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Role of Complement in Humoral Immunity

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Abstract

Purpose of review: Antibody mediated rejection (AMR) after solid organ transplantation remains an unsolved problem and leads to poor early and late patient outcomes. The complement system is a well-recognized pathogenic mediator of AMR. Herein we review the known molecular mechanisms of disease and results from ongoing clinical testing of complement inhibitors after solid organ transplant.

Recent findings: Activation and regulation of the complement cascade is critical not only for the terminal effector function of donor-specific antibodies, but also for the regulation of T and B cell subsets to generate the anti-donor humoral response. Donor specific antibodies (DSA) have heterogenous features, as are their interactions with the complement system. Clinical testing of complement inhibitors in transplant patients have shown good safety profiles but mixed efficacy to date.

Summary: The complement cascade is a critical mediator of AMR and clinical trials have shown early promising results. With the steady emergence of novel complement inhibitors and our greater understanding of the molecular mechanisms linking complement and AMR, there is greater optimism now for new prognostic and therapeutic tools to deploy in transplant patients with AMR.

Keywords

Antibody mediated rejection; Complement; DSA

Introduction

Advances in recipient-donor matching and immunosuppression have greatly improved post-transplant allograft survival. However, anti-donor humoral immunity remains a persistent barrier to optimal solid organ transplant outcomes. Antibody-mediated rejection (AMR) is mediated by pre-formed or de novo generated donor-specific antibodies (DSA) and can occur alone, or alongside cellular rejection [1]. DSA are most commonly directed against

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human leukocyte antigens (HLA) I or II but can be directed against non-HLA molecules as well [2], and mediate injury through both complement dependent and independent effector mechanisms [3].

Generation of a robust humoral response against the donor graft requires cognate interactions among specialized germinal center (GC) cells, including T-follicular helper (Tfh) and GC B cells (GCB), to produce high affinity class switched pathogenic antibodies [4,5]. The complement system has a central role in the regulation of these interactions, and is a key effector mechanism of alloantibody-induced damage [6].

The complement system is comprised of over thirty soluble and membrane bound proteins, the effector molecules of which are primarily zymogens requiring cleavage for activation [7]. Classically considered an effector arm of innate immunity, the complement system is now well recognized as an essential factor for promoting adaptive immune function, including humoral immunity [8,9]. While circulating complement is predominately generated in the liver and crucially acts as an important cell-independent effector mechanism in antibody-mediated graft injury, complement components are also produced by other cell types, including activated endothelial cells, antigen presenting cells (APCs), T cells and B cells, and activates locally to enhance cellular function and augment inflammation [10].

Complement activation can occur via three distinct pathways: the classical, mannose binding lectin (MBL), and alternative pathway. The classical pathway requires antibody-antigen complexes to be recognized by C1q, which then forms the C1qrs complex to cleave C4 and initiate the cascade. Mannose binding lectin (MBL) can recognize mannose expressed on bacterial surfaces, ficolins and collectins, as well as the Fc fragment of bound immunoglobulins (akin to C1q), to permit mannose associated serine proteases (MASPs) to cleave C4 [11]. The alternative pathway requires no pattern recognition and instead relies on low level spontaneous hydrolysis and cleavage of C3 in a factor B- and factor D-dependent manner with a “tick over” mechanism [12]. Initiation of the complement cascade generates C3 convertases and converge at a central amplification loop to cleave C3 into an anaphylatoxin (C3a) and opsonin (C3b), which via the alternative pathway, generates additional C3 convertases. Subsequent cleavage of C5 generates C5b and the anaphylatoxin C5a. The former ligates with C6-C9 to form the membrane attack complex (MAC), creating pores in cell membranes that lyse non-nucleated cells and leads to activation of nucleated cells [13]. B cells, macrophages and dendritic cells express various complement receptors that recognize specific complement opsonins and anaphylatoxins [9].

To limit off-target damage, the complement cascade is tightly regulated at multiple points via circulating and cell surface bound proteins. Circulating C1 inhibitor (C1INH) deactivates both the C1qrs and MASP complexes, while the surface bound regulators decay accelerating factor (DAF, CD55) and CD59 degrades C3 convertases and inhibits the MAC complex, respectively. Factor I with its cofactors, factor H and membrane bound cofactor protein (MCP) further irreversibly cleave C3b into the inactive form iC3b and ubiquitous carboxypeptidases rapidly inactivate the anaphylatoxins C3a and C5a [14].

Activation and regulation of the complement cascade is critical to the generation of the DSA response and the subsequent graft injury caused by alloantibodies. Herein we will review our current understanding of these pathways in solid organ transplantation and how complement-targeted therapeutics are being tested to improve patient outcomes in AMR.

Complement and regulation of T helper cells

The complement system's regulation of T cell function [15] is primarily mediated by local immune cell-derived complement, with a smaller contribution from the liver-derived circulating complement [16]. During cognate T cells interactions with endothelial cells and APCs, engagement of the T cell receptor (TCR) and the costimulatory molecule CD28 induces protein expression of the complement components C3, C5, factor B, and factor D, and reduces expression of the complement regulator DAF on the cell surface [17,18]. Secreted and activated locally, C3a, C5a, and C3b bind in an autocrine manner to their receptors C3a receptor 1 (C3aR1), C5a receptor 1 (C5aR1) and CD46, respectively, to stimulate the synthesis of IFN-γ and promote Th1 polarization [19–21].

More recent paradigm shifting work has also established that complement activates intracellularly in both mice and humans to regulate cell survival and function [19,20]. In resting T helper cells, the protease cathepsin L constitutively cleaves intracellular C3 to generate C3a, which binds to C3aR expressed on lysosomal membranes leading to downstream activation of the mammalian target of rapamycin (mTOR) and enhancing cell survival [19]. During diapedesis, binding of integrin lymphocyte function-associated antigen (LFA)-1 on the T cell surface induces intracellular C3 synthesis, which is then cleaved upon TCR stimulation [22]. Moreover, intracellular C5a has been shown to enhance cell activation through generation of mitochondrial reactive oxygen species and to increase the NLRP3-dependent production of IL-1beta to promote Th1 polarization [20].

C5aR1 signaling on CD4 T cells can also promote Tfh polarization. Ligation of C5aR1 induces the expression of the transcription factor c-Maf and the prototypical Tfh cytokine IL-21. In a murine model of pulmonary graft vs host disease after stem cell transplant, genetic ablation or pharmacologic blockade of C5aR1 reduced Tfh cell differentiation, GC B cell expansion and the formation of autoantibodies, which resulted in attenuation of established disease [23]. How this mechanism applies after solid organ transplantation remains to be tested.

Signaling through the anaphylatoxin receptors C3aR and C5aR has been also shown to play a critical role in the function of regulatory T cells (Treg), which suppress immune activation. Blockade of C3aR and C5aR signaling in conventional CD4 T cells initiates TGF-β1 signaling that results in induction of regulatory T cells [24], and also augments Treg suppressive capacity [25]. T follicular regulatory cells (Tfr) are a unique subset of nTregs that are localized in B cell follicles and regulate the Tfh-GC B cell interaction [26], but whether and how C3a/C5a signaling specifically impacts Tfr function remains unknown.

Complement effects on B cells in lymphoid organs

Expression of complement receptors, including CR1/CD35 and CR2/CD21, which bind C3b/C4b and C3d, respectively, has been shown on B cells of both mice and humans

[27]. B cells can transport C3-coated immuncomplexes to follicular dendritic cells via CD21 ligation [28] and binding of C3d-coated antigen to the CD21/CD19/CD81 co-receptor augments B cell receptor (BCR) signaling [29]. Complement-mediated enhancement of BCR signaling is necessary to promote early naïve B cell survival [30], and antigen-specific B cells devoid of the CD21 and CD35 complement receptors fail to survive during the GC reaction, consistent with the concept of complement signaling as a necessary survival mechanism during times of cellular stress [31].

Recent work by Cumpelik et al. built on these observations and showed that heightened complement signaling is mediated through coordinated changes in the surface expressed complement receptors and regulators on GCB cells [32]. The work newly demonstrated that induction of Bcl6, the canonical transcription factor for GCB cell differentiation, crucially leads to simultaneous downregulation of DAF (CD55) and upregulation of CD59. GCB cells are thus able to augment C3-convertase activity (and subsequent C3aR1/C5aR1 signaling) while concurrently protecting themselves from MAC-induced lysis and injury. Genetic or pharmacologic blockade of this mechanism significantly abrogated antibody production and maturation in their models [32].

Complement-activating DSA

The direct effects of complement activation on allografts by DSA have been well described and reviewed in depth previously [3]. During humoral rejection, complement activates via the classical and MBL pathways to induce inflammation and graft injury through the anaphylatoxins C3a/C5a and insertion of MAC [33]. In kidney transplantation, deposition of C4d in the capillaries of the allograft was previously a required diagnostic criterion of AMR, but observations detailing the existence of AMR without evidence of complement activation have led to updates to the Banff histologic criteria [34].

The DSA response is composed of a heterogenous mix of antibody subclasses (IgM and IgG) that also change over time, complicating mechanistic studies. However, by assessing a cohort of patients who developed DSA in the first year post-transplant, Lefaucher et al. were able to describe the antibody composition among those who developed accelerated acute AMR, slow chronic AMR, and patients who never developed AMR. The study found that transplant recipients with an IgG3 component in their DSA response had a higher incidence of acute AMR and worse prognosis, while those with an IgG4 response had a more indolent course of chronic rejection. Moreover, detection of C1q binding by DSA could be used to stratify patients with any type of AMR compared to those without AMR [35].

Since specific subclasses of antibodies bind C1q efficiently (eg IgM, IgG3) while others do not (eg IgG4), the significance of C1q binding ability of DSA in AMR has been investigated by several groups. Loupy et al. followed graft outcomes in over 1000 kidney transplant recipients, stratifying for presence of anti-HLA DSA and C1q binding ability, and found that patients who developed C1q-binding anti-donor DSA in the first year post-transplant had significantly worse 5 year graft survival the lowest eGFR at 1 year, and the poorest graft histology on 1 year protocol biopsies [36]. However, a subsequent study by Sicard et al. that assessed complement activation in patients diagnosed with AMR did not find C1q binding as a statistically significant risk factor for graft loss, but did identify serum C3d,

a more terminal marker of complement activation, as an important prognostic factor [37]. Importantly, C1q-binding status and C3d levels correlated tightly with the strength of the DSA response in the respective studies suggesting an element of confounding to some of these observations.

Taken together the current data implicate classical pathway complement activation as an important component and possible biomarker of anti-donor humoral immunity. However, further studies are needed to clarify mechanism to improve our interpretation of these findings as we apply them to patient care.

Complement therapeutics in AMR

Early clinical trials targeting the classical pathway in patients with or at risk for AMR have shown a good tolerability and safety profile, but have been underpowered to draw significant conclusions on efficacy [38]. C1-inhibitor (C1INH) is an FDA approved treatment for hereditary angioedema and is sold commercially as a product derived from pooled human plasma (eg. Berinert) or in a recombinant form (eg Ruconest, Cinryze). A phase I/II study that added C1-inhibitor (C1INH) to a standard of care desensitization protocol for highly sensitized patients undergoing kidney transplantation showed no drug-related adverse events and demonstrated biochemical evidence for decreased complement activation (increased C3 and C4 levels), but also no clear effect on prevention of AMR [39]. A subsequent placebo-controlled phase 2 study of C1INH therapy as add-on to standard of care treatment for patients with acute AMR within the first month of transplant by Montgomery et al. showed no significant effect on early day 20 post-treatment biopsy scores but did show a trend toward improved kidney function in the C1INH arm. Intriguingly, a *post hoc* analysis of a subset of the participants who underwent 6-month protocol biopsies showed that almost half of patients randomized to placebo compared to none of those who received C1INH had transplant glomerulopathy, which is associated with poor long term graft survival [40]. Unfortunately, a phase III study of C1INH in treatment of AMR was terminated due to futility after an early time point interim analysis (NCT02547220) but based on the findings by Montgomery et al, it is possible that C1 blockade during AMR provides benefit in the long term and only a modest effect on early outcomes.

In an alternative strategy, the novel humanized anti-C1s antibody BIVV009 was shown to be safe in a small set of stable kidney transplant recipients with late AMR and able to block classical pathway complement activation in a short pilot study [41]. An ongoing study is currently testing the newer anti-C1s antibody (BIVV020), which can be administered subcutaneously, for prevention and/or treatment of AMR (NCT05156710). Data from anti-C1s trials may also be mechanistically insightful in separating the effects of the classical and MBL pathways in AMR, since C1INH non-specifically dissociates the C1qrs complex as well as the MASPs [42].

Several groups have also looked at blocking the complement cascade more distally. Preclinical studies testing C5 blockade in sensitized murine heart [43] and kidney [44] transplant models showed striking efficacy with anti-C5 treatment inducing >100 days of graft survival of both heart and kidney transplants despite persistence of DSA. Histologic analysis was consistent with development of accommodation, a poorly understood state

of graft resistance to persistent circulating DSA [45]. The researchers demonstrated that C5-blockade associated accommodation required changes in both the recipient and the allograft [43], though the exact mechanisms remain to be described.

Unfortunately, human trials of C5 blockade using eculizumab to prevent or treat morbidity AMR in human transplant recipients have had mixed results. Stegall et al performed an initial phase II trial testing eculizumab as a strategy to reduce AMR in highly sensitized living donor kidney transplant recipients and showed a significant reduction in biopsy-proven AMR at 3 months compared to standard of care historic controls (2/26 vs 21/51) [46]. Unfortunately, a subsequent randomized control trial in a similar group of sensitized living donor recipients was unable to replicate the benefits (NCT01399593) [47] and a trial testing eculizumab as treatment of AMR in kidney transplant patients was terminated early due to lack of efficacy (NCT01895127). An ongoing study using C5 inhibition to prevent AMR in sensitized cardiac transplant recipients (NCT02013037) has shown early promise with a reduction in biopsy proven AMR and a trend toward improved allograft vasculopathy at one year. But the trial design uses a single experimental arm and historic controls (similar to Stegall et al.) and 90% of the eculizumab treated patients underwent some form of pre-transplant desensitization therapies [48].

Upstream of C5, C3 blockade has shown promise in sensitized primate kidney recipients. The inhibitor Cp40 prevents activation of C3, blocking the central amplification loop and reducing generation of both C3a and downstream C5 activation [49]. Rhesus monkeys maximally sensitized with allogeneic skin transplants rapidly rejected kidney transplants (median survival time 4 days). Addition of Cp40 was able to prolong graft survival (median survival time 15.5 days, with one animal survival to almost 50 days) and was associated with lower T and B cell proliferation and diminished CD8 T cell activation [50]. A human C3 inhibitor (AMY-101) is now being tested in human clinical trials but in non-transplant conditions (NCT0369444, NCT04395456). The elevated infectious risks associated with blocking the central C3 amplification loop will need careful consideration if being tested in already immunocompromised transplant population.

Altogether the data suggest complement's primary effects in human solid organ AMR are likely heterogeneous and that while no single prevention or treatment strategy is likely to be universally effective, properly targeted complement inhibition has great therapeutic promise.

Conclusion

While AMR remains a challenge in transplantation, new findings have advanced our understanding of complement's role in both mediating and generating the DSA response after solid organ transplantation [6,7]. First-in-kind and phase II clinical trials testing complement inhibitors at all levels of the cascade have provided strong safety data but mixed clinical efficacy, owing to sample size, heterogeneity of the anti-donor antibody response, and the diverse complement-dependent and independent effector mechanisms of AMR [39,41,48,49].

Ongoing work testing novel complement inhibitors and continuing work defining the spectrum of disease broadly encapsulated as AMR will help refine our understanding of how to deploy complement inhibition to improve long term outcomes. The field is poised for exciting breakthroughs thanks to a burgeoning market of complement-related therapeutics and a new era of personalized precision medicine.

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Key Points:

- The various components of the complement cascade have heterogeneous effects on antibody mediated rejection after solid organ transplantation.
- Complement is necessary for the generation and the injurious effector function of donor specific antibodies.
- Complement inhibitors continue to be tested for both the prevention and treatment of AMR after solid organ transplantation but have had mixed success to date likely due to heterogeneity of the disease and patient population.