Inhibition of Complement: Tackling of Both Innate and Adaptive Immune Responses to Dampen Rejection

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Immunosuppression regimen that is necessary to keep rejection in check has been known to have its adverse effects, especially when prolonged and sometimes lifelong usage is necessary, as in the case of some transplants. Opportunistic Cytomegalovirus¹ and multidrug resistant *Pseudomonas*² infections have been reported to be accompanying immunosuppression along with oft noted metabolic dysfunctions. The histological heterogeneity of a vascular composite allograft (VCA) has been suggested to elicit different levels of immunogenicity from its components with skin being the most immunogenic followed by bone, muscle and so on.³ It is evidently a more complex immune milieu that one has to deal with in the VCA compared with solid organ transplants. Nevertheless, the lessons learnt from organ transplantation with regard to the principle actors in the recurrent acute rejection episodes and chronic rejection can be used in tackling some of the same problems with VCA. The involvement of innate immunity in the ischemia-reperfusion injury, one of the major causes of inflammation in rejection, is being studied in tandem with the activation of adaptive immunity with T cell mediation and the involvement of major histocompatibility complex incompatibility to better understand the broad underlying mechanisms leading to the immunogenicity.

Deservedly, attention is being paid to the complement system which seems to act in the intersection of innate and adaptive immunity and drives inflammatory responses both by opsonization that leads to lysis of pathogens and also by facilitating the secretion of proinflammatory cytokines (Figure 1).⁴ Complement component 3 (C3), the common product of classical, lectin, and alternate pathways of complement activation leads to the lysis of its pathogenic target, mediated by the downstream products of C3. The cleavage products of C3 and C5, namely, C3a and C5a, respectively are proinflammatory and contribute to cytokine production, which could broadly be classified as an innate immune response. It has been shown recently⁵ that classical pathway of complement activation on endothelial cell surface not only

contributes to endothelial cell activation but also contributes to generation of chemoattractant C3a and C5a that exacerbate the leukocyte infiltration.

This multidimensional nature of complement system has been elegantly characterized in the work of Zhu et al⁶ in an article published in this issue. Atkinson and colleagues⁷ have previously shown that a Complement receptor 2 (CR2) targeted inhibitor of C3 activation, CR2-Crry, had better bioavailability and efficacy than Crry-Ig and did not impair the host immunity to infection at the same time, in a mouse model of intestinal ischemia/reperfusion injury. In the current study being highlighted in this issue Zhu et al assessed the effect of complement inhibition in heterotopic hind limb transplants in mice and compared this pan-complement inhibition with C3 deficiency. Studies designed to understand the role of anaphylatoxins C3a and C5a in VCA were also presented where the recipients were deficient in C3aR and C5aR. The observations that pan-complement inhibition by CR2-Crry and C3 deficiency confer better protection from ischemia/reperfusion related inflammation in VCA and significantly lower the characteristics of rejection in histopathology, complement deposition, inflammatory cell influx, and P-selectin expression compared to C3aR^{-/-}C5aR^{-/-} point toward the fork in the road that C3 activation takes where one branch leads to innate immune responses and the other to adaptive immunity pathways.

Furthermore, the authors observed that the dual therapy with CR2-Crry and a subtherapeutic dose of cyclosporine A was significantly better at increasing median survival in the VCA recipients compared not only to the PBS controls but also to the groups of mice that received only either Cr2-Crry or Cyclosporine A. This is a welcome finding considering the effects of immunosuppression on the patient's ability to fight infection as mentioned above. Presented in the study also are data concerning the histology and immunohistology, complement deposition and flow cytometric analysis of splenic cell populations that buttress the hypothesis proposed. Going forward, understanding the mechanism for enhanced activity with C3 inhibition, unequivocally will also help judge the clinical benefits and weigh the pros and cons of therapeutic use of complement inhibition. Efforts in this direction are already underway in the form of clinical trial and preclinical studies of recombinant human fusion proteins and the studies on complement inhibition will certainly enhance the current knowledge.

With the recent reports of complement component 5 (C5) inhibition with eculizumab providing an efficient way to combat antibody mediated rejection⁸ and atypical hemolytic

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FIGURE 1. Complement system influences both innate and adaptive immune responses.

uremic syndrome⁹ after kidney transplants, these are exciting times to be following the ongoing preclinical and clinical efforts in complement inhibition. The current knowledge of complement inhibition, particularly the clinical utility of plasma-derived C1 inhibitor are reviewed recently¹⁰ and make for an engaging reading. Improvements in immunosuppression are welcome whether the transplant is conducted in a life threatening situation as is the case in most of the solid organ transplants or in the case of VCA where the patient usually elects the procedure for the physical and psychological boost it provides.

REFERENCES

1. Meningaud JP, Benjoar MD, Hivelin M, et al. Procurement of total human face graft for allotransplantation: a preclinical study and the first clinical case. *Plast Reconstr Surg.* 2010;126:1181–1190.
2. Gordon CR, Avery RK, Abouhassan W, et al. Cytomegalovirus and other infectious issues related to face transplantation: specific considerations, lessons learned, and future recommendations. *Plast Reconstr Surg.* 2011;127:1515–1523.
3. Lee WP, Yaremchuk MJ, Pan YC, et al. Relative antigenicity of components of a vascularized limb allograft. *Plast Reconstr Surg.* 1991;87:401–411.
4. Dunkelberger JR, Song WC. Complement and its role in innate and adaptive immune responses. *Cell Res.* 2010;20:34–50.
5. Valenzuela NM, Thomas KA, Mulder A, et al. Complement-mediated enhancement of monocyte adhesion to endothelial cells by HLA antibodies, and blockade by a specific inhibitor of the classical complement cascade, TNT003. [published online ahead of print September 29, 2016]. *Transplantation.* doi: 10.1097/TP.0000000000001486.
6. Zhu P, Bailey S, Lei B, et al. Targeted complement inhibition protects vascularized composite allografts from acute graft injury and prolongs graft survival when combined with subtherapeutic cyclosporine A therapy. *Transplantation.* 2017;101:e75–e85.
7. Atkinson C, Song H, Lu B, et al. Targeted complement inhibition by C3d recognition ameliorates tissue injury without apparent increase in susceptibility to infection. *J Clin Invest.* 2005;115:2444–2453.
8. Khan SA, Al-Riyami D, Al-Mula Abed YW, et al. Successful salvage treatment of resistant acute antibody-mediated kidney transplant rejection with eculizumab. *Sultan Qaboos Univ Med J.* 2016;16:e371–374.
9. Nester C, Stewart Z, Myers D, et al. Pre-emptive eculizumab and plasmapheresis for renal transplant in atypical hemolytic uremic syndrome. *Clin J Am Soc Nephrol.* 2011;6:1488–1494.
10. Berger M, Baldwin WM 3rd, Jordan SC. Potential Roles for C1 Inhibitor in Transplantation. *Transplantation.* 2016;100:1415–1424.