COMPLEMENT INVOLVEMENT IN RENAL TRANSPLANTATION

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ABSTRACT

The complement system is involved in several renal diseases and in renal transplantation (RTx). The authors review the complement cascade and its involvement in innate and adaptive immunity in the field of RTx. The complement cascade is involved in several steps of RTx: ischaemia—reperfusion injury (IRI), T cell-mediated acute rejection (TMR), antibody-mediated rejection (ABMR), and progressive kidney injury and fibrosis. The high frequency of complement involvement in RTx is the subject of several studies because complement could be a relevant target in treating the aforementioned conditions. There is an increasing number of ongoing clinical trials aimed at verifying the efficacy and safety of many drug candidates. The anti-C5 monoclonal antibody is already approved to prevent and treat ABMR and is the subject of trials investigating the treatment of other conditions such as IRI, TMR, and progressive fibrosis. Other molecular targets, such as C1, C3, C5a, and C5a receptor, are the subject of international trials and could prove to be effective in the near future.

Keywords: Renal transplantation, complement cascade, ischaemia—reperfusion injury, acute and chronic rejection, renal fibrosis, therapies targetting complement.

INTRODUCTION

The complement system is an essential component of the innate immune system and plays an indispensable role in the elimination of invading microorganisms as a first line of defence.[1,2] The complement system bridges innate and adaptive immunity. In addition, another key component of the immune system, the cross-talk between Toll-like receptors and the complement system, has been a key area of research.[3]

Complement Cascade

Complement activation occurs through three major pathways: the classical pathway (CP), the alternative pathway (AP), and the mannose-binding lectin pathway (LP), all of which generate the C3 convertase enzyme complex that cleaves C3 into C3a and C3b, thus leading to the complement cascade with activation of C5 convertase and terminal pathway activity.[4] The AP is constantly activated at low levels in healthy subjects. The activation and progression of the cascade are strictly controlled by complement-regulating proteins (Figure 1).[5] A number of soluble regulators are involved in the control of complement activation. C1 inhibitor (C1-INH) prevents auto-activation of the initial complex formed in the CP. C4b-binding protein is a decay-accelerating factor (DAF, CD55) for C3 convertase in the CP and a co-factor for cleavage of C4b opsonin by complement factor I (CFI). Similar activity in the AP is provided by complement factor H, which is involved in the decay of convertase and C3b inactivation by CFI. Clusterin and vitronectin both act on terminal complexes and prevent their insertion into cell membranes. Also, carboxypeptidase N is a part of fluid-phase regulatory activity of the three pathways, acting as an anaphylatoxin inhibitor. Finally, cell surface-bound regulatory proteins such as complement receptor 1 (CR1), membrane co-factor protein (MCP, CD46), and DAF shorten the half-life of cell surface-assembled C3 and C5 convertase.

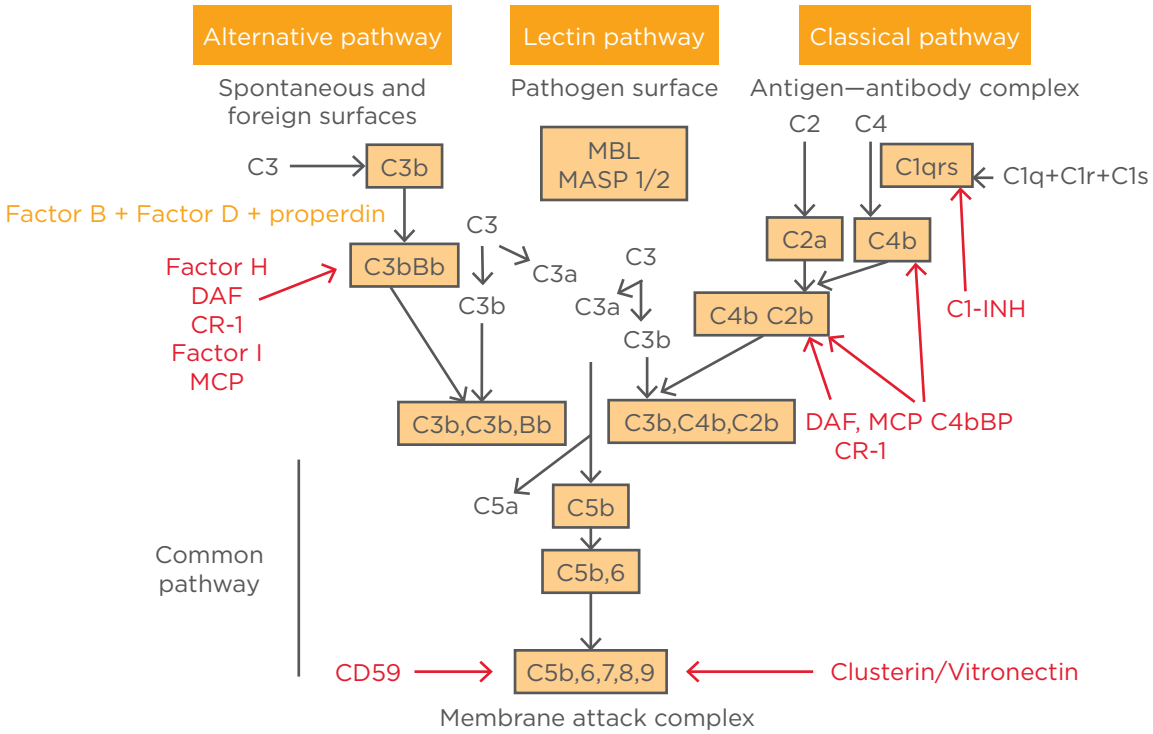

Figure 1: Representation of the classical, lectin, and alternative pathways of complement activation, including regulatory molecules (red).

MBL: mannose-binding lectin; MASP 1/2: mannan-binding lectin-associated serine protease 1/2; C1-INH: C1 inhibitor; DAF: decay-accelerating factor; CR-1: complement receptor 1; MCP: membrane co-factor protein.

Complement-mediated injury will proceed if the triggered activation of any complement cascade outweighs the inhibitory potential of the pathway regulators.[6,7]

Evidence emerging over the past 15 years supports the concept that the complement cascade, which has been traditionally considered a component of innate immunity, also regulates kidney ischaemia—reperfusion injury (IRI), acute T cell-mediated rejection and humoral alloimmunity that underlie transplant rejection, as well as post-transplant recurrence of glomerular diseases such as complement-mediated and progressive kidney injury that result in late graft failure. All these data support the need for further studies testing the efficacy of targetting complement and its receptors for the improvement of RTx outcomes.[8]

COMPLEMENT AND ISCHAEMIA—REPERFUSION INJURY

Early evidence from *in vivo* models indicated that IRI following transplantation is related to donor kidney-derived C3 and not to systemic recipient C3.[9] Further studies using *in vivo* models support the conclusion that IRI upregulates production of complement components by kidney endothelial and tubular cells, as well as by infiltrating immune cells. Local activation through the AP yields C3a and C5a, which amplify local inflammation and injury through autocrine and paracrine interaction with their receptors expressed by cells within the graft.[10,11] It should be highlighted that the majority of kidneys transplanted in humans are retrieved from cadaveric donors. Damman et al.[12] found higher gene expression of C3 and increased deposition of C3d in kidney biopsies obtained from deceased-donor grafts. de Vries et al.[13] detected soluble C5b-9 following reperfusion of kidneys from deceased donors, but not from living-donor kidneys. Whole-genome expression profiling of human renal allograft protocol biopsies at implantation confirmed significantly higher expression levels of complement genes in deceased-donor kidneys.[14] Van Werkhoven et al.[15] found that brain death initiates systemic complement activation, upregulates C5a receptor (C5aR) expression by tubular cells, and is associated with induction of intrarenal cytokines.

Table 1: Anti-complement agents in clinical trials for ischaemia—reperfusion injury.

Complement inhibitor	Target	Major mechanism of action
Eculizumab	C5	Inhibition of C5b-9 and C5a formation
rhC1-INH	C1r, C1s, plasmin, C3b, kallikrein, XIa, XIIa, MASP1, MASP2	• Regulatory effect on coagulation • Inhibition of the alternative pathway • Control of the release of bradykinin
sCR-1	C3b, C4b	Inactivation of C3 and C5 convertase

rhC1-INH: recombinant C1 inhibitor; MASP 1/2: mannan-binding lectin-associated serine protease 1/2; sCR-1: soluble complement receptor 1.

Moreover, the complement component C5a, which is generated by the donor brain death, may act directly on the C5aR expressed by tubular cells and infiltrating cells.

C3 is implicated in the activation of the renin—angiotensin system and in the epithelial—mesenchymal transition.[16,17] This observation also supports the concept that synthesis of complement components by renal epithelial cells is a mediator of tubular damage in proteinuria-associated renal diseases and transplantation. Indeed, several studies document that intragraft complement activation contributes to chronic dysfunction. Accordingly, C3—/— kidney isografts transplanted into wild-type recipients were protected from progressive renal failure.[18]

Going into molecular details, Simone et al.[19] documented that complement activates reduced nicotinamide adenine dinucleotide phosphate enzymes in renal IRI. In addition, complement has a critical role in the induction of the endothelial—mesenchymal transition (EndMT) during renal IRI and these data shed light on the pathogenic factors that regulate this particular form of endothelial dysfunction, which has an important role in the regulation of renal fibrosis.[20] Castellano et al.[21] documented that activation of the CP and LP of the complement system occurs primarily at the level of the endothelial cells during IRI. As EndMT contributes to the development of tissue fibrosis, the same authors investigated the possible role of complement in the induction of EndMT in a swine model of renal IRI by using recombinant C1-INH *in vivo*. They observed that the activation of the Akt pathway was pivotal for C3a and C5a-induced EndMT *in vitro*. In accordance, the inhibition of complement *in vivo* led to the abrogation of Akt signalling with hampered EndMT and tissue fibrosis.[22]

Several drug candidates are currently undergoing evaluation in clinical trials investigating the prevention of IRI through the inhibition of complement (Table 1). Eculizumab, a humanised monoclonal antibody (mAb) directed against the C5 component of the complement cascade, is already used to treat atypical haemolytic uraemic syndrome (aHUS) and antibody-mediated rejection (ABMR) and may be capable of preventing IRI. Studies evaluating the role of eculizumab in the prevention and treatment of IRI and delayed graft function (DGF) in kidney allograft are currently ongoing.[23-25]

The beneficial effect of recombinant C1-INH on IRI has been widely studied by Castellano et al.[21] Purified or recombinant C1-INH is a serine protease inhibitor first recognised for its ability to regulate the activity of the C1 complex, but it also acts at the level of mannose-binding lectin (MBL) and thereby inhibits complement activation via the CP and LP.[26] To date, one trial (NCT02134314) with C1-INH has been initiated to investigate the prevention of DGF in patients receiving a deceased-donor RTx. Soluble CR1 (sCR1) is another protein that regulates C3 convertase. CR1 itself is a cell-surface glycoprotein expressed by erythrocytes, monocytes, neutrophils, B cells, some T cell subsets, dendritic cells (DCs), and podocytes, and it modulates the complement cascade at multiple levels.[27] The effect of Mirococept (APT070, a form of sCR1) has been widely described by

Sacks et al.[28] and is currently the subject of a large-scale study evaluating its use in the prevention of IRI in cadaveric RTx.[29]

The aforementioned findings indicating that brain death is associated with complement activation in the donor kidney prior to organ removal raise the intriguing possibility that complement inhibition in the donor could be an effective prophylactic therapy to prevent IRI in the new host. Innovative study design will need to be developed to test this possibility.[8]

COMPLEMENT, ALLOREACTIVE T CELLS, AND T CELL-MEDIATED REJECTION

Pratt et al.[30] documented that C3 produced by an allograft and the recruited immune cells is a trigger that not only induces post-perfusion injury, but also late rejection-associated allograft injury. Indeed, a recent study[31] documented that intragraft-generated complement may affect the systemic immune response to antigens requiring a functional AP of complement activation. The C3 cleavage products C3b and C3d deposited on antigen-presenting cells (APCs) may increase antigen uptake and presentation to T cells, which aids the generation of alloreactive clones. Indeed, C3-positive APCs have been shown to potentiate the T cell response *in vitro*.[30] T cell activation by the complement system enhances expansion of effector T cell clones by limiting antigen-induced apoptosis.[32] Moreover, data published in 2013 indicate that complement also modulates regulatory T cell (Treg) induction, function, and stability.[33,34] According to a recent study,[35] peripheral murine natural Tregs express C3aR and C5aR, and signalling through these receptors inhibits Treg function.

Important confirmatory studies in humans were published in 2013 and documented that C3a and C5a are generated in *in vitro* cultures of human T cells responding to allogeneic DCs.[36] To summarise, complement activation through any pathway generates C3a and C5a. These anaphylatoxins bind to both APCs and T cells to stimulate T cell proliferation and activation.[37] Li et al.[38] documented that a deficiency of C5aR limited the adaptive response of recipient T cells to alloantigens. C1q appears to have a regulatory role in the threshold for T cell activation by DCs.[39] It should be highlighted that all resident renal cells may contribute to generate complement components. Also, endothelial cells have been documented to be able to generate C3 when stimulated with tumour necrosis factor alpha *in vitro*.[40,41] Moreover, C5aR expression was increased in renal tissue and in cells infiltrating the tubular interstitium in human kidney transplants undergoing acute rejection.[42] The same authors documented that the infiltration of monocytes/macrophages was significantly attenuated in transplanted mice treated with a C5aR antagonist, perhaps as a result of levels of monocyte chemoattractant protein 1 and intercellular adhesion molecule 1. However, a murine model of RTx with C4 deficiency demonstrated that a cell-mediated rejection may occur in the absence of CP or LP activation.[43] This suggests that the AP may play a key role in cell-mediated rejection. However, more recent studies documented that renal injury may also be mediated via activation of MBL-associated serine protease 2. These studies also documented that LP activation does not require C4.[44]

Whether complement antagonists may be therapeutically useful in controlling T cell alloreactivity while simultaneously promoting Treg induction, function, and stability in transplant patients remains to be determined.[8] Anti-C5 mAb and C5aR antagonists are currently being tested in humans for other indications, providing opportunities to assess their effects on human alloreactive T cells *in vivo* (NCT01363388).

COMPLEMENT AND ANTIBODY-MEDIATED REJECTION

ABMR involves donor-specific antibodies (DSAs) and the CP of complement activation. C1 complex is activated after binding to DSAs. Once activated, C3 is cleaved into C3a and C3b. C3b amplifies the AP, while C3a and C5a recruit macrophages and neutrophils, which cause additional endothelial injury. The overall result is that arteries and basement membranes are remodelled, leading to fixed and irreversible anatomical lesions that permanently compromise graft function.[45,46] C4d, a degradation product of C4, binds at the site of complement activation and remains covalently attached and detectable by immunochemistry.[47] As a consequence, C4d staining has become a valuable tool for diagnosing ABMR. Importantly, diagnostic sensitivity depends on staining methodology and cases of C4d-negative ABMR have been reported.[48] Indeed, high endothelial-specific gene expression in RTx biopsy samples

with DSAs but without C4d have been reported.[49] C4d-negative ABMR is characterised by the high intragraft endothelial gene expression of alloantibodies, by histology typical of chronic or acute ABMR, and by poor outcomes. Lack of complement deposition may have various explanations: i) low sensitivity to C4d[50,51] due to a technical issue; ii) some DSAs, although showing poor complement-fixing ability, may nonetheless activate endothelial cells;[52] iii) the various prophylactic strategies used to prevent ABMR may decrease the burden of complement activation within capillaries.[53]

Eculizumab has been successfully used to reduce the level of antibodies in highly sensitised patients with positive cross-matches prior to transplantation.[54-56] In a larger case—control study, the patients with DSAs were treated with eculizumab plus plasmapheresis before and after transplantation, and then compared with historical controls.[57] Eculizumab treatment proved successful in significantly reducing ABMR and decreasing the 1-year transplant glomerulopathy incidence rate. Anti-C5 mAb also successfully reversed established ABMR.[58] In addition, recent data also document complement involvement in antibody-mediated chronic rejection where the 'bad' activity of antibodies may also be involved in previously considered 'chronic lesions' (e.g. transplant glomerulopathy).[59,60] Finally, in light of the association between anti-human leukocyte antigen antibodies and chronic ABMR, ongoing studies are testing the efficacy of eculizumab in preventing graft loss in RTx recipients with DSAs (NCT01327573).

COMPLEMENT INVOLVEMENT IN THE RECURRENCE OF GLOMERULAR DISEASES AFTER TRANSPLANTATION

Some glomerular diseases are clearly mediated by complement activation. These diseases may recur after transplantation and may be treated by anti-complement drugs. aHUS is associated with a high rate of recurrence and poor outcomes after RTx. Recurrent thrombotic microangiopathy is very rare in patients who develop end-stage renal failure following HUS caused by Shiga-toxin-producing *Escherichia coli*, whereas disease recurrence is common in patients with aHUS.[61] The recurrence rate[62] of C3 glomerulopathy after RTx is estimated at approximately 60%, as derived from the small case series of Servais et al.[63] and Little et al.,[64] and confirmed in the recent article by Zand et al.[65] In such conditions anti-complement therapy with eculizumab could be useful.[66] In the case where C3 dysregulation prevails (some dense-deposit diseases and C3 glomerulonephritis) an anti-C3 therapy might be useful.[67]

COMPLEMENT, PROGRESSIVE KIDNEY INJURY, AND FIBROSIS

Alterations in complement activation within the kidney have been implicated in multiple diseases leading to renal fibrosis, among which is renal allograft rejection.[68] The role of complement activation in the modulation of immunity and pathogenesis of renal fibrosis in the context of IRI is a field of several avenues of research. IRI of the kidney is a well-established cause of renal fibrosis. Factors such as sustained innate immune activation, endothelial cell dysfunction, hypoxia, and chronic microvascular injury have all been implicated in the promotion of fibrosis.[69] As mentioned above, several studies[70,71] point to the EndoMT and highlight a central role for the endothelium in progression to fibrosis, and a novel role for complement in the modulation of endothelial cell activation and EndMT. In further support of the concept that intragraft complement production modulates progressive kidney injury, proteomic studies of kidney allograft tissue by the Salomon group demonstrated a strong association between interstitial fibrosis/tubular atrophy (IF/TA) and the AP.[72] An ongoing study of chronic anti-C5 mAb therapy in RTx recipients (NCT01327573) could provide further insight into the role of complement as a mediator of progressive graft dysfunction and IF/TA.

CONCLUSION

Emerging evidence has recently suggested that the complement cascade is a common pathogenetic mechanism in many kidney diseases and in RTx rejection. The complement system is now recognised as a pervasive, multifaceted mediator of transplant injury in animal models and in human transplant recipients. The development of pharmacological agents that block human complement components and receptors in the setting of RTx now represents the basis of the concept that targetting the complement system in RTx recipients will improve graft and patient survival rates.

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