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Review

New milestones ahead in complement-targeted therapy

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ABSTRACT

The complement system is a powerful effector arm of innate immunity that typically confers protection from microbial intruders and accumulating debris. In many clinical situations, however, the defensive functions of complement can turn against host cells and induce or exacerbate immune, inflammatory, and degenerative conditions. Although the value of inhibiting complement in a therapeutic context has long been recognized, bringing complement-targeted drugs into clinical use has proved challenging. This important milestone was finally reached a decade ago, yet the clinical availability of complement inhibitors has remained limited. Still, the positive long-term experience with complement drugs and their proven effectiveness in various diseases has reinvigorated interest and confidence in this approach. Indeed, a broad variety of clinical candidates that act at almost any level of the complement activation cascade are currently in clinical development, with several of them being evaluated in phase 2 and phase 3 trials. With antibody-related drugs dominating the panel of clinical candidates, the emergence of novel small-molecule, peptide, protein, and oligonucleotide-based inhibitors offers new options for drug targeting and administration. Whereas all the currently approved and many of the proposed indications for complement-targeted inhibitors belong to the rare disease spectrum, these drugs are increasingly being evaluated for more prevalent conditions. Fortunately, the growing experience from preclinical and clinical use of therapeutic complement inhibitors has enabled a more evidence-based assessment of suitable targets and rewarding indications as well as related technical and safety considerations. This review highlights recent concepts and developments in complement-targeted drug discovery, provides an overview of current and emerging treatment options, and discusses the new milestones ahead on the way to the next generation of clinically available complement therapeutics.

Contents

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1. Introduction

Therapeutic inhibition of the human complement system is far from a recent concept, and the use of complement inhibitors for the treatment of arthritic diseases or transplantation-related complications was already suggested almost 50 years ago [1,2]. Yet despite several breakthroughs and tremendous progress in target characterization and inhibitor design, the translation of this appealing proposition into the clinic has taken way more time and effort than anticipated [3–5]. It has only been in the past decade that complement-targeted therapy has finally moved into the awareness of the broader research community, clinicians and the pharmaceutical industry alike. The introduction of the first complement-specific inhibitors to the clinic and the discovery of new diseases strongly associated with inappropriate complement activation have clearly contributed to this important milestone. Meanwhile, complement inhibitors are being successfully used in several diseases, numerous novel inhibitors have entered clinical development, and our growing clinical experience is finally allowing an evidence-based discussion about the potential and limitations of this approach [5–7]. Along the way, the field has seen a remarkable diversification in terms of targets, indications, and inhibitory concepts, suggesting an even broader application of complement inhibitors in the clinic.

The attractiveness and challenges of selecting the complement system as a target for therapeutic intervention are both founded in its intricate functional and molecular organization [8–10]. As a key part of the innate host defense machinery, complement contributes to the rapid recognition and elimination of particles, such as microbial intruders or apoptotic cells, that impose a potential threat. The response has to be rapid and comprehensive to prevent risk to the host, but selective enough to avoid damage to healthy cells. Complement typically achieves this delicate balance by employing a cascade-type network of close to 50 proteins, including activators, regulators, and receptors (see below and Fig. 1), and through extensive crosstalk with other defense systems ranging from innate and adaptive immune pathways and the cytokine system to coagulation [8–10].

However, the sheer number of interactions and processes involved in this immune triage also renders complement prone to error, with potentially devastating clinical consequences [11,12]. For example, transplants and biomaterials are often recognized as foreign intruders that induce an “appropriate” complement response against an inappropriate target. Massive confrontation with infection- or damage-related triggers, such as during sepsis or trauma, can lead to an excessive complement-driven inflammatory reaction that can cause more damage than the underlying insult. An inability to efficiently clear immune complexes or accumulating debris can contribute to autoimmune, age-related, and neurodegenerative disorders. Also, in many cases, dysregulation of the complement network as a result of deficiencies, gain- or loss-of-function mutations, and other genetic alterations, will exacerbate tissue damage and inflammation initiated by various causes.

The unique position of complement as an early danger sensor, acting directly on the triggering cell or material surface, and as an orchestrator of downstream cellular and humoral immune responses makes complement an interesting pharmacological target [6,7]. Inhibiting or reshaping the complement response can prevent much of the disease-driven damage before it propagates further and may be more efficient than blocking individual cytokines or other later-stage mediators. Yet the complexity and diversity of the complement reaction and crosstalk also impose challenges, and it is unlikely that a single therapeutic approach will be effective on all complement-related disorders. Moreover, some clinical conditions may be associated with but not dominated by complement activity, and may therefore not benefit significantly from complement-targeted intervention. The identification of promising indications, the selection of the appropriate complement target, and the choice of the ideal inhibitors are therefore critical for arriving at a successful therapeutic strategy.

2. Spoiled for choice: points of intervention in the complement cascade

2.1. The complement system in health, disease and therapy

In order to achieve selectivity toward foreign and altered cells while allowing rapid reactivity, complement relies on a tiered and closely regulated cascade system (Fig. 1) [8,10]. Circulating recognition molecules detect damage- or pathogen-associated molecular patterns on target surfaces and induce distinct complement activation routes. The classical pathway (CP) is primarily triggered by the binding of C1q to antibody-antigen complexes, whereas initiation of the lectin pathway (LP) typically involves the recognition of carbohydrate structures by mannose-binding lectin (MBL), ficolins, or certain collectins. These recognition events lead to the activation of the plasma proteins C4 and C2 by recognition molecule-associated serine proteases and the formation of C3 convertases on the activating surface. Binding of the abundant plasma component C3 to these convertases induces its cleavage, with covalent deposition of the opsonin C3b. In addition, continuous “tick-over” activation of C3 in solution and/or on surfaces via the alternative pathway (AP) also leads to C3b deposition.

Whereas healthy host cells express and recruit a panel of regulators to keep activation in check, the complement response is quickly amplified on non- or insufficiently protected surfaces, culminating in the generation of potent effectors. Enabled by two serine proteases (factors B and D), surface-deposited C3b can form additional C3 convertases to transform more C3 into C3b, thereby generating an amplification loop that is fueled by the AP and often dominates the overall response. An increasing density of C3b gradually leads to a shift in convertase reactivity toward complement component C5, the cleavage of which results in the generation of C5b and formation of lytic or sublytic membrane attack complexes (MAC).

The activation of C3 and C5 also leads to the release of the anaphylatoxins C3a and C5a, respectively, which act as potent immune modulators. C5a, in particular, has strong chemotactic and pro-inflammatory activities that, among other effects, recruit immune cells to the site of activation. The opsonins C4b and C3b and their degradation fragments (e.g., iC3b, C3dg) bind to various complement receptors (CR) and mediate adherence and immune complex removal (via CR1), phagocytosis (mostly via CR3, CR4, and CRIg),