Should Complement Activation Be a Target for Therapy in Renal Transplantation?

Neil S. Sheerin
Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom

In the past two decades, there has been a significant expansion in the number of immunosuppressive drugs available to prevent acute transplant rejection. These primarily target lymphocyte function, which is a critical mediator of allograft injury; however, because of this progress, each new agent potentially offers a smaller incremental benefit in terms of preventing rejection and prolonging graft survival. It may therefore be timely to consider therapeutic agents that inhibit other components of the immune system.

The complement system is part of the innate immune system but is also intricately linked to adaptive responses. It consists of more than 30 soluble and membrane-bound proteins and is activated by three pathways. The Fc region of multimeric IgG and IgM complexed with antigen activates the classical pathway. In contrast, the alternative and mannose-binding lectin pathways do not require antigen but instead are triggered by activating surfaces such as bacterial cell walls or damaged endothelium. The pathways converge with the assembly of C3 and C5 convertases that cleave and activate multiple copies of the pivotal complement components C3 and C5, initiating the effector functions of complement. The membrane attack complex, C5b-9, is assembled by the terminal pathway and forms a membrane-spanning pore that either is cytolytic or, in lower concentrations, can have profound effects on cell phenotype.

The opsonins C3b, iC3b, and C3d are recognized by receptors on leukocytes promoting cell activation. As complement proteins are cleaved, the anaphylotoxins C3a and C5a are also generated. These small proteins signal through specific G protein–coupled receptors expressed primarily on myeloid but also nonmyeloid cells, including epithelial cells of the kidney. They have a multitude of actions, inducing chemotaxis and cell activation, and have significant effects on adaptive immune responses.

Whether the pleiotropic effects of complement activation influence renal transplant outcome has been extensively studied. There are certain situations when complement is involved in graft rejection, for example in hyperacute rejection in a pre-sensitized patient or in xenotransplantation, when the classical pathway of complement is activated by preformed antibody. Another circumstance in which complement activation damages a transplant kidney is during ischemia and reperfusion. Damage to the endothelium impairs its capacity to control complement activation allowing the alternative pathway to proceed uninhibited. There is evidence that the membrane attack complex, C3a, and C5a all may contribute to this phase of injury; however, it has proved more difficult to demonstrate a role for complement activation during acute rejection.

Interest in this area has increased recently with the introduction of C4d staining of transplant biopsies as an indicator of humoral rejection. Complement component C4 is part of the classical pathway and is activated by antibody binding to the surface of endothelial cells. It is degraded to the relatively stable, biologically inert fragment C4d the detection of which serves as a marker of previous antidonor antibody binding. Although C4d staining is embedded in the Banff scoring system of transplant rejection, its presence does not prove that complement activation is an important mediator of acute humoral rejection.

So is now the time to consider complement activation as a target for therapeutic intervention in clinical renal transplantation? There are two reasons that this may be the case. First, there is an increasing amount of experimental evidence, primarily from animal models, that complement activation is an important cause of transplant injury. Second, interventions that can effectively inhibit complement activation or block the action of complement activation products are now available.

In this issue of the JASN, Gueler et al.4 use human biopsy tissue and a mouse model to assess the role of C5a in renal transplantation. The receptor for C5a is expressed on macrophages and neutrophils infiltrating the graft as well as some tubular and glomerular cells. The in vitro data in the article suggest that expression on both native and infiltrating cells is important. In a fully mismatched transplant model, treatment with a C5a receptor antagonist significantly improved survival. The timing of treatment was critical and was most effective when started before transplantation. This suggests an important role for C5a in the injury that occurs as a result of ischemia reperfusion. This notion is consistent with other reports demonstrating a role for C5a in renal ischemia reperfusion injury induced by cross-clamping of the renal artery. Both C5a antagonists5,6 and C5a receptor gene silencing7 reduce damage in this model. Also, in a syngeneic mouse transplant model, when the kidney was perfused ex vivo with a C5a receptor antagonist, there was a reduction in the level of injury.8

The situation is more complex than this. Starting treatment after reperfusion improves renal function and prolongs graft...
survival, although to a lesser degree. Treatment may still be affecting the ischemia reperfusion phase even though given after reperfusion, because this is not just a short-lived injury that occurs immediately after reperfusion but instead an inflammatory process that can continue for some time. Alternatively, C5a could be involved in other pathways that lead to graft injury, and of particular interest is its potential to augment the alloimmune response. In the report by Gueler et al., blocking the C5a receptor prevents graft rejection and reduces the recipient’s response to donor in a mixed lymphocyte reaction. This could be due to nonspecific effect of C5a on tissue injury in the reperfusion phase. Blockade of the C5a receptor reduces tissue injury, thereby limiting the supply of antigen, altering the maturation of antigen-presenting cells, and therefore decreasing the alloresponse. That treatment was required only for 6 d after transplantation to prolong survival to 12 wk supports this explanation.

Other published results support a more specific role for complement, in particular the anaphylotoxins, in the development of both B cell and T cell immunity. The generation of C5a locally at the site of interaction between antigen-presenting cells and T cells provides a survival signal for T cells and is required for development of effector functions. This is a significant effect and is sufficient to modify the survival of murine cardiac allografts. In the study by Gueler et al., blocking C5a receptor signaling at a time when an allo-specific T cell response is developing is sufficient to prevent later rejection. The mechanism by which T cell reactivity remains suppressed is not known.

In conclusion, whatever its mode of action, C5a is clearly important in transplantation and represents a potential new target for therapy. Most of the data to support this statement so far have been generated in rodent transplant models. The challenge is to translate these findings into clinical practice. It has not always been easy to make the transition between rodent and clinical transplantation, but complement inhibition may be one area where this will prove successful.

DISCUSSIONS

None

REFERENCES


See related article, “Complement 5a Receptor Inhibition Improves Renal Allograft Survival,” on pages 2302–2312.

Uric Acid Levels Increase Risk for New-Onset Kidney Disease

Rajesh Mohandas* and Richard J. Johnson*†
*Division of Nephrology, Hypertension and Transplantation, University of Florida, Gainesville, Florida; and †Division of Renal Disease and Hypertension, University of Colorado, Denver, Denver, Colorado


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Despite our best efforts, the past decade has seen little progress in the treatment of chronic kidney disease (CKD). The mainstay of

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Correspondence: Dr. Richard J. Johnson, Division of Renal Diseases and Hypertension, University of Colorado, 12700 E. 19th Avenue, Research Complex 2, 7th floor, Aurora, CO 80045. Phone: 303-315-8771; Fax: 303-315-0189; E-mail: richard.johnson@uchsc.edu

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