacodynamics. For instance, assessing whether a single antibody with dual specificity to CD40/CD40L and C3/C5 is feasible, or if a construct involving a nanobody (specific to C3/C5) tagged to an antibody targeting CD40/CD40L might be more effective.

Additionally, designing a cleavable nanobody targeting C3/C5 that can be released *in vivo* could potentially enhance its penetration into inflamed tissues, improving its efficacy at sites of inflammation. This innovative approach could pave the way for more tailored and effective treatments for complex autoimmune diseases by concurrently addressing multiple key pathological pathways.

Alternatively, combining siRNA-mediated suppression of complement production (such as targeting C3 or C5) with therapies that aim to suppress autoantibody production presents a clinically feasible approach. The robust and durable suppression demonstrated by siRNA in reducing C5 production makes it an attractive candidate for combination therapy [16]. By concurrently targeting both pathways – complement production and autoantibody generation – this combined approach can offer a comprehensive and potentially more effective treatment strategy for autoimmune diseases. This synergy between different therapeutic modalities, leveraging the strengths of each approach, has the potential to yield improved clinical outcomes by addressing multiple facets of the complex pathogenesis seen in autoimmune diseases. Further research and clinical trials will be crucial in determining the safety, efficacy, and optimal combinations for such dual-targeted therapies.

Concluding remarks

Complement plays a crucial role in the innate immune system in host defense, yet aberrant activation or dysregulation of the complement system contributes to a spectrum of diseases. While complement-targeted therapies have demonstrated safety and efficacy in conditions characterized by hemolysis and certain autoimmune diseases, their potential extends to broader applications. Autoimmune diseases characterized by inflammation, known for their multifaceted and complex pathogenic mechanisms, may require more comprehensive therapeutic approaches. This could

involve not only targeting the complement system but also combining these therapies with interventions aimed at other immune components. The anticipated evolution of complement-targeted therapeutic modalities, especially when integrated with strategies addressing different immune pathways, holds promise for effectively managing autoimmune diseases. This multifaceted approach acknowledges the intricate interplay between various components of the immune system and aims to create more tailored and effective treatments for these conditions. Ongoing research and development in this field are crucial for the advancement of therapies that address the diverse and complex nature of autoimmune diseases.

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