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Complement as a multifaceted modulator of kidney transplant injury

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Improvements in clinical care and immunosuppressive medications have positively affected outcomes following kidney transplantation, but graft survival remains suboptimal, with half-lives of approximately 11 years. Late graft loss results from a confluence of processes initiated by ischemia-reperfusion injury and compounded by effector mechanisms of uncontrolled alloreactive T cells and anti-HLA antibodies. When combined with immunosuppressant toxicity, post-transplant diabetes and hypertension, and recurrent disease, among other factors, the result is interstitial fibrosis, tubular atrophy, and graft failure. Emerging evidence over the last decade unexpectedly identified the complement cascade as a common thread in this process. Complement activation and function affects allograft injury at essentially every step. These fundamental new insights, summarized herein, provide the foundation for testing the efficacy of various complement antagonists to improve kidney transplant function and long-term graft survival.

Introduction

Kidney transplantation is the treatment of choice for end-stage kidney disease. Advances in immunosuppression, HLA matching, and improvements in medical care have reduced acute rejection rates to less than 10%, but long-term graft survival remains suboptimal, as kidney transplant half-lives are only 8 to 11 years (1). As a consequence, the extension of allograft survival is one current focus of transplant research. An improved understanding of the pathophysiology of acute and chronic allograft injury will likely guide development and implementation of novel therapies capable of prolonging kidney transplant survival.

Current concepts are that kidney transplant injury is initiated by surgical trauma and the requisite associated ischemia-reperfusion (IR) injury, the latter being particularly detrimental in recipients of deceased donor allografts. IR rates following transplantation are increasing (2), and kidney graft survival is worse in recipients with significant IR injury (3). Donor-reactive T cells and anti-HLA antibodies are established mediators of transplant injury and must be controlled by appropriate immunosuppression. Inadequate immunosuppression predisposes to acute cellular rejection and antidonor HLA alloantibody formation, both of which are associated with progressive interstitial fibrosis and tubular atrophy (IF/TA) and shortened graft survival (4–6). In contrast, excessive immunosuppression not only predisposes to infectious complications, but is associated with multiple toxicities including direct kidney damage (7) and indirect effects of drug-induced diabetes (8) and hypertension (9).

Emerging evidence over the past 15 years supports the concept that the complement cascade, traditionally considered a component of innate immunity, unexpectedly regulates kidney IR injury, T cell and humoral alloimmunity that underlie transplant rejection, and progressive kidney injury that results in late graft failure. This body of literature, to be reviewed herein, suggests that complement components produced by the liver as well as by kidney cells and immune cells play crucial roles as pathogenic mediators of

transplant rejection in animals and humans. The data support the need for further efficacy testing of targeting complement and/or its receptors to improve kidney transplant outcome in humans.

Overview of the complement cascade

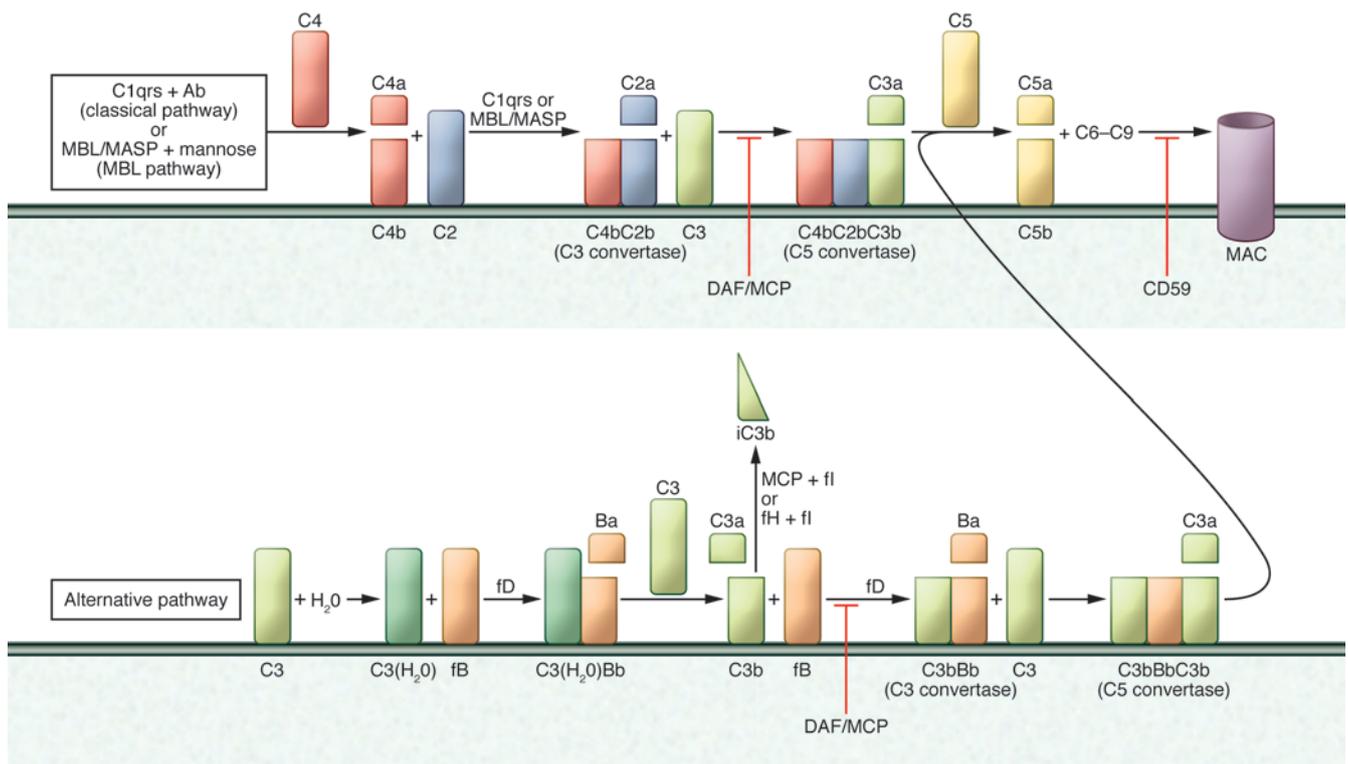
The complement system is composed of over 30 soluble and membrane-bound proteins that are activated as a cascade by three initiating pathways: (a) the lectin pathway triggered by carbohydrates present on bacteria surface, (b) the classical pathway triggered by cross-linking, cell-bound subclasses of IgG and IgM antibodies, and (c) the alternative pathway that undergoes spontaneous activation on cell surfaces (Figure 1 and ref. 10).

The three pathways converge to form C3 convertases, multimeric protein complexes with enzymatic activity (10). Cleavage of C3 yields C3a and C3b, the latter of which triggers formation of the C5 convertase. Subsequent C5 cleavage initiates formation of the membrane attack complex (MAC, C5b-9) on the target cells. In addition to the MAC, soluble and surface-bound split products, including C3a, C3b, iC3b, C3dg, and C5a, mediate inflammation by directly lysing target cells, serving as chemoattractants, functioning as opsonins, and activating innate immune cells such as macrophages and neutrophils (11).

Complement activation is tightly regulated (Figure 1) so as to prevent bystander damage to self cells (11). This regulation is accomplished through the expression of membrane-bound and soluble complement-regulating proteins. Decay accelerating factor (DAF or CD55) is a glycosylphosphatidylinositol-anchored, membrane-bound complement regulator that accelerates the decay of cell surface-assembled C3 convertases. DAF limits downstream complement activation and restricts production of the aforementioned cleavage products (12). Notably, DAF only functions intrinsically, limiting complement activation on the cell surface upon which it is expressed, but not on proximally located pathogens, which lack DAF expression. Human CD46 (murine homolog Crp), also known as membrane cofactor protein (MCP), has similar decay-accelerating function, but also exhibits cofactor activity. In conjunction with soluble factor I, this membrane-bound regulator inactivates C3b to iC3b, thereby preventing re-formation of the C3 convertase. Other examples of complement regulators include

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**Figure 1**

Schematic representation of the complement cascade. C1q,r,s cross-linking of antibodies activates the classical pathway. Mannose-associated serine proteases (MASPs) bind to mannose motifs expressed on bacteria to activate complement via the MBL pathway. Subsequent cleavage and assembly of C4 and then C2 form the C4bC2b C3 convertase. C3 spontaneously binds to H₂O, forming C3(H₂O), which binds to cell surfaces and initiates factor B-dependent (fB-dependent) and fD-dependent assembly of the alternative pathway C3 convertase (C3bBb). The latter cleaves C3 into C3a and C3b, amplifying complement activation. Addition of a second C3b molecule to either C3 convertase forms the C5 convertase, which cleaves C5 into C5a and C5b. C5b, in conjunction with C6 to C9, comprises the MAC. C3b functions as an opsonin, whereas C3a and C5a have inflammatory and chemotactic properties. DAF (CD55) and MCP (CD46) are cell surface-expressed complement regulators that accelerate the decay of all surface-assembled C3 convertases, thereby limiting amplification of the downstream cascade. MCP and fH also have cofactor activity: in conjunction with soluble fI, they irreversibly cleave C3b to iC3b, thereby preventing re-formation of the C3 convertase. CD59 inhibits formation of the MAC.

CD59 (protectin), a cell surface-expressed regulator that inhibits formation of the MAC at the C9 step; factor H, a soluble complement regulatory protein that exhibits both decay-accelerating and cofactor activity; and CR1, which limits amplification of the complement cascade and MAC formation by inhibiting C3 convertases.

The majority of the complement components circulating in the blood (systemic compartment) are produced by the liver. Complement proteins are also generated by tissue-resident (e.g., tubular cells in the kidney, ref. 13) and migratory/immune cells, including T cells and APCs (14). Theoretically, non-liver cell-derived complement could activate and function locally without affecting systemic complement activation.

Complement and IR injury

The pathophysiology of post-transplant IR injury and delayed graft function (DGF) has been reviewed elsewhere in detail (15). Briefly, IR injury results from tissue hypoxia, mitochondrial damage, and ATP depletion, followed by the generation of free oxygen radicals upon reperfusion, which initially damage endothelium. Ensuing inflammation driven by TLR signaling and locally secreted cytokines, chemokines, and complement amplify the inflammation, resulting in tubular injury and kidney dysfunction.

Early evidence implicating a role for complement in IR injury derived from mouse models in which complement deposition and loss of membrane-bound complement regulators were described during kidney IR injury and overexpression of Crry ameliorated IR injury (16, 17). IR injury was later shown to be dampened in complement-depleted mice (18, 19) and in C3-deficient (16, 19), factor B-deficient (20) or C5-deficient (21) mice, while mice deficient in DAF (22) or in Crry and factor H (23, 24) (in which restraint on complement activation is lifted) were more susceptible to IR injury. Strikingly, IR injury studies performed in animals following transplantation of WT or C3-deficient kidneys into syngeneic WT or C3-deficient recipients showed that donor kidney-derived C3, and not systemic recipient C3, is the predominant mediator of IR injury (25).

Peng et al. (26) used C3a receptor- (C3aR-), C5aR-, and C3aR/C5aR-deficient mice and models of renal IR injury to demonstrate that deficiency of either or both of these receptors protected mice from injury. The C3aR/C5aR- and C5aR-deficient mice were most protected. Studies performed in BM chimeras showed that the absence of C3aR and C5aR on either renal tubular epithelial cells or circulating leukocytes attenuated renal IR injury, indicating that expression of C3aR and C5aR on both renal cells and circulat-



ing leukocytes contributes to the pathogenesis of renal IR injury. In these studies, protection from injury was associated with less cellular infiltration and lower mRNA levels of kidney injury molecule-1, proinflammatory mediators, and adhesion molecules in post-ischemic kidneys. One specific mechanism is that C3a produced in response to IR injury drives renal tubular epithelial cell production of chemokines (27). Together, the animal model data support the conclusion that IR injury upregulates production of complement components by kidney endothelial and tubular cells as well as by infiltrating immune cells. Local activation through the alternative pathway yields C3a and C5a, which amplify local inflammation and injury through autocrine and paracrine ligations with their receptors expressed on cells in the graft.

A role for complement activation in human IR injury was evaluated by de Vries et al. (28). These investigators detected soluble C5b-9 following reperfusion of deceased donor but not living donor kidneys. Whole genome expression profiling of 53 human renal allograft protocol biopsies obtained at implantation confirmed significantly higher expression levels of complement genes in deceased donor kidneys (29). Extending these findings prior to surgical removal of the donor organ, van Werkhoven et al. found that brain death initiates systemic complement activation, upregulates C5aR expression in renal tubular cells (30), and is associated with induction of intrarenal inflammatory cytokines. The authors hypothesized that complement activation that occurs in the donor accounts in part for the poorer outcomes of grafts harvested from deceased compared with living donors.

The recognition that complement participates in the pathogenesis of post-transplant IR injury has prompted investigators to test whether complement inhibitors are effective therapies. An analog of the human complement-regulatory protein CD35 (CR1; blocks complement activation at the C3 convertase step) has been conjugated to a myristoylated peptidyl tail, such that when administered by intravenous perfusion of the harvested organ *ex vivo* it will self-insert into the lipid bilayer of the EC membranes (31). Patel et al. used this approach to show that the reagent was effective in preventing post-transplant kidney IR injury in a rat model (32). The human reagent microcept (APT070) is currently being studied in a clinical trial for prevention of DGF (31). Eculizumab (Soliris; Alexion Pharmaceuticals Inc.), a humanized anti-C5 mAb that is FDA approved to treat paroxysmal nocturnal hemoglobinuria is also being tested for efficacy in preventing post-transplant DGF (NCT01403389; NCT01919346).

The aforementioned findings indicating that brain death is associated with complement activation in the donor kidney prior to organ removal raise the intriguing concept that complement inhibition in the donor could be an effective prophylactic therapy to prevent IR injury. Innovative study designs involving randomized treatment of organ donors and collaborations between organ procurement agencies and multiple transplant centers will need to be developed to test this possibility.

Complement and alloreactive T cells

Complement and effector T cells. Building upon the paradigm-shifting observation published in 2002 that WT mice do not reject allografts from C3-deficient donors (33), work from several groups, including ours, uncovered an unexpected role for complement as a regulator of T cell immunity. During cognate interactions between T cells and APCs, both partners upregulate and secrete alternative pathway complement components C3, fB, and fD, as well as the

common pathway protein C5, and upregulate surface expression of C3aR and C5aR (34, 35). These changes are a consequence of costimulatory molecule signaling via CD28/CD80/CD86 and CD154/CD40 (35), which simultaneously and transiently reduce cell surface-expressed DAF (thereby lifting restraint on complement activation). Locally produced C3a and C5a bind to their receptors and function as autocrine and paracrine stimulators of the T cell and the APC (34, 35). Signaling via these GPCRs in T cells activates PI3K γ and induces phosphorylation of the intracellular signaling molecule AKT (14, 35), upregulating the antiapoptotic protein Bcl2 and downregulating expression of the proapoptotic molecule Fas. Together, these complement-dependent mechanisms enhance T cell proliferation and diminish T cell apoptosis (14). The evidence also indicates that C3aR and C5aR signaling is required for T cell homeostasis, as T cells deficient in both receptors spontaneously undergo accelerated cell death *in vitro* and *in vivo* (35).

On DCs and macrophages, C3a/C3aR and C5a/C5aR ligations induce upregulation and release of innate cytokines (e.g., IL-12, IL-23) and costimulatory molecules (e.g., CD80, CD86) (35–38). APCs deficient in C5aR/C3aR or C3 produce less IL-12, express lower levels of CD80, and are weaker T cell stimulators than WT APCs, while DCs and macrophages obtained from mice genetically deficient in DAF produce more IL-12 and induce stronger T cell responses than cells from WT animals (35–38). Independent of the phenotype of the APC, T cells deficient in C3aR and C5aR signaling respond poorly to WT and *Daf1*^{-/-} APCs and undergo accelerated cell death (14, 35).

Alloresponses are dampened in WT chimeric mouse recipients of C3^{-/-} BM, despite normal serum complement. In contrast, C3-deficient chimeric hosts repopulated with WT BM exhibited normal T cell alloreactivity (14, 39). Analogously, BM chimeras produced using C5aR-deficient donors or recipients confirmed that T cell immunity is dependent on C5aR expression on BM-derived cells (14, 39).

Complement and T cell-mediated rejection. Studies performed in transplant models revealed WT mice reject *Daf1*^{-/-} heart allografts with accelerated kinetics (39), and that the accelerated rejection is due to a complement-dependent augmentation of antidonor T cell immunity. Collaborative work additionally showed that donor or recipient DAF deficiency accelerates skin graft rejection (34) and overcomes the immune privilege of the eye by enhancing pathogenic T cell alloimmunity induced by normally tolerogenic corneal transplants, resulting in rapid corneal rejection (40).

CD8⁺ T cells, the principal mediators of solid organ transplant rejection, require helper signals derived from CD4⁺ T cells in order to become optimal pathogenic effector cells (CD4-deficient mice do not reject cardiac allografts; ref. 41). Current concepts regarding how CD4⁺ T cells help alloreactive CD8⁺ T cells are that during cognate TCR/APC interactions, CD154 expressed on CD4⁺ T cells transmits activating signals to APCs through ligation with CD40 (42, 43). This in turn upregulates costimulatory molecule (CD80/86) and MHC expression on the APC and induces proinflammatory cytokines (e.g., IL-12), which together facilitate optimal CD8⁺ T cell activation, expansion, differentiation, and survival. Building upon previous findings linking complement to T cell activation, our research group provided experimental evidence, using *in vivo* transplant models, that immune cell-derived complement is a crucial molecular intermediary underlying how CD4 cells provide help to alloreactive CD8⁺ T cells required for rejection (44).



Local complement production also influences effector CD8⁺ T cell responses to allogeneic vascular ECs (45). Experiments performed using in vitro culture systems and in vivo heart transplantation models showed that complement is produced by ECs and regulates T cell function and expansion (46). The effects of EC-derived complement are transmitted in part through C5aR signaling on T cells (45).

C5a/C5aR interactions also modulate T cell-dependent kidney transplant rejection in rodents (47). Together with the findings that anti-C5 mAb synergizes with CTLA4-Ig to prevent T cell priming, limits T cell trafficking to an allograft, and prolongs transplant survival in mice (48), the body of work supports the conclusion that complement is a physiologically important regulator of pathogenic T cell immunity that causes allograft rejection in animal models.

Important confirmatory human experiments published in 2013 showed that C3a and C5a are generated during in vitro cultures of human T cells responding to allogeneic DCs (49). Both partners express the receptors for C3a and C5a (50–53), and C3aR and C5aR antagonists inhibit human T cell proliferation (49). Recombinant C3a/C5a promote human CD4⁺ T cell expansion, bypassing the inhibitory effects of CTLA4-Ig, and inducing AKT phosphorylation. Lowering human DC C3a/C5a production by siRNA knockdown of DC-expressed C3 reduces human T cell alloresponses. Conversely, downregulating DC expression of DAF increases immune cell C3a/C5a and augments human alloreactive T cell proliferation, identifying APCs as the dominant complement source (49). In vitro studies by Zhou et al. also showed that different subsets of human DCs produce complement, and that C5aR/C3aR signaling regulates DC activation and function (54). Pharmacological C5aR blockade reduced human anti-mouse graft-versus-host disease (GVHD) scores and inhibited T cell responses in NOD/SCID/ γ c^{null} mouse recipients of human peripheral blood mononuclear cells, verifying that the C5aR-dependent effects on human T cells apply in vivo (49).

In further support of the clinical relevance of local complement in human transplantation, the quantity of RNA message for alternative pathway complement components and complement receptors, including C5aR and C3aR, is higher in human allograft biopsies with histologic evidence of rejection compared to non-injured control tissue (47, 55).

Complement and Tregs. Tregs are instrumental for tolerance induction and maintenance (56) in rodents and are associated with improved long-term transplant outcomes in humans (56, 57). Data published in 2013 indicated that complement also regulates Treg induction, function, and stability (58, 59). Our laboratory demonstrated that peripheral murine natural Tregs (nTregs) express C3aR and C5aR, and that signaling through these receptors inhibits Treg function (60). Genetic and pharmacologic blockade of C3aR/C5aR signal transduction in nTregs augments their in vitro and in vivo suppressive activity, abrogates autoimmune colitis, and prolongs allogeneic skin graft survival. Mechanisms involve C3a/C5a-induced phosphorylation of AKT and, as a consequence, phosphorylation of the transcription factor Foxo1, which results in lowered nTreg Foxp3 expression. Two additional sets of data showed that genetic deficiency or pharmacologic blockade of C3aR/C5aR signaling augments murine induced Treg (iTreg) generation, stabilizes Foxp3 expression, resists iTreg conversion to IFN- γ /TNF- α -producing effector T cells, and as a consequence, limits the clinical expression of GVHD (58, 59).

Immune cell-derived complement also modulates human Treg generation and function (58, 61). Pharmacologic antagonists to human C3aR and C5aR augment in vitro generation and stability of human iTreg from naive precursors. In NOD/SCID/ γ c^{null} mouse recipients of human peripheral blood mononuclear cells, we showed that pharmacologic C5aR blockade enhances human iTreg generation and stability and results in better disease protection (61). These clinically relevant translational findings provide proof of concept that C3a/C3aR and C5a/C5aR ligations are viable targets for facilitating iTreg-mediated transplant tolerance.

Building upon previously published evidence that coengagement of the TCR and the complement regulator CD46 promote regulatory IL-10 production (62), these new results underscore the crucial role of complement in modulating the balance between pathogenic and protective adaptive T cell responses. Whether complement antagonists can therapeutically control T cell alloreactivity while simultaneously promoting Treg induction, function, and stability in transplant patients remains to be determined. 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 transplant injury

Donor reactive anti-HLA antibodies are generally accepted as pathogenic mediators of acute and chronic transplant injury (63). It has been known for decades that complement depletion impairs antibody production (64). One mechanism involves antigen-bound C3dg (a C3b cleavage product; see Figure 1) binding to B cell-expressed complement receptor 2 (CD21), which facilitates antigen presentation to B cells and lowers the threshold for B cell activation (65, 66). Isotype switching in B cells that results in IgG production is dependent upon T follicular helper (T_{FH}) cell/B cell interactions (reviewed in ref. 67), transmitted in part by IL-21/IL-21 receptor, and CD40/CD154, ligations. As outlined above, T cell immunity is regulated by locally produced complement, indicating that complement could impact antibody production indirectly through regulating T cell immunity. To our knowledge, there are no data addressing whether complement specifically alters induction, function, or stability of T_{FH} cells. Regardless of the specific mechanism, C3-deficient mice fail to produce high-affinity IgG responses against major histocompatibility antigens in skin grafts (68), demonstrating the relevance of complement's influence over antibody formation in response to transplant antigens. Whether complement blockade impacts anti-HLA antibody formation in human transplant recipients has not been tested.

Once produced, anti-HLA antibodies can bind to donor tissue and mediate damage through multiple mechanisms including those that are complement dependent (69). An unequivocal role for alloantibody-initiated, complement-dependent human kidney transplant injury was first documented in the 1969 Terasaki article (70), in which the authors showed that patients with serum containing antibody capable of inducing complement-dependent donor cell lysis strongly predicted hyperacute kidney transplant rejection. The importance of complement as an effector mechanism of antibody-initiated allograft injury was illustrated by studies using anti-C5 mAb in presensitized murine allograft recipients (71). These experiments revealed that inhibition of the C5 convertase, in combination with cyclosporine and short-term cyclophosphamide treatment, prevented acute rejection and resulted in prolonged allograft survival despite persistent antidonor IgG in the sera and in the graft (71). Extending the ther-

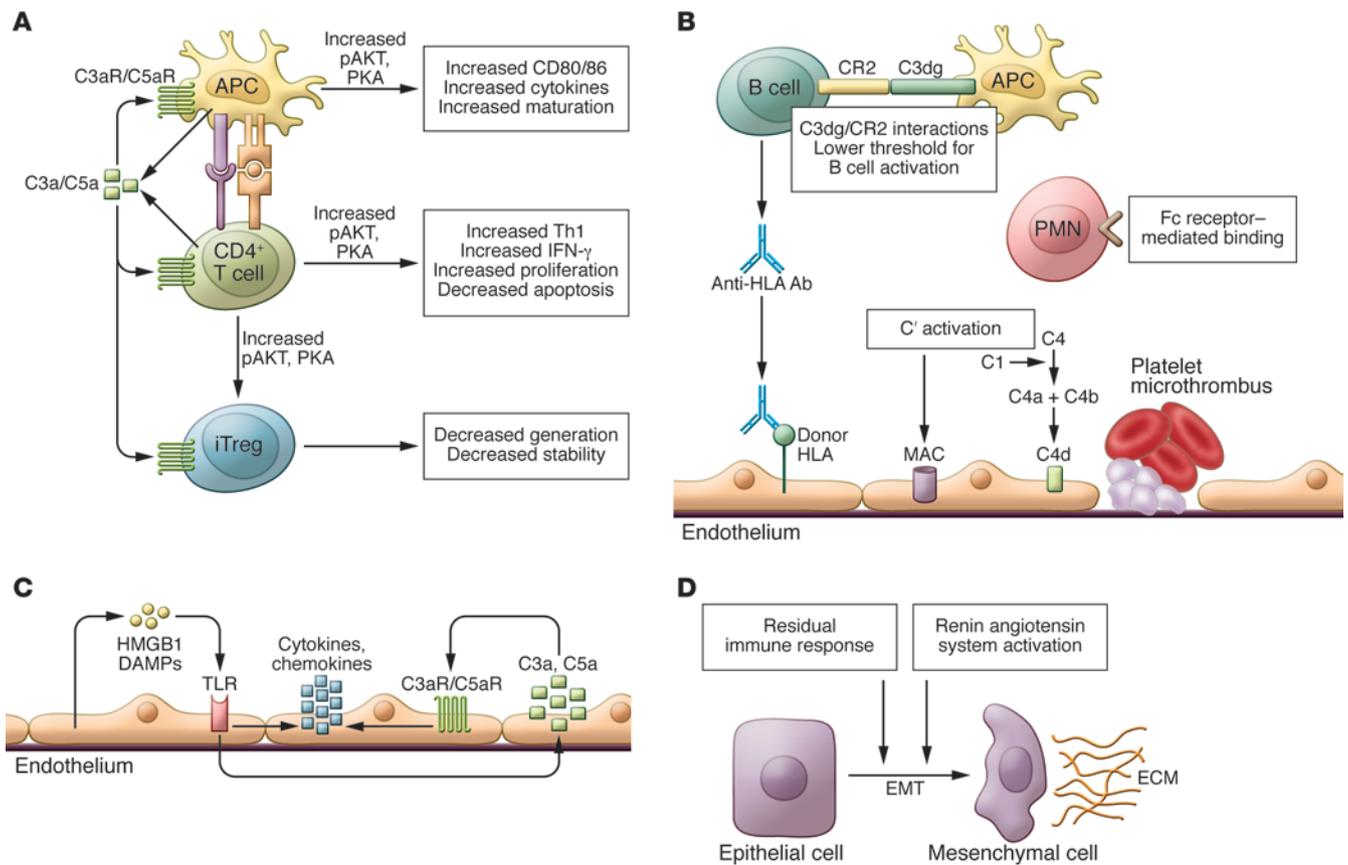


Figure 2

Overview of pathogenic mechanisms linking complement to kidney transplant injury. **(A)** During cognate interactions between alloreactive T cells and APCs, alternative pathway complement components are released and undergo activation, yielding C3a and C5a. Upon binding to their respective G protein–coupled receptors, these anaphylatoxins stimulate PKA and induce PI3K γ -dependent pAKT, together amplifying alloreactive Th1 T cell expansion and inhibiting Treg induction, function, and stability, thus facilitating acute and chronic graft rejection. **(B)** The antigen-bound complement degradation product C3dg binds to B cell–expressed CR2, lowering the threshold for B cell activation and antibody production. Complement may indirectly enhance antibody production by augmenting T cell help (not shown). Classical pathway–dependent, complement-mediated effector mechanisms initiated by cross-linking tissue-bound, donor-reactive (IgG) antibodies also contribute to allograft injury. Insertion of the MAC into the EC results in EC activation. C3a and C5a mediate chemoattraction and activation of polymorphonuclear (PMN) cells, which, through Fc receptors, ligate Fc portions of antibodies bound to endothelium, contributing to injury. **(C)** IR leads to the production of ROS, which in turn promote release of DAMPs, including HMGB1, chemokines, cytokines, and complement components, by ECs and tubular and infiltrating cells. Through alternative complement pathway activation, locally generated C3a and C5a contribute to EC and tubular cell activation and injury, enhancing inflammation and graft immunogenicity. **(D)** Locally produced (intra-graft) and activated complement contributes to progressive injury and fibrosis, in part through stimulating the renin angiotensin system and driving epithelial-mesenchymal transition.

apeutic approach to humans, the anti-human C5 mAb eculizumab plus plasma exchange reduced the incidence of antibody-mediated rejection in 26 sensitized kidney transplant recipients compared with a historical control group of 51 patients treated with a plasma exchange–based protocol alone (72). Anti-C5 mAb also successfully reversed established antibody-mediated rejection (73). In light of the association between anti-HLA antibodies and chronic antibody-mediated graft rejection, ongoing studies are testing the efficacy of eculizumab in preventing graft loss in kidney transplant recipients with donor-specific antibodies (NCT01327573).

From a diagnostic/biomarker standpoint, investigators hypothesized that detection of serum anti-HLA antibodies capable of binding C1q would enhance the prognostic utility of serum alloantibody analysis in kidney transplantation (74, 75). The latest iteration of the single antigen bead technology currently used for detecting anti-HLA antibodies (76) additionally identifies those antibodies

that bind C1q. A 2013 population-based study of 1,016 kidney transplant recipients suggested that, among patients with anti-HLA antibodies, those that were C1q⁺ had the worst graft survival (77).

Colvin and colleagues pioneered the use of C4d staining in graft tissue as a diagnostic test for antibody-mediated allograft rejection (AMR) (78). C4d is an activation byproduct of classical pathway complement activation and its detection in graft tissue is more sensitive than detection of immunoglobulin. As a consequence, C4d staining has become a valuable tool for diagnosing AMR. Importantly, diagnostic sensitivity depends on staining methodology and cases of C4d⁻ AMR have been described (79).

Complement and kidney graft injury and fibrosis

Mechanisms of late graft failure are complex and involve immune and non-immune mechanisms (80), but late graft loss routinely results in pathological evidence of progressive glomerulosclerosis,



IF/TA, and arteriosclerosis (81, 82). The functional and structural changes of chronic renal allograft failure share similarities with those observed in other forms of chronic progressive kidney disease, in which decline of functioning nephron mass has been considered the key event (83).

Unexpectedly, several pieces of evidence suggest that intragraft complement activation contributes to this progressive kidney injury. C3^{-/-} kidney isografts transplanted into WT recipients were protected from toxin-induced tubular damage, proteinuria, and progressive renal failure, despite the presence of abundant circulating C3 (84). Follow-up work showed that C3 is implicated in the activation of the renin-angiotensin system and in the epithelial-to-mesenchymal transition (85, 86), supporting the concept that synthesis of complement components by renal epithelial cells is one critical mediator of tubular damage in proteinuria-associated renal disease. As proteinuria is one hallmark of kidney graft dysfunction (87), these results raise the possibility that kidney-derived complement participates in the development of IF/TA after transplant.

Indirect associative evidence linking complement to progressive transplant injury derives from studies of complement gene polymorphisms and transplant outcomes in humans. Specific C5 polymorphisms in both the donor and the recipient have been associated with worse late graft function, but interestingly not with the risk of acute rejection (88). Although controversial, some additional evidence suggests that donor kidney expression of a specific polymorphic variant of C3 is associated with worse post-transplant outcomes (89, 90). 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 strong associations between IF/TA and the alternative pathway, but not the classical pathway, complement components (91). An ongoing study of chronic anti-C5 mAb therapy in kidney transplant recipients (NCT01327573) could potentially provide further insight into the role of complement as a mediator of progressive graft dysfunction and IF/TA.

Conclusions

The complement system is now firmly established as a pervasive, multifaceted mediator of transplant injury in animal models, and studies from multiple groups have largely confirmed that these newly recognized mechanisms apply to human transplant recipients (Figure 2). This success of translational immunology, along with the development of pharmacologic agents that block human complement components and receptors (92, 93), now allows for testing of the intriguing concept that targeting complement in kidney transplant recipients will improve graft survival and patient health.

Acknowledgments

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