Published in final edited form as:

Curr Opin Immunol. 2010 October ; 22(5): 631–633. doi:10.1016/j.coi.2010.09.003.

Immunogenetics and transplantation

Allan Kirk and

Department of Surgery, Emory University, Atlanta, GA 30322, USA, adkirk@emory.edu

Terry B Strom

Department of Medicine, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA, URL: adkirk@emory.edu

Abstract

It is well recognized that allospecific T cell activation is required for rejection. However, the process of allospecific T cell activation is largely controllable with current agents. Accordingly, short-term outcomes in allotransplantation have uniformly improved, a testament to the importance of the T cell-centric view of current therapy; thus, the field's attention has turned toward lagging long-term outcomes. The inexorable chronic graft destruction that continues to define clinical transplantation suggests that there are important aspects of alloimmunity that are un-mollified by simple T cell-directed immunosuppression. Indeed, in the past decade it has become clear that the full biological phenomenon collectively recognized as rejection incorporates an almost Gordian network of factors, both inflammatory and regulatory, that shape the phenotype of allorecognition. T cell responses, including the T cell dependent allograft response, are contextually determined by the state of innate immunity in which T cells interact with antigen. Organs utilized for transplantation are usually obtained from deceased donors by a surgical procedure and then placed into cold preservation solutions before surgery implantation into the recipient. Brain death, ischemia reperfusion, hypoxia and hemostasis related injuries dramatically influence the state of innate immunity within the transplant. Overall, each of these processes activates innate immunity into a pro-inflammatory mode that is known to promote tissue destructive forms of adaptive immunity. These pathways and cell types have been left largely untargeted, or at least under recognized, and it is these finer points of rejection that serve as the focus of this issue of Current Opinion in Immunology...

The impact of hemostasis that is, platelet activation and coagulation occurring within the organ in the peri transplant period upon immunity have probably failed to receive sufficient attention. The superb review by Qu and Chaikof clearly and thoroughly delineates the numerous and intricate forms of interaction of hemostasis associated signaling pathways with innate and adaptive immunity. Overall hemostasis serve to activates a 'local state of inflammatory that serves as an adjuvant system for antigen presentation' and thereby acts to stimulate both innate and adaptive immunity. The opportunity to effectively curtail the adverse effects flowing from hemostasis-induced inflammation is explored in both translational and molecular perspectives.

The influence of pro-inflammatory and anti-inflammatory cytokines upon the viability and phenotypic commitments made by antigen activated T cells is well known. Less well known are the effects of the non-APC cellular elements of the innate immune system upon the allograft response. The reviews covering the intriguing and crucially important effects of mast cells and NK cells on the allograft response are provocative highly informative. As we learn the response of NK and mast cells, like those of T cells, are contextually determined and danger signals elicited from ischemia reperfusion, hypoxia and hemostasis related injuries serve to activate mast and NK cells into pro-inflammatory and cytotoxic effector cells. These cells are able under certain conditions to participate in graft rejection. Yet these

cells are also able to produce tolerance promoting anti-inflammatory as well as rejection provoking cytokines. Indeed as detailed by de Vries and Noelle dominant type allograft tolerance is at least under certain conditions totally dependent upon cytokines elaborated by mast cells while mast cell degranulation can break tolerance. The role of various mast cell produced cytokines and chemokines in tolerance and rejection tolerance is crucially examined leaving no doubt that this system is of crucial importance in determining whether rejection or tolerance in a given host.

NK cells, cells endowed with a prodigious capacity for expressing a wide range of cytokines and chemokines, directly and indirectly influence in a bi-directional fashion the function of APCs, effector and regulatory T cells and thereby influence the allograft response as emphasized by Gill. While more is known about the ability of NK cells to participate in rejection there is no doubt that they can also aid tolerance induction. In this regard it is notable that dominant allograft tolerance can also be NK cells dependent as host NK cells can lyse MHC class-I incompatible donor APCs migrating from the graft into host lymphoid tissue through a perforin mediated pathway, thereby reducing the immunogenicity of the transplant [1,2].

Few pathways have emerged at the interface of activation and regulation with more relevance than the mTOR pathway. Indeed, few pathways remain so uncomfortably categorized, as well. Recent literature has pointed to the mTOR pathway not only as an important means of preventing T cell responsiveness, but also paradoxically augmenting it [3]. In the offering from Peter, Waldmann and Cobbold, a unifying view of this crucial pathway is presented that recognizes that both regulation and inflammation are energy consuming processes that are subject to metabolic control. That there is a central regulatory point for both is elegantly efficient.

The balance between tolerance and immunity has been increasingly recognized as a nurtured state that is at least partly dependent on T cells with specific regulatory function. The past decade has seen immense progress in understanding the specific types of T regulatory cells (Tregs), both induced and acquired, and it is clear that these cells actively thwart autoimmune disease. It is reasonable to assume then that alloimmunity is equally influenced by active regulation. Wood and colleagues present an excellent review of regulatory T cells. In addition to giving a current overview of the identifying characteristics of the relevant subpopulations of T regs, they provide encouraging insight the use of these cells as therapeutic agents. While it is debatable whether Tregs provide a surveillance function in preventing alloimmunity, there is little doubt that they are drawn to the site of an alloimmune response [4] and probably mollify the ongoing response. It is possible that this containment function, present at physiologic concentrations of Tregs, could be amplified into a therapeutic function at super-physiologic levels. Indeed, the burgeoning clinical experience into this approach is discussed in detail.

The biology of MHC molecule recognition defines alloimmunity, and the importance of MHC-specific alloantibody formation has become a central focus of long-term clinical transplant outcomes. However, the spectrum of antibodies formed in response to an allograft appears to have more depth than would be suggested by class-I and class-II specificity. Smith and his colleagues and Zhang and Reed provide a comprehensive overview of the role of anti-MHC and non-MHC antibodies, including newly appreciated MHC class-I related antibody responses in the allograft response. Indeed, there is growing evidence that damaged tissues evoke autoantibody responses that, in the case of non-polymorphic molecules, can harm an allograft. Antibodies to some minor, non-MHC polymorphisms may also contribute to graft injury; perhaps not through overt hyperacute rejection, but rather through continuous influence on the graft endothelium. Zhang and Reed have been leaders in defining the

nuances of acquired antibody responses particularly beyond the routine MHC-specific alloantibody. They provide a comprehensive review of the less recognized, and as such less well targeted, antibody responses that may influence long-term graft survival. The review by Smith and his colleagues provides insight as to the stimulants of antibody formation and B cell biology as it relates to the initiation of antibody formation and the survival of antibody producing B cells.

Vaughan and Sacks have compiled a thoughtful update on the utility of genomics enabled by sequencing of the human genome on transplant outcomes and management. Analysis of polymorphisms in the HLA complex and in other genes that are strong candidates to predict graft outcomes or inform as to pharmacodynamics and thereby aid in patient management are reviewed. In addition the emergence of biomarkers derived from transcriptional or proteomic profiles as potential aids to patient management are crucially review.

Biographies

Allan D. Kirk is Professor of Surgery and Pediatrics at Emory University and Scientific Director of the Emory Transplant Center. He is a practicing transplant surgeon with a particular interest in immunosuppressive management in children and adults, and the initial translation of novel immune management strategies into the clinic. In addition to his clinical and laboratory work, he also serves as the Editor-in-Chief of the American Journal of Transplantation.

Terry Strom received his MD from the University of Illinois. He trained in internal medicine, nephrology and transplant immunology in two Harvard affiliated hospitals Beth Israel Hospital and the Peter Bent Brigham Hospital. He has spent his entire career in these hospitals as a clinician and scientist. Currently he is a Professor of Medicine at Harvard and Co-Scientific Director of the Transplant Institute at Beth Israel Deaconess Hospital.

References

1. Yu G, Xu X, Vu MD, Kilpatrick ED, Li XC. NK cells promote transplant tolerance by killing donor antigen-presenting cells. *J Exp Med*. 2006; 203:1851–1858. [PubMed: 16864660]
2. Laffont S, Seillet C, Ortalda J, Coudert JD, Guery JC. Natural killer cells recruited into lymph nodes inhibit alloreactive T-cell activation through perforin-mediated killing of donor dendritic cells. *Blood*. 2008; 112:661–671. [PubMed: 18505782]
3. Araki K, Turner AP, Shaffer VO, Gangappa S, Keller SA, Bachmann MF, Larsen CP, Ahmed R. mTOR regulates memory CD8 T-cell differentiation. *Nature*. 2009; 460:108–112. [PubMed: 19543266]
4. Veronese F, Rotman S, Smith RN, Pelle TD, Farrell ML, Kawai T, Benedict Cosimi A, Colvin RB. Pathological and clinical correlates of FOXP3+ cells in renal allografts during acute rejection. *Am J Transplant*. 2007; 7:914–922. [PubMed: 17286616]