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Locally produced and activated complement as a mediator of alloreactive T cells

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1. ABSTRACT

Immune-mediated rejection remains a significant obstacle preventing long term survival of transplanted organs. Emerging information derived from multiple groups has recently shown that the complement system, traditionally considered a central arm of innate immunity and a primary effector arm of antibody-mediated immunity, plays an additional key role as a regulator of adaptive alloreactive T cell immunity. Complement components produced by immune cells are activated locally and the resultant activation products guide the development of effector T cell immune responses. In the context of organ transplantation, manipulation of local complement activation influences the strength and effector functions of alloreactive T cells which are central mediators of immune mediated rejection. Further definition of the molecular basis underlying complement's effects on cellular alloimmunity has the potential to provide novel targets for the prevention and treatment of injury to solid organ transplants.

2. INTRODUCTION

Organ transplantation is an illustrative example of how the complement system integrates with alloreactive T cells and alloantibodies to generate an aggressive effector immune response, which if left unchecked will result in graft injury and ultimately organ failure. While classical pathway-initiated complement activation is an established effector mechanism of alloantibody mediated graft injury, recent functional studies have extended the role of complement in organ transplantation by highlighting the importance of local, as opposed to systemic/serum, complement synthesis and activation in immune activation. The focus of the present review is to summarize these new insights into how local, graft-derived complement specifically influences the function of alloreactive T cells and subsequently the pathophysiology of transplantation. Recent overviews of complement function have been published elsewhere (1, 2).

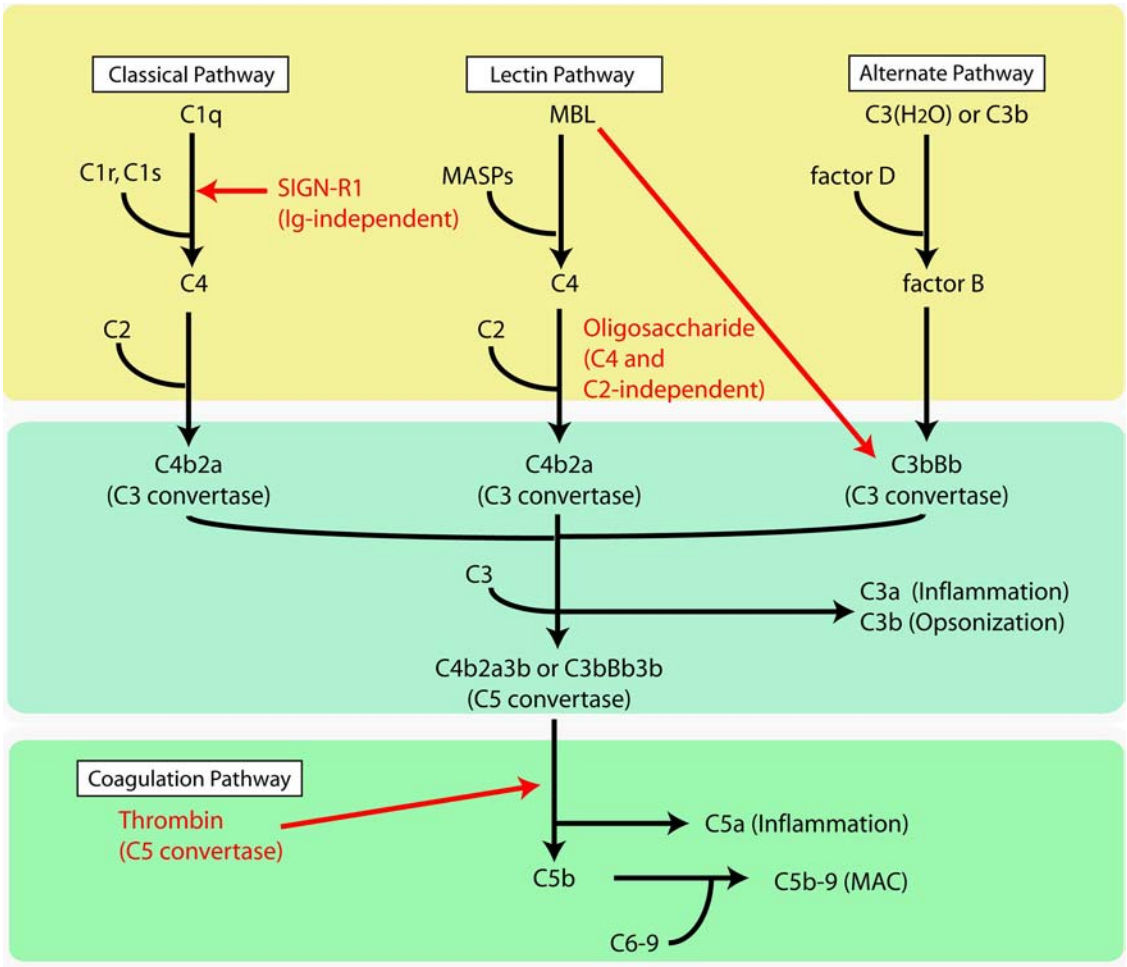

Figure 1. The complement cascade. Bypass activation pathways are highlighted in red.

3. OVERVIEW OF THE COMPLEMENT CASCADE

The complement system, traditionally considered a central arm of innate immunity and a primary effector arm of antibody-mediated immunity, consists of a set of soluble and cell surface proteins including components, receptors and regulators. Through pattern-recognition, the complement system plays a major role in host defense and the inflammatory response, and forms an important link between innate and adaptive arms of immune response (1, 2).

Complement can be activated through three main routes, namely the classical, alternative, and mannose binding lectin (MBL) pathways (Figure 1). The convergence point of the three pathways is the assembly of C3 convertases that cleave C3 into C3a and C3b, subsequently forming C5 convertases that cleave C5, releasing C5a and resulting in C5b-9 formation (membrane attack complex, MAC).

Complement proteins present in serum or body fluid, such as C3, C1q and MBL, can bind directly to the surface of certain pathogens, triggering complement activation on their surfaces. Besides initiating the formation of the MAC that mediates direct microbial killing, cleavage of the pivotal component C3 generates several biological effectors, including the surface associated fragment C3b and its derivatives (e.g. iC3b, C3dg) and released activation fragments C3a and C5a, which can bind to their receptors on a variety of cell types participating in microbial elimination and inflammation (Fig 1). For example, CR3, CR4 and the newly identified CRIg (3), which are present on many leukocytes, recognize C3b- or iC3b-coated (opsonised) pathogens and altered self-tissues/molecules leading to uptake by phagocytes. Complement receptors CR1 and CR2 that are present on immune cells (e.g. B cells and follicular dendritic cells) also recognise (C3b, C3dg)-opsonised antigen, augmenting the retention of antigen and facilitating the antigen-specific B cell response in secondary lymphoid tissue. Receptors C3aR and C5aR (7 transmembrane-spanning G-protein coupled receptors) found on both myeloid and non-myeloid cells, detect complement activation products C3a and C5a, which initiate a series of pro-inflammatory responses, such as contraction of smooth muscle cells, increasing in the

permeability of blood capillaries and chemotaxis. In addition to their known effector functions in the innate response, recent evidence for C3a and C5a as regulating adaptive immunity has emerged (see below).

Current dogma is that activation of the classical pathway requires immune complexes, that MBL-mediated complement activation is dependent on the classical pathway components (C4 and C2), and that C3 activation (which can occur spontaneously via the alternative pathway) is required for the formation of the C5 convertase. New findings reveal that MBL can induce C3 deposition by engagement of the alternative pathway and formation of the C3 convertase C3bBb in the absence of C2 or C4 (4), thrombin can directly activate C5 and generate C5a (5), and SIGN-R1 (a mannose receptor) can assemble the C3 convertase independently of either antibody or factor B (6). The discovery of these "bypass" pathways highlights the complexity of the system and cautions against too focused an approach with therapy using inhibitors that block a single factor in the cascade.

4. THE ROLE OF COMPLEMENT IN TRANSPLANT REJECTION

Given the known functions of complement in both innate and adaptive immunity, and the pathophysiological complexities of organ transplantation (including tissue trauma, ischemia reperfusion injury, immune-mediated rejection), inappropriate or excessive complement activation in the transplant setting could significantly impact allograft injury through multiple mechanisms. We will summarize some advances in our understanding of how complement activation contributes to the inflammatory response and modulates allospecific T cell immunity leading to allograft rejection. The effects of complement on B cell and alloantibody-mediated injury has had extensive review elsewhere (7, 8).

4.1. Complement contributing to the inflammatory response

Tissue injury upon reperfusion of a vascularised organ after an extended period of ischemia is unavoidable following transplantation. Multiple studies, using complement deficient animals and complement inhibitors, have demonstrated that absence of specific complement components or activators (e.g. C3, C4, C5, C6, C9, factor B, factor D) or receptors (e.g. CR2) protected animals from I/R injury (9-15). The deficiency of complement control proteins (e.g. CD59, CD55) can exacerbate I/R injury, and anti-complement treatment (e.g. CVF, sCR1, C1-inhibitor, anti-C5 antibody, C5aR antagonist, *Crry*) can reduce, I/R injury (9-15). The trigger for complement activation as a result of ischemia and reperfusion could be natural antibody, C3 (H_2O) or unidentified endogenous molecules (16). MBL deficient animals were also protected from I/R injury (17-19), suggesting that MBL as a pattern recognition molecule could play a dual role in modifying inflammatory responses to infectious and non-infectious injuries. It is possible that the MBL pathway could initiate complement activation that is amplified via the alternative pathway loop, thus explaining the predominant role for the alternative pathway in renal models previously observed (12, 20).

While it had largely been assumed that systemic complement, not locally produced complement, mediated I/R injury, Farrar and colleagues found that kidney-derived synthesis of C3 played an essential contributory role (9). Post-ischemic acute renal failure in mouse isografts was prevented if the donor kidney was C3 deficient regardless of circulating C3 levels. In contrast, injury to wild type kidney transplants occurred in the absence of recipient C3 (9). Together these findings suggest that the main target for therapeutic reduction of complement mediated injury is the extravascular pool of C3 generated by local/kidney synthesis, which occurred mainly in the tubular epithelium.

Membrane associated complement regulators that enhance the decay and/or prevent the formation of C3 convertases or promote the proteolysis of C3b can protect mammalian tissue against complement mediated damage. Bao *et al.* showed that following transplantation into WT recipients, kidney isografts deficient in the complement regulator *Crry* developed increased inflammatory injury (e.g. inflammatory cell infiltration, tubular damage, and interstitial fibrosis) and poorer graft function, compared with WT donor kidneys, suggesting that unrestricted complement activation in an organ graft could significantly contribute to local inflammatory injury (21). Another study in non-transplant renal I/R injury found that increased ischemic injury coincided with reduced local expression of *Crry* and increased C3 mRNA, suggesting that loss of complement inhibition and/or increased local synthesis of complement contributed to activation of the alternative pathway (11). Together the data imply that increased local synthesis and unrestrained activation of complement contribute to initial inflammatory injury of the transplant.

4.2. Complement modulating allospecific T cell responses

In addition to its role in innate immunity, complement provides a critical link with the adaptive immune response. Complement regulation of antibody production is perceived to involve C3-opsonised antigen binding to complement receptor (CR2) on follicular dendritic cells and B cells, thus augmenting the retention of antigen and facilitating antigen-specific B cell activation in secondary lymphoid tissue (7, 8, 22). While a role for complement as a regulator of B cell immunity is well established, regulation of T cell immunity by complement is at an early stage of enlightenment.

The T cell response is initiated by contact with antigen presenting cells (APC) and mediated/regulated by the action of effector, memory and regulatory cells. Given the function of the complement system in detecting and responding to exogenous and endogenous stimuli through its range of pattern recognition proteins and innate receptors, and given the presence of several complement receptors and regulators on APCs and T cells, the complement system could participate in modulating T cell responses in diverse ways, including direct effects on APCs and/or T cells and acting at the immuno-synapse between APCs and T cells. Because recent progress in this field has

been reviewed elsewhere (23, 24), we will focus on transplant-reactive T cell responses.

Based on a pivotal observation in 2002 showing that donor kidney synthesis of C3 had a critical effect on the recipient anti-donor T cell response (25), a series of publications has since confirmed that murine cells with ability to present antigen to recipient T cells express a range of complement components (26-30). Since donor-derived APCs are an important constituent of solid organ transplants and play a crucial role in the initiation and maintenance of the T cell alloresponse (31, 32), it is possible that local synthesis of C3 by donor APCs acts in a co-operative manner augmenting T cell recognition of donor antigen on graft passenger leucocytes that migrate from the donor organ soon after transplantation. Zhou *et al.* provided evidence that APC-autonomous C3 was imperative for normal T cell priming, since the absence of C3 led to reduced responsiveness of alloreactive CD4 T cells (30, 33) *in vitro* and *in vivo*. This result has been confirmed using bone marrow chimeric mice in which T cell immunity was diminished in animals with normal circulating C3 but containing C3 deficient APCs (Heeger, presented at American Transplant Congress, 2007).

Conversely, augmented T cell immunity occurred when donor APC lacked the negative complement regulator CD55 (DAF) (26, 27), and this augmented T cell immunity was associated with accelerated rejection of skin (26), heart and corneal transplants (Esposito and Medof ME. 2004, International Proceedings, 12th International Congress of Immunology and 4th Annual Conference of FOCIS). The augmented T cell immunity required local production of factor D or C3 (26, 27).

Mechanistically, the augmented T cell immune response detected in the absence of APC DAF was partially blocked by anti-C5 mAb suggesting C5 or one of its downstream activation products (C5a or MAC, see Fig 1) is an important mediator (26). This work also showed that interaction of antigen primed APCs with T cells bearing TCRs specific for the antigens rapidly induce the syntheses of the alternative pathway components C3, factor B, and factor D and concomitantly down-regulate DAF demonstrating physiological relevance (26). Together with the findings from C3 deficient animals, these data reveal that complement, produced and activated locally during cognate T cell APC interactions, participates in the development of T cell immune responses.

In addition to the stimulation of naïve T cells, DC synthesis of C3 affected several other signature functions of DCs. In contrast to $C3^{+/+}$ DCs, $C3^{-/-}$ DCs, upon LPS stimulation, released less IL-12 (DC maturation marker and Th1 polarizing molecule), which is a potent inducer of IFN production leading to the development of Th1 responses (26, 27, 29, 30). Consistent with reduced IL-12 production, $C3^{-/-}$ DCs induced naïve $CD4^+$ T cells to produce a higher level of Th2 cytokine (IL-4) and a lower level of Th1 cytokine (IFN) (26, 27, 29, 30). Conversely, more IL-12 was detected when CD4 T cells were stimulated with DAF deficient, as opposed to WT, APCs, a result that led to augmentation of T cell IFN-γ production (27).

Production of the anti-inflammatory cytokine IL-10 by T cells and the percentage of forkhead/winged helix transcription factor foxp3 positive T cells were significantly higher in T cells stimulated by $C3^{-/-}$ DCs, the enriched $CD4^+CD25^+foxp3^+$ T cell preparation generated by $C3^{-/-}$ DC stimulation significantly inhibiting T cell activation and T cell proliferation (29). The implication of these findings is that the regulatory-T cell driving capacity of DCs may also be significantly influenced by C3.

How complement modulates the immunoregulatory machinery of APCs remains incompletely understood. C3 is the central component in the complement cascade situated at the cross road of the three pathways of complement activation resulting in the generation of complement effector products. Current evidence implicates complement fragments C3a and C5a acting as ligands for their respective receptors C3aR and C5aR, engagement of which on APCs (26-28, 34) and on T cells (34, 35) can induce activation. T cell/allo-APC stimulations performed in serum-free medium yielded C5a, markedly enhanced C5a production occurred during interactions with DAF-deficient APCs and C5a production was essentially eliminated by the absence of APC C3 (27, 34). Furthermore, APCs deficient in C5aR produced less IL-12 during transplant-reactive T cell/APC interactions, and this resulted in diminished priming of IFNγ-producing alloreactive T cells (27, 34) implicating local production of C5a as a key mediator of proinflammatory T cell immunity. C3a and its receptor can also modulate alloreactive T cells (28, 34). The absence or blockade of the C3aR on bone marrow-derived DCs markedly diminished T cell immunity *in vitro* and *in vivo*, again associated with a decrease in IL-12 and an increase in IL-10 production (28, 34). Finally, C3b and its derivatives interacting with CR1-4 and CRIg (36), and membrane attack complexes assembled on cells could also contribute to T cell activation and proliferation. Together these findings reveal that locally produced and activated complement that occurs during T cell/allo-APC interactions plays a key role in regulating the strength and function of T cell alloimmunity.

Other work has clearly shown that activation of complement receptors present on T cells can transduce diverse signals, differentially impacting T cell responses (e.g. T cell inhibition, T cell activation and regulatory T cell generation). Cross-linking CD35 (CR1) inhibits T-cell proliferation and IL-2 production (37); activation of CD46 (MCP) on human CD4 T cells induces the generation regulatory T cells and suppresses bystander T cell proliferation (38, 39); and murine CD4 T cells lacking complement regulator CD59 (CD59) respond more vigorously to *in vitro* stimulation with CD3-specific antibody (40). These observations suggest that these complement regulators can lower T cell activation by inhibiting T cell proliferation and/or by promoting the generation of regulatory T cells. Most of the work carried out so far relates to non-transplant related T cell responses

although DAF can negatively modulate alloreactive T cell responses and prolong graft survival *in vivo* (26). Whether this will have therapeutic potential in humans warrants further investigation.

Which activation pathways trigger the effect of complement on allostimulation is of interest, not only because it may provide clues as to the tissue stress factors and molecular patterns that contribute to graft rejection, but also because it may offer more specific targets for therapeutic intervention. Heeger *et al.* found that splenocytes prepared from mice with deficiency in factor D (an activator of the alternative pathway of complement activation) elicited a reduced T cell response (26). Zhou *et al.*, found that macrophages and dendritic cells prepared from factor B (fB) (a key component of the alternative pathway) deficient mice stimulated a reduced alloreactive CD4 T cell response (30). These results suggest that complement activation through the alternative pathway can modulate allostimulation. In contrast C4 deficiency in donor or recipient mouse had no obvious effect on allograft survival (41). While these findings suggest that complement activation and renal allograft rejection are independent of the classical and lectin pathway, and indicate that the alternative pathway is the main trigger for complement mediated rejection in these models, lack of involvement of C4 does not necessarily exclude a role for MBL because lectin-mediated activation of the alternative pathway appears able to bypass C4 and C2 (4).

Consistent with the murine data showing that graft-produced C3 influences renal allograft survival, a recent report implicates graft-derived C3 as a mediator of human kidney transplant rejection (42). Donor organs expressing a specific polymorphic variant of C3 had a significantly worse outcome than those expressing an alternate polymorphism. The precise mechanism through which this mutation alters allograft injury in human transplant recipients remains unclear.

5. IMPLICATIONS FOR THERAPY

Linking local complement activation to I/R injury and T cell mediated injury has multiple implications for designing therapeutic strategies to prolong graft survival. As one example, monoclonal antibodies with activity against C5 (e.g. pexelizumab) are being tested in several clinical settings including IR injury (43, 44). Based on promising results in these other scenarios (43, 44) a study of anti-C5 mAb to prevent reperfusion injury in cardiac transplantation and potentially in renal transplantation would thus seem appropriate. Anti-C5 mAb has also been effective in preventing antibody-mediated injury in murine transplant models of sensitized recipients (45, 46). While these studies have clearly demonstrated that complement inhibition can limit the effector functions of alloantibodies, it is possible that some of the therapeutic efficacy is related to anti-C5 induced blockade of T cell activation, an issue that will require further study.

In an alternative strategy for preventing IR injury, Patel *et al* explored the possibility that intragraft delivery of membrane targeted complement regulator could protect the donor kidney from complement mediated post-ischemic damage and thus increase the number of successful transplants, using a rat renal isograft model (10). Graft non-function was associated with prolonged cold-storage for periods up to 24 hours. Treatment with the membrane targeted fragment of CR1 (APT070) increased the number of surviving grafts compared with control-treated grafts (63.6% vs. 26.3%). This confirmed earlier findings in isograft and allograft models with lesser degrees of reperfusion damage, strongly suggesting that locally targeting complement components at the area where complement is produced, activated and deposited, and causes most damage, is an effective strategy to prevent complement mediated organ I/R injury (47). In addition, it is possible that benefit could derive from the therapeutic targeting of complement on the cell surface of donor APC, which appears to make them less immunogenic and to elicit a tolerogenic T cell cytokine response (27). A phase 2a safety study has indicated that the strategy for treating donor organs with the adherent regulator is both feasible and safe in man (Sacks personal communication). Whether overexpression of complement regulatory proteins will impact the strength of the induced alloreactive T cell response remains to be tested.

6. CONCLUSION

Basic science findings elucidating novel complement activation pathways and highlighting the role of local complement production and activation, particularly during T cell immune responses, have provided important insights into how complement exerts control over adaptive immunity. Clinical application of the these findings in the context of transplantation is beginning, as genetic and therapeutic studies have recently provided evidence that blocking local complement activation can potentially limit allograft injury. These initial studies have identified the need for further analysis of potential clinical applications in larger groups of patients. Parallel study of mechanism is imperative, in particular to define the means by which complement influences the T cell response against alloantigen, including the generation of effector, regulatory and memory cell subsets. Outstanding questions include the relative importance of specific complement receptors and regulators that modulate the actions of complement on APC and T cells. Current progress shows the complement system to be an ideal model for pursuing the integration of innate and adaptive immune responses and their co-manipulation in transplant settings for the purpose of improving organ survival and function.

7. ACKNOWLEGEMENT

Peter N. Lalli, Wuding Zhou contributed equally to this manuscript

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