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Developments in anti-complement therapy; from disease to clinical trial

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ABSTRACT

The complement system is well known for its role in innate immunity and in maintenance of tissue homeostasis, providing a first line of defence against infection and playing a key role in flagging apoptotic cells and debris for disposal. Unfortunately complement also contributes to pathogenesis of a number of diseases; in some cases driving pathology, and in others amplifying or exacerbating the inflammatory and damaging impact of non-complement disease triggers. The role of complement in pathogenesis of an expanding number of diseases has driven industry and academia alike to develop an impressive arsenal of anti-complement drugs which target different proteins and functions of the complement cascade. Evidence from genetic and biochemical analyses, combined with improved identification of complement biomarkers and supportive data from sophisticated animal models of disease, has driven a drug development landscape in which the indications selected for clinical trial cluster in three 'target' tissues: the kidney, eye and vasculature. While the disease triggers may differ, complement activation and amplification is a common feature in many diseases which affect these three tissues. An abundance of drugs are in clinical development, some show favourable progression whereas others experience significant challenges. However, these hurdles in themselves drive an ever-evolving portfolio of 'next-generation' drugs with improved pharmacokinetic and pharmacodynamics properties. In this review we discuss the indications which are in the drug development 'spotlight' and review the relevant indication validation criteria. We present current progress in clinical trials, highlighting successes and difficulties, and look forward to approval of a wide selection of drugs for use in man which give clinicians choice in mechanistic target, modality and route of delivery.

1. Introduction

Scientists have strived for decades to develop drugs to treat complement-mediated diseases. By the end of the 20th century, many anti-complement agents had shown promise *in vitro* and in animal models, but few drug candidates had progressed to man and those that did were not developed further. Among the preclinical molecules being tested at that time were antibodies against complement components which blocked function, such as anti-mouse C5 and anti-human C5 (Frei et al., 1987; Thomas et al., 1996); their function *in vitro* and efficacy in animal models of disease was readily established (De Vries et al., 2003; Huugen et al., 2007; Ravirajan et al., 2004). By the early 21st century the humanised anti-human C5 monoclonal antibody, eculizumab, was progressing through clinical development and, in 2007, it was approved by the FDA for use in the rare but devastating disease: paroxysmal nocturnal haemoglobinuria (PNH) (Brodsky et al., 2008; Hillmen et al., 2006; Rother et al., 2007). Clinical validation of anti-complement therapy was a landmark in complement drug discovery; this breakthrough, combined with ground-breaking data emerging from genome wide association studies (GWAS), which demonstrated key roles of complement in wide-spread disease (Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005; Klein et al., 2005), drove a renaissance in anti-complement drug discovery. This has brought us to the current day with many new drugs progressing through late stage clinical development and numerous others in discovery or preclinical stages (Morgan and Harris, 2015; Ricklin et al., 2018).

There are a number of challenges associated with developing drugs against complement, including the sheer quantity of circulating protein, the central role of complement in fighting infection, and the identification of an appropriate target and an appropriate disease, or drug indication (Harris, 2018). In a number of diseases, complement plays a driving role in pathogenesis, whereas in others, complement is an 'exacerbator' of disease, inducing increased pathology initiated by a different disease trigger, thus driving inflammation and tissue damage

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(Ricklin et al., 2016). PNH is an example of the former, where a deficiency in complement regulators renders erythrocytes and other cells, such as platelets, susceptible to complement attack and subsequent lysis or activation (Hill et al., 2017; Hillmen et al., 1992). In this disease, identification of an appropriate drug target is less challenging as the pathogenic mechanism is clear; inhibition of MAC formation using eculizumab prevents intravascular haemolysis and rapidly improves quality of life for patients. The choice of target may not be so clear in other potential indications, and even in PNH, the quest for optimal target selection continues and many drug candidates are currently being evaluated. In the last decade, technological advances have accelerated genetic and biochemical analyses to the point where understanding of intricate disease mechanisms is facilitated and rationale for specific indication selection is strengthened. The number of potential targets in the complement system is expanding as the role of complement beyond lysis and in cross-talk with other biological systems, such as coagulation, is becoming clearer. Companies and academic institutes are developing drugs which target every pathway in the system and these drugs include small molecules, peptides, biologics, antibodies and DNA-based therapeutics.

Due to the cascade nature of complement and the large number of proteins involved, selecting distinct points of intervention may result in different therapeutic effects. For a detailed insight into the function of the complement system we refer to recent reviews on the topic and only provide a brief overview of the system here (Fig. 1) (Holers, 2014; Ricklin and Lambris, 2013). In most cases, complement is triggered by foreign or altered surfaces. In the classical pathway, recognition of immune complexes (and other non-immunoglobulin moieties) by C1q activates the associated serine proteases, C1r and C1s, which cleave the plasma proteins C2 and C4 to form a C3 convertase complex (C4b2a) on the activating surface. The same result is achieved when pattern recognition proteins of the lectin pathway (mannose-binding lectin [MBL], ficolins, collectins) bind to pathogen carbohydrate patterns and induce MBL-associated serine proteases to cleave C2/C4. The generated C3 convertases activate C3, resulting in the deposition of C3b (opsonisation) and the release of C3a. Through interplay with the proteases factor B and D (FB, FD), surface-bound C3b forms additional C3 convertases. The alternative pathway is primarily responsible for the rapid amplification of opsonisation on unprotected cells and also provides a means of constant background activity. The continuous deposition of C3b and stabilisation of convertases by properdin leads to a gradual shift to the assembly of C5 convertases, which cleave C5. Whereas the released C5a is among the strongest chemoattractants and pro-inflammatory modulators, primarily via binding to C5a receptor 1 (C5aR1), the C5b fragment can induce the assembly of membrane attack complexes (MAC) that damage or induce lysis of attacked cells. To

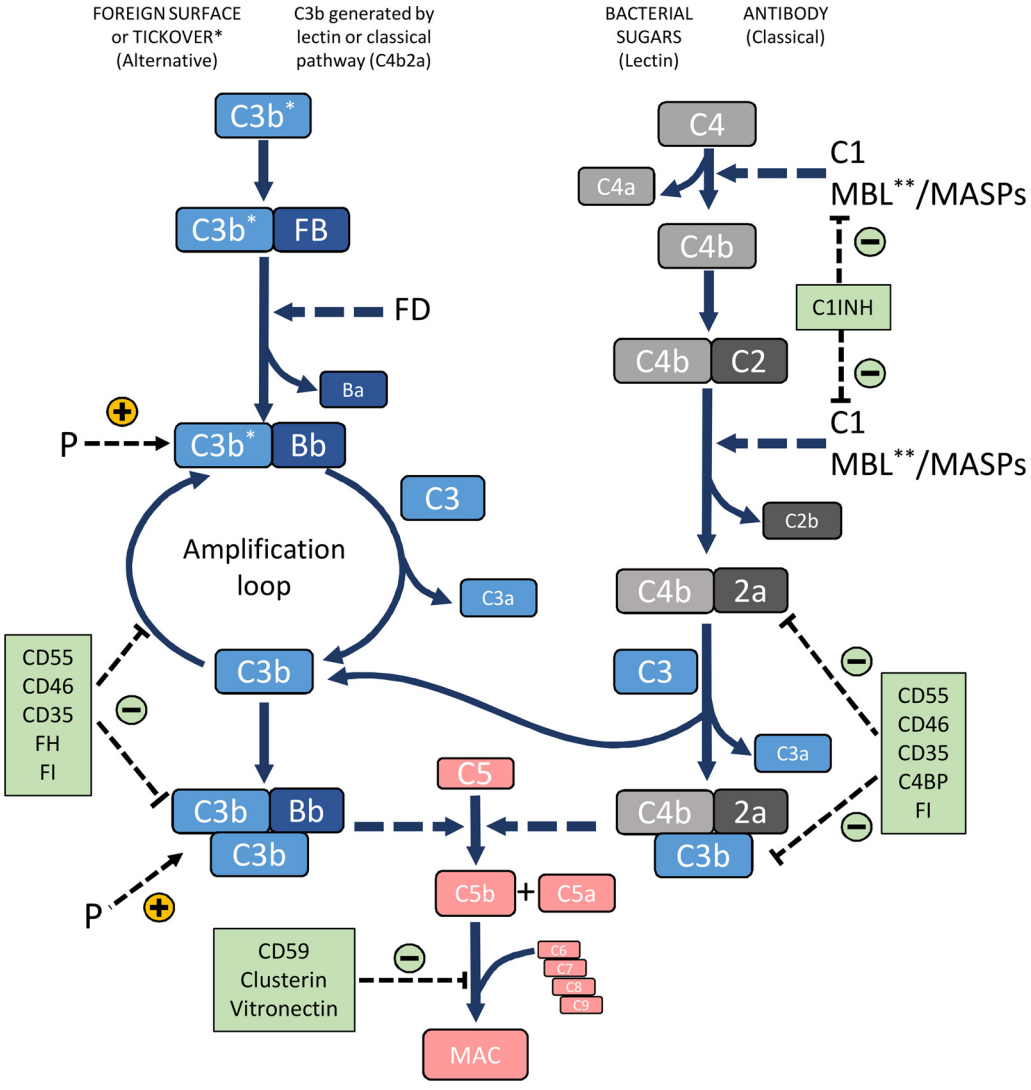

Fig. 1. Activation and control of the complement cascade. Activated C3 (C3b) deposited on a target surface can bind factor B (FB) which is activated by factor D (FD) to form the C3-cleaving enzyme (convertase) C3bBb. This enzyme cleaves further C3 to C3a and C3b, the latter decorates the surface (opsonisation) or binds the C3 convertase to form the C5 convertase, C3bBbC3b. Both the C3 and C5 convertase can be stabilised by properdin (P). Activation of the classical and lectin pathways results in covalent binding of C4b to the target surface, this binds C2 which is activated by C1r/s or the mannose-binding lectin-associated serine proteases (MASPs) to form the classical/lectin C3 convertase, C4b2a. Further cleavage of C3 to C3b results in formation of the C5 convertase, C4b2a3b. Cleavage of C5 marks the start of the lytic, or terminal, pathway. C5a is highly proinflammatory, while C5b binds C6 to initiate formation of the MAC (membrane attack complex); C7, C8 and multiple molecules of C9 bind to C5b6 to form the transmembrane pore. There are many proteins which control the cascade, either at the initiation level (C1-inhibitor [C1INH] inhibits C1r/s and the MASPs), or at the level of C3b and the convertase enzymes (including CD55, CD46, CD35, factor H [FH], factor I [FI] and C4-binding protein [C4BP]). Various proteins either inhibit C9 polymerisation and thus formation of the MAC on the membrane (CD59) or render it soluble (clusterin, vitronectin), resulting in soluble terminal complement complexes. *Tickover and contact with foreign surfaces may generate hydrolysed C3, i.e. C3(H2O), which shares structural and functional properties with C3b. **Alongside mannose-binding lectin (MBL), the lectin pathway may also be initiated by ficolins and collectins.