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REVIEW

Complement cascade and kidney transplantation: The rediscovery of an ancient enemy

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Abstract

The identification of complement activity in serum and immunohistochemical samples represents a core element of nephropathology. On the basis of this observation, different experimental models and molecular studies have shown the role of this cascade in glomerular disease etiology, but the absence of inhibiting drugs have limited its importance. Since 2006, the availability of target-therapies re-defined this ancient pathway, and its blockage, as the new challenging frontier in renal disease treatment. In the graft, the complement cascade is able to initiate and propagate the damage in ischemia-reperfusion injury, C3 glomerulopathy, acute and chronic rejection, atypical hemolytic uremic syndrome and, probably, in many other conditions. The importance of complement-focused research is revealed by the evidence that eculizumab, the first complement-targeting drug, is now considered a valid option in atypical hemolytic uremic syndrome treatment but it is also under investigation in all the aforementioned conditions. In this review we evaluate the importance of complement cascade in renal transplantation diseases, focusing on available treatments, and we propose a speculative identification of areas where complement inhibition may be a promising strategy.

Key words: Complement; Eculizumab; Kidney transplantation

Core tip: Complement cascade is involved in different types of renal disease, from glomerulonephritides to pre-eclampsia, and the availability of new drugs, able to inhibit different steps of the cascade, re-defined this ancient pathway, and its blockage both in native and transplanted kidneys, as a new challenging frontier in renal disease treatment. In this review we evaluate the importance of complement cascade in renal transplantation diseases, focusing on available treatments, and we propose a speculative identification of areas where complement inhibition may be a promising strategy.

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INTRODUCTION

Complement was initially identified by Ehrlich and Morgenroth in the 19th century as a factor that "complemented" the bactericidal action of immune cells[1]. Muller-Eberhard in 1960 described the cascade and hypothized its involvement in some different diseases[2,3]. Despite the overt demonstration of a complement activation in serum and immunohistochemical samples, the exact role of

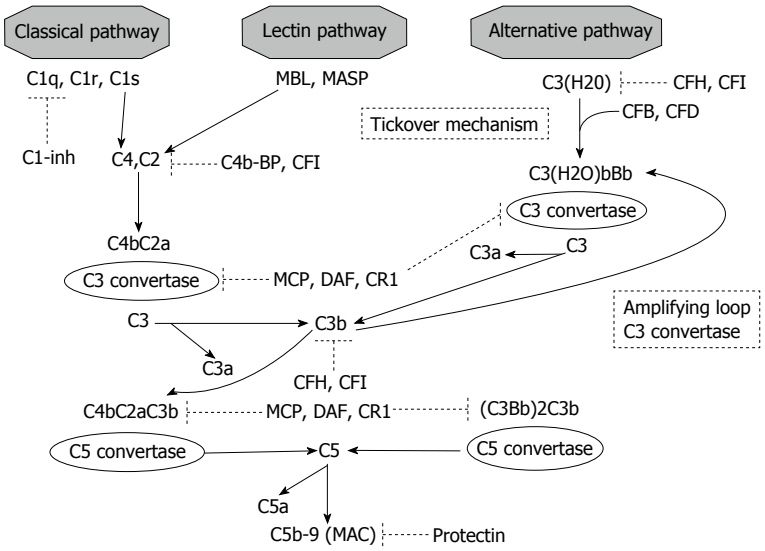

Figure 1 Complement cascade and regulatory proteins. MBL: Mannose binding protein; MASP: MBL-associated serine proteases; CFB: Complement factor B; CFD: Complement factor D; CFH: Complement factor H; CFI: Complement factor I; C1-inh: C1 inhibitor; C4b-BP: C4 binding protein; MCP: Membrane cofactor protein; DAF: Decay accelerating factor; MAC: Membrane attack complex.

this cascade remained unclear for a long time.

Recently, the increasing evidence of a key role of complement cascade in many renal diseases, from glomerulonephritides to pre-eclampsia[4-9], and the availability of new drugs able to inhibit different steps of the cascade, re-defined this ancient pathway, and its blockage, as the new challenging frontier in renal disease treatment.

In this review we evaluate the importance of complement cascade in renal transplantation diseases, with an initial general description and a subsequent in-depth evaluation. A separate section is dedicated to treatment, analyzing areas where complement inhibition may represent a promising strategy.

Description of complement cascade

The complement cascade represents a direct defense against bacterial infection and a "scavenger" for immune complexes and apoptotic cells[10].

As summarized in Figure 1, three pathways are involved in complement activation: (1) Classical pathway: C1q binds IgG and IgM, apoptotic cells, or acute-phase proteins promoting cascade progression; (2) Lectin pathways: two trigger proteins (mannose-binding lectin-MBL- and ficolins) activate complement after the adhesion to bacterial surface; and (3) Alternative pathway: in this important and well studied pathway, the first step is represented by the constant and spontaneous hydrolysis of C3.

In the classical pathway, the conformational change induced by C1q binding causes C1r and C1s activation. These proteases are both able to generate C4b from C4. After C2 cleavage and generation of C4b2a (a C3 covertase), the last step (C3 cleavage), generates the C5 convertase C4b2a3b[11,12].

In the lectin pathways, MBL interaction with one of its two associated serine proteases (MASPs-1 or MASP-2), promotes C3 cleavage[13,14].

Although the activation in previously reported pathways is due to a direct stimulation derived from binding on different epitopes, the alternative pathway is constitutively active, a condition called "tickover mechanism". In this manner, if necessary in response to an appropriate stimulus, the host enables a rapid and strong activation of the cascade.

As first step, the modification induced by factors B and D on hydrolyzed C3 creates C3(H_2O)Bb, a C3 covertase. C3bBb is the result, after C3 cleavage and C3b generation, of another interaction with factors B and D ("amplification loop"). C3bBb is also able to generate C3b and to enhance alternative pathway. The interaction of C3b with C3bBb is the final causative factor for alternative pathway C5 convertase formation (C3bBb3b)[13].

C5a, one of the product of C5 cleavage, is able to combine with final components of the cascade (C6, C7, C8, C9): this final step generates, in all three pathways, the membrane attack complex (MAC)[11,12].

Regulatory mechanism

The cascade regulation has a key role, because an uncontrolled activation, secondary to defects or mutations in regulatory proteins, is referred to be the triggering cause of some complement-mediated diseases (*i.e.*, atypical hemolytic syndrome).

The alternative pathway is the more controlled cascade, as predictable by the evidence of its continuous and spontaneous activation depending on C3 hydrolysis.

The regulatory proteins are divided in two types: fluid-phase and membrane-bound molecules (Figure 1): (1) The fluid-phase regulators are serum proteins. C1 inhibitor is able to arrest classical activation by blocking C1q dissociation, and, in high concentration, can inhibit both the lectin-binding and alternative pathways[11]. Factors H and I act a pivotal role cleaving C3b and conse-

quently regulating the alternative pathway. Factor I is also able to hydrolyze C4b in presence of C4 binding protein; and (2) The second type of regulatory proteins, not pathway specific, are membrane-bound regulators. In most cases, these molecule are anchored to the cell membrane through a glycophosphatidylinositol component. Factor I inhibits complement in association with two of them, membrane cofactor protein (MCP) and CR1; CD35 and complement receptor of immunoglobulin also accelerate C3 and C5 convertase degradation. CD55 enhances C3 convertase spontaneous degradation. Protectin (CD59) directly inhibits MAC formation[11,14].

Effects of complement cascade activation

Three different effectors are activated by complement cascade: (1) Anaphylatoxins (C3a and C5a): stimulators of different inflammatory pathways (tumor necrosis factor-α, upregulation of histamine, cytokine, chemokine, and eicosanoid production)[15]; (2) opsonins (C3b, iC3b, and C3d): these molecules are responsible for the "scavenger" ability of complement by direct binding to the surface of target cells and immune complexes facilitating their elimination[16]; and (3) MAC: C5b-9 generation on cell membrane leads to opsonization, and finally to osmotic lysis of pathogens and damaged cells[17].

COMPLEMENT-MEDIATED DISEASES IN KIDNEY TRANSPLANTATION

In this section, we summarized renal transplant diseases where, at the present time, complement activation shows its involvement. In every paragraph we enunciate the effect of complement inhibition in the mitigation of the damage, if present; a separate section is dedicated to available treatments and future perspectives.

Ischemia-reperfusion injury

An important limitation in long-term outcomes of cadaveric transplants is the inevitable ischemia-reperfusion injury. In the past decade, the use of preservation fluids and machine-reperfusion instruments have expanded the availability of organs reducing delayed graft function, but did not abrogate this kind of damage. The ischemia-reperfusion injury remains, for the same age and risk factors, the corner-stone which differentiate living from deceased donors.

As known, the reperfusion of the graft activates some different processes, such as release of reactive oxygen species, alteration of endothelial permeability and gene transcription. All these conditions ended on an inflammatory infiltrate and kidney injury[18,19].

The complement cascade is activated in the ischemia-reperfusion mediated damage. The alternative pathway seems to explain the major role, as suggested by the absence of antibody deposition in kidney biopsy after reperfusion in animal models[20]. As a further confirmation, C3 and CFB deficient mice are resistant to ischemia-reperfusion injury, despite C4 knockout mice suffered from this damage[21]. C3 expression after reperfusion, probably related to methylation of *C3* gene promoter as observed after cold ischemia[22], is associated with a diminished graft survival[23].

Recent data have shown that a kidney from a mice with C3 deficiency is not affected from ischemia reperfusion injury after transplantation in a normal mice, and per contrast, the inverted transplant combination is associated with damage, suggesting the idea that the C3 production in the kidney, and not circulating C3, can be considered[24].

In a swine model, the presence of MASP and MBL deposits after ischemia-reperfusion suggests also an activation of lectine pathway[25] and a more complex overall picture.

In humans, increased serum C5a and C5aR expression in kidney biopsy are both found in brain-dead donors[26], and also a transient MAC-release is demonstrated after reperfusion[27].

The blockage of complement cascade shows a protective effect: small interfering RNA (siRNA) against C5a receptor, C5a antagonists and C1q inhibitors display a limitation of ischemia-reperfusion injury in different models[21,25].

Atypical hemolytic uremic syndrome

Microangiopathic hemolysis, thrombocytopenia and renal damage characterize atypical hemolytic uremic syndrome (aHUS)[28], a condition with poor prognosis both on native and transplanted kidneys. aHUS has also an important recurrence rate in the graft (from 60% to 100%)[29], and this evidence paves the way to the application of preventive strategies to mitigate/abrogate this damage.

In the past decade, the identification of alternative pathway role in aHUS pathogenesis[30] has completely changed the treatment and management of aHUS. It is now well-known that an overactivation of alternative pathway explains almost all cases of aHUS[29,31].

Patients with mutations on C3 or on regulatory proteins complement factor H (CFH), complement factor I (CFI), complement factor B (CFB) experienced high recurrence rates[31]. Mutations on MCP or on diacylglycerol kinase-ε, on the contrary, exposed patients to a very low rate of recurrence, because the graft expressed normal proteins[31,32].

Patients who had autoantibodies against regulatory protein (*i.e.*, anti-CFH antibodies) are in midstream: surprisingly cases of recurrent aHUS are observed even when the immunosuppressive regimen have successfully reduced the antibody titer[33].

The role of eculizumab in aHUS, both on treatment and prevention of recurrences, is discussed separately. Here we anticipate that all previously adopted strategies (plasma infusion, abrogation or minimization of calcineurine inhibitors (CNI)-for its potential inductive effect in aHUS) failed in treatment and prevention of aHUS[29]; also mammalian target of rapamycin inhibitors, proposed as alternative to CNI, are recognized as an independently

associated risk factors for aHUS[34].

C3 glomerulopathies

One of the most important innovation in nephropathology is the introduction of C3 glomerulopathy definition. This entity is intended as a condition in which the immunohistochemical samples show C3 glomerular accumulation with scanty immunoglobulin deposition[35], including deposit dense disease and membranoproliferative type I and type Ⅲ in which the C3 deposition is isolated or predominant[36].

This pathological reclassification implies a new clinical insight: C3 glomerulopathy is a complement-mediated condition where alternative pathway activation plays, as in aHUS, a pivotal role. Genetic and serological tests revealed CFH, CFI, MCP, C3 and factor B mutations in a low but significant percentage of patients, and positive C3 nephritic factor (an immunoglobulin able to stabilize C3bBb reducing its inactivation)[37]. In most cases, with or without positive genetic/serological tests, elevated levels of soluble C5b-9 are demonstrable, surrounding evidence of a smoldering complement activation[36,37].

The recurrence rate of C3 glomerulopathy on renal transplantation could be approximately estimated on about 60%, as derived from two small case series of Servais *et al*[37] and Little *et al*[38] and confirmed in the recent paper of Zand *et al*[39].

The treatment, or the prevention, of the recurrence is far from being defined. Anti-cellular immunosuppression with rituximab, cyclofosfamide or mycophenolate mofetil with or without plasma therapy are ineffective both in native and transplanted kidneys[40,41]; as observed in aHUS, a post-treatment negativization of C3 nephritic factor is not sufficient to prevent a recurrence in the graft[41]. As for aHUS, the role of eculizumab in C3 glomerulopathies treatment is discussed in a separate section. We anticipate that no clinical trial have already evaluate the potential role of anti-C5 drugs in disease prevention, but some papers suggest promising effects of Eculizumab in recurrence treatment[41,42].

Other glomerulonephritides

The role of complement activation is demonstrated in some different glomerulonephritides.

In animal model of membranous glomerulonephritis, for example, nephrotic-range proteinuria was abrogated after complement deprivation[43]. Recent studies in humans showed a direct correlation between podocyte injury and complement activation[44]. Recently, antibodies against the phospholipase A2 receptors (PLA2R) were correlated with idiopathic membranous nephritis[45]: curiously, the anti-PLA2R antibodies are mainly an IgG4, which is the subtype with a low ability in classical pathway activation.

Complement cascade is also directly involved in systemic lupus erythematous (SLE). Patients with genetic deficiency in classical pathway proteins may develop SLE[46] and complement products excretion (C5a and MAC) increased during disease "flares"[47].

Recently, an complement involvement has been demonstrated in other antibody-mediated nephritis, *i.e.*, ANCA-vasculitis[48], antiphospholipid antibody syndrome[49] and crioglobulinemic disease[50]. As a consequence, complement inhibition is a key point of interest in these conditions.

Renal allograft rejection

Complement exerts an effect in the immune activity, and C5a-C5aR interaction plays the critical role. It has been shown that natural regulatory T cells express both C5aR and C3aR, and a blockage of these receptors in mice induces a tolerance profile in autoimmune condition and organ transplants[51]. It was also reported that anaphylatoxins can stimulate T-cell proliferation and activation[52]. Moreover, an indirect confirmation of the alternative pathway causative role is suggested by the evidence that a murine model with C4 deficiency transplanted with a kidney graft derived from a donor with the same defect experienced a T-cell mediated rejection[53].

The cascade involvement in acute antibody mediated rejection (ABMR) represents an interesting issue, both for therapeutic and diagnostic point-of-views.

Anti-Human Leukocyte Antigen antibodies, especially against donor specific molecules (anti-DSA), are identified as the pivotal cause[54] of ABMR, but, at the same time, a wide spectrum of lesions in presence of positive DSA tests has been reported, ranging from nearly normal histological samples to acute and rapidly destructive rejections[55]. So, the differentiation between "bad" or "not so bad" antibodies acquired a growing interest.

Moreover, some data show that the "bad" activity of antibodies can be also involved in previously considered "chronic" lesions (*i.e.*, transplant glomerulopathy)[56,57] and the application of acute rejection therapeutic approaches in these conditions seems to be able to abrogate or at least mitigate the progression to chronic allograft disfunction[58,59].

We know that antibodies can activate complement cascade both with classical and lectin pathway. This activation leads to C4 cleavage and C4d deposition on peritubular capillaries, which is considered a "footprint" of both acute and chronic ABMR[60].

Recently, patients with C1q-binding antibodies demonstrates a poorer outcome than patients with no-fixing antibodies at 1 and 5 years, with a significant difference in acute rejection rates and C4d positive staining[61]. This evidence definitely paves the way to evaluate the efficacy of complement blockage drugs to prevent or treat antibody-related diseases.

The reduction in C4d deposition with a better long term outcomes in patients with an increased expression of CD55 provides a further confirmation[62].

ANTI-COMPLEMENT STRATEGIES

Eculizumab

Eculizumab (Soliris®, Alexion Pharma) is an anti-C5 fully humanized monoclonal antibody able to abrogate terminal complement activation[63]. Eculizumab completely

changed the prognosis and the clinical course of paroxysmal nocturnal hemoglobinuria, a complement-dependent disease[63,64]. Efficacy, well-toleration, absence of major side-effects and the potential usefulness in all condition in which complement is involved increased the interest about this drug worldwide.

An important precaution is to adopt a combined antimeningococcal vaccination and antibiotic treatment, because MAC-inhibition is associated with a "splenectomy-like" effect (and a consequent high risk of infection) and already available vaccines are unable to cover all meningococcal subgroups, as demonstrated by the development of meningococcal infection in a patient vaccinated before eculizumab treatment[65].

At the present time 50 studies are evaluating the effect of this drug in different subsets: more in detail 10 of these refers to transplant area, 15 to nephrologic diseases.

Regarding to C3 glomerulopathy, McCaughan *et al*[41] successfully treated a patient with a recurrence of deposit dense disease which had no previous response to rituximab and plasmapheresis despite a normalization in C3 nephritic factor titer; Bomback *et al*[42] in the first trial, demonstrated a diffuse but not consistent response: best outcomes are obtained in subjects with high levels of serum C5b-9, suggesting the idea that patients with a "burst" of complement are the best candidate to this therapy. In renal transplantation, eculizumab has been successfully adopted in desentitization protocols[66] and, as a rescue treatment, in some cases of ABMR[67,68].

Regulatory agencies in United States and Europe (Food and Drug Administration and European Medicine Agency) approved eculizumab in aHUS treatment on native kidneys after struggle results of some experiences[69,70]. Also in renal transplantation eculizumab is effective in aHUS treatment[71] and recurrence prevention[72,73].

Future perspectives

Some different strategies of complement cascade blockage are part of ongoing trials. One research hypothesis is to silence the expression of C5a receptor. Mice treated with an infusion of siRNA have a prolonged graft survival, with reduced inflammatory response on kidney biopsies[74].

In a murine model of crescentic glomerulonephritis CCX168, a small molecule able to inhibit C5a receptor, abrogates extracapillary proliferation[48]. Inhibition of antibody-mediated complement activation can be also provided by stimulating the natural inhibitory activity, or interfering with other parts of classical pathway.

Berinert® (CSL Bhering) is a concentrate of C1q esterase approved for the treatment of ereditary angioedema[75]: a prospective and randomized trial in sensitized patients [NCT01134510] is investigating its effect in reducing antibody-mediated rejection rate.

Some authors proposed Mirococept (APT070), a derived form of complement receptor 1 able to attenuate myocardial and intestinal ischemia-reperfusion damage in rats[76], as a promising option for the reduction of delayed graft function.

Other molecules (a C3 cyclic peptide inhibitor - POT-4, Alcon-, an anti-C5 antibody-LFG316, Novartis-, and a C5 aptamer-ARC1905, Ophthotech) are under investigation in age-related macular degeneration.

CONCLUSION

In the past few years we acquired an enormous amount of evidences that undoubtedly confirmed the central role of complement cascade in different pathologies and an inhibitor of complement activation, Eculizumab, shows is safety and usefulness, also in renal transplantation. However, the issue is far from settled.

At the present time, the next step is, not any more, if the use of the drug is a successful strategy, but when we have to consider this therapy and, nevertheless, how long. For example, in aHUS, eculizumab prevents the recurrence when used in induction regimen but, as previously reported on native kidneys, the risk of relapses in cases of suspension or prolongation of the treatment over the defined period is intolerable[63]. Moreover, the treatment of the relapse with a readoption of eculizumab fails in some cases[69]. If the drug is started only at the time of the recurrence, the outcomes were strictly time-dependent, with poorer results in patient treated afterwards[62]. Similar data are emerging in the treatment of other conditions, as C3 glomerulopathy[36]. In theory, a suspension is a safe option only in those conditions where complement activation is a transient phenomenon, as in ischemia-reperfusion damage. In antibody-mediated damage the question is still debating.

As known, a limit of the lifelong approach is the cost-per-patient, so the adoption of instruments able to individuate the subset of patients where a minimization/interruption of the drug could be safe (*i.e.*, functional or serological tests of complement activation) is one of the future challenges.

In conclusion, the re-discovery of the key role of complement activation and the availability of new drugs with a direct ability in complement inhibition are modifying our treatment protocols and offer a new potential amelioration in graft and patient survival rates. Long term outcomes and randomized clinical trials for the new indications are desirable, in view of a better therapy individualization.

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