The emerging role of complement inhibitors in transplantation

Véronique Frémeaux-Bacchi[1,2] and Christophe M. Legendre[3,4,5]

[1]Laboratoire d'Immunologie Biologique, Hôpital Européen Georges Pompidou, AP-HP, Paris, France; [2]INSERM UMRS 1138, Cordeliers Research Center, Complement and Diseases Team, Paris, France; [3]Service de Néphrologie—Transplantation, Hôpital Necker, AP-HP, Paris, France; [4]Université Sorbonne Paris Cité, Paris, France and [5]Unité INSERM U845, Hôpital Necker, Paris, France

The role of complement in the biology of kidney transplantation is becoming more and more significant, especially but not only because we now have access to drugs inhibiting complement. After describing the main characteristics of complement biology, both activation of the complement cascade and the many regulatory factors, we will review the precise role of complement in kidney transplant biology. Complement activation has been involved in ischemia–reperfusion injury, in the recurrence of several diseases such as atypical hemolytic uremic syndrome, C3 glomerulopathies, and antiphospholipid syndrome, as well as the process of antibody-mediated rejection, either acute or chronic. There are many potentially interesting drugs interfering with complement inhibition that have been or may be studied in kidney transplantation. Currently, the bulk of data concerns eculizumab, a monoclonal antibody blocking the complement cascade at the C5. Its efficacy has been demonstrated in the treatment and prevention of recurrence of atypical hemolytic uremic syndrome with an overall good safety profile. Although it has been reported to be efficacious to prevent antibody-mediated rejection, properly designed trials are currently being performed to state this efficacy. In addition, randomized trials are, in the process, regarding the prevention of ischemia–reperfusion injury after kidney transplantation.

Kidney International advance online publication, 16 September 2015; doi:10.1038/ki.2015.253

KEYWORDS: acute rejection; complement; delayed graft function; hemolytic uremic syndrome

Correspondence: *Véronique Frémeaux-Bacchi, INSERM UMRS 1138, Cordeliers Research Center, Complement and Diseases Team, 15 rue de l'Ecole de Médecine, Paris 75006, France.*
E-mail: veronique.fremeaux-bacchi@egp.aphp.fr

Received 25 January 2015; revised 30 April 2015; accepted 12 June 2015

The complement system is part of innate immunity, and it acts as a first line of defense against pathogens and a guardian of the host homeostasis. Complement activation initiates a cascade reaction, which leads to the cleavage of inert plasmatic components that generate bioactive components, including C3b, C3a, C5a, and C5b-9, with pro-inflammatory, chemo-attractant, and cell-damaging functions. Complement activation is tightly regulated to protect host cells from its toxic effects.[1] A set of at least seven proteins in plasma (C1 INH, C4b-binding protein, factor H, and factor I) or cell membranes (decay-accelerating factor, membrane cofactor protein, and CR1 (CD35)) modulate the complement proteins and protect host cells and tissues from complement damage. It has become more and more obvious that the 'classical' conception of complement as a first line of defense against pathogens is too restrictive, and complement has a major role in several diseases that involve the kidney and influences the outcome of kidney transplant.[2,3]

The present article emphasizes the emerging knowledge of the relative contribution of the complement activation pathways to transplanted kidney tissue injury and focuses on the role of complement inhibitors in kidney transplantation.

THE COMPLEMENT SYSTEM

Schematically, the complement includes three different pathways of activation and multiple bioactive molecules (Figure 1). It is a highly complex system that is regulated by processes operating at various levels in a fluid phase (plasma) and on cell surfaces.[4] These three pathways primarily differ in their recognition target, which includes antibodies in the classical pathway (CP), carbohydrates in the lectin pathway, and a permanent low-level activation in the alternative pathway (AP).

Antigen–antibody complexes in the CP activate the C1 component, which associates a pattern recognition molecule, C1q, and a heterotetramer of C1r and C1s proteases. Hexameric clustering of immunoglobulin G (IgG) to the target surface elicits a mechanical stress on the C1 complex that triggers the conversion of C1r and C1s into active proteases and the generation of the CP C3 convertase, C4b2a, after the cleavage of the next two reacting components of the

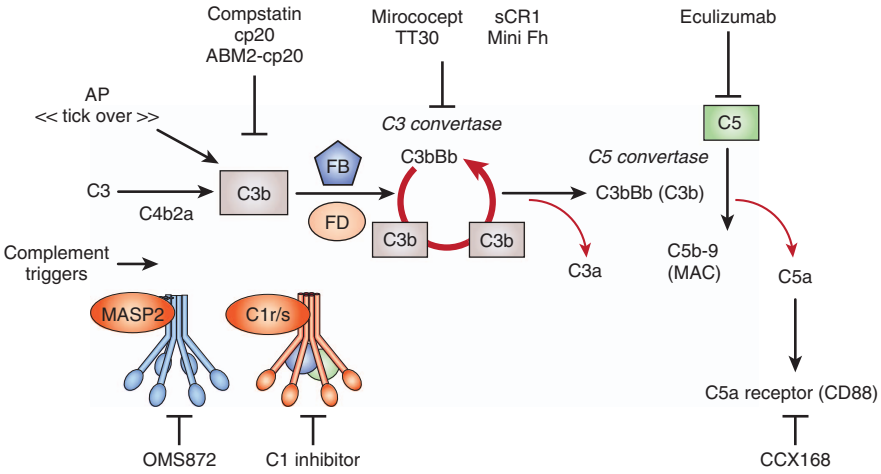

Figure 1 | The complement cascade with the target values for therapeutic drugs. The complement cascade includes the classic, alternative, and mannan-binding lectin pathways. A complex series of enzymatic proteins that are triggered in a cascade manner leads to the formation of the classical pathway C3 convertase (C4b2a) and the alternative C3 convertase (C3bBb). The C3 convertases cleave C3 into C3a and C3b. C3b binds to other C3 convertases to form C2a4b3b and C3bBb. C3b is also known as C5 convertase. C1 inhibitor is a suicide inhibitor that inhibits C1r and C1s. Soluble CR1 is a recombinant protein that inhibits C3 and C5 convertases. The peptide compstatin or the chimeric peptide Cp 20 or ABM2-Cp20 binds C3b and inhibits the activation of alternative pathway (AP). The anti-human C5 (eculizumab) blocks C5 cleavage. TT30 (a fusion protein between CCP1-4 FH and CCP1-4 CR2), mini FH (fusion protein between CCP1-4 FH and CCP19-20FH), and APT070 (Mirococept) are three short consensus domains of human CR1 with a membrane-targeting amphiphilic peptide that regulates C3 convertase. The antagonist of human C5aR/CD88 (CCX168) blocks the interaction between C5a and its receptor.

CP, C4 and C2. For example, C1q binds to the Fc portion of the pretransplant or *de novo* donor-specific anti-human leukocyte antigen (HLA) antibodies (DSAs), mainly IgGs, particularly IgG1 and IgG3, and activates the CP.[5]

Activation of the lectin pathway occurs after the binding of five different lectin pathway-specific carbohydrate recognition molecules, such as mannan-binding lectin and ficolins-associated serine proteases, particularly MASP2, to carbohydrate residues on microorganisms. Subsequently, complements C4 and C2 are cleaved, and the CP C3 convertase C4b2a is formed. Mannan-binding lectin binds to altered-self endogenous ligands that arise in pathological conditions, such as ischemia/reperfusion (I/R) injury, which leads to lectin pathway activation.[6]

No specific initiation is needed for the AP. It is constantly activated at low levels by the 'tick-over' of C3, which includes two proteins, Factor B and Factor D, that lead to the creation of the AP C3 convertase, C3bBb. C3bBb is a short-lived complex, and stabilization of this complex by properdin (the only positive regulator of the complement system) is required to ensure an efficient host defense. The convergence point of all three pathways is the cleavage of C3 into the active covalently bound C3b to cells and the liberation of the anaphylatoxin C3a into the circulation. The AP amplifies the level of C3b deposition on the target and the generation of C3a. This loop is the heart of the complement cascade.

C3b binds to the C3 convertase of the CP or the AP to form the C5 convertases, C4b2a (C3b)n and C3bBb (C3b)n, respectively, which then cleave C5. Cleavage of C5 leads to the generation of the anaphylatoxin C5a, the formation of sC5b9 in the circulation, and the insertion of the membrane attack complex on the cell surface. The AP is the most efficient pathway, and it is responsible for >80% of membrane attack complex formation on target cells. Anaphylatoxins C3a and C5a recruit phagocytes at the site of complement activation and generate an inflammatory environment.

Complement amplification depends on the balance between C3 convertase formation rate, which upregulates C3 cleavage, and the C3 breakdown cycle that downregulates it. Fluid phase and membrane-bound proteins regulate the complement system to prevent excessive activation of primarily the AP. Factor H (FH) is a major regulatory protein in plasma that efficiently controls the amplification loop of complement pathways. FH binds C3b and polyanionic surface markers to prevent the formation of the C3 convertase and induce its dissociation. FH is a cofactor for C3b proteolysis by Factor I. The C1 inhibitor specifically binds to and inactivates C1r and C1s, and therefore this inhibitor tightly regulates CP activation. The C4 binding protein C4bp increases the decay of C3 convertase in the CP, and Factor I inactivates C4b to C4d. The covalently linked C4d to the endothelium surface is an inactive stable degradation product that provides little C4 activation. Cell surface membrane cofactor protein and CR1 limit the number of active convertases by acting as cofactors for Factor I-mediated cleavage of C3b and C4b to their inactive products, iC3b/C3dg and C4d, respectively. Finally, the decay-accelerating factor inhibits the assembly or membrane insertion of the membrane attack complex complex and promotes the dissociation of the AP and CP C3 convertases with CR1.