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Transplantation: Moving to the next level

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This issue of Immunological Reviews bridges two traditionally separate fields. While the average immunologist may think of "transplantation" as a single entity, it has, for largely practical reasons, been split into two separate fields, namely hematopoietic cell transplantation (HCT) and organ transplantation. In allogeneic HCT, which was originally used as a rescue therapy for the marrow toxicity of high-dose chemotherapy and/or irradiation employed to treat a hematologic malignancy, the recipient's immune system is severely compromised and the greatest concern has been the attack of immune cells in the donor inoculum on the severely immunocompromised recipient. This attack, which caused the sometimes fatal syndrome known as graft-vs-host disease (GVHD), was so severe when HLA barriers were transgressed that until recently the practice of HCT has been largely confined to the HLA-identical or near-identical donor situation, severely limiting the availability of this curative therapy. Even in the present day, as approaches to performing HLA-mismatched HCT have permitted more widespread transplantation in this setting, the incidence of significant GVHD is in the 30–40% range in the least immunogenic combination involving HLA-identical sibling donors, despite the use of pharmacologic immunosuppression as GVHD prophylaxis(1). Thus, GVHD remains a major cause of morbidity and mortality following HCT.

While it was recognized as early as the 1970s that GVHD was mediated by T cells in the donor graft and could be eliminated by depletion of these T cells, it also became apparent in the same period that this attack was associated with a beneficial effect in patients with malignant disease(2). This effect came to be known as the graft-vs-leukemia/lymphoma (GVL) effect and is mediated in large part by the same cells that cause GVHD, namely donor T cells recognizing recipient alloantigens. While T cell depletion of the donor graft greatly attenuates GVHD, this has been associated with increased relapse rates of several malignancies(3), increased graft failure(4) and, when the intensity of conditioning is increased to promote engraftment, with a high incidence of serious opportunistic infection due to the failure of the thymus in heavily pretreated adults to rapidly generate new T cells from the hematopietic cell graft(5). Thus, the separation of GVHD and GVL has been the central challenge throughout the >50 years that allogeneic HCT has been practiced clinically. Several advances in our understanding of GVHD and GVL have suggested ways in which this alloresponse can be harnessed for its beneficial GVL effect while minimizing GVHD. A particularly promising approach revolves around controlling the trafficking of alloreactive T cells so that they remain in the lymphohematopoietic system where the hematologic malignancy resides without trafficking into the epithelial GVHD target tissues, namely the skin, gut and liver. This trafficking into epithelial tissues requires inflammation

in the local epithelial sites(6). The recipient conditioning used for HCT provides a ready source of these innate stimuli due to disruption of epithelial barriers, which allows translocation of microbial products into the tissues (reviewed in (7)) and also inherently induces production of inflammatory cytokines, chemokines and adhesion molecules that can promote T cell trafficking into these tissues(8). In the paper by Wang and Yang in this issue, the complex role played by one of these cytokines, interferon gamma, in mediating these various phenomena that promote both GVHD and GVL is discussed in detail(9). In the article by Fuchs et al(10), a strategy for curtailing the GVH response after alloreactivity has been initiated in vivo is described from its inception in animal models to its current role in permitting HLA-mismatched HCT. The paper by Miller et al explores the potential of a non-T cell lymphocyte population, natural killer cells, to mediate GVL effects through “missing self” recognition without causing, and even potentially inhibiting GVHD. Another approach to achieving both anti-tumor effects and immunity to microbial pathogens in HCT recipients involves cell therapy with donor T cell populations that are selectively depleted of GVH reactivity or the use of expanded antigen-specific donor T cells, which may be modified in a manner to allow their destruction in the event that GVHD results from infusion of such products. These approaches are in the article of Brenner et al(11).

In contrast to the problem of GVH reactivity in HCT, the field of solid organ transplantation has been more concerned with immune responses in the host-vs-graft (HvG) direction, largely due to the fact that recipients are less completely immunodepleted, do not receive proinflammatory treatments such as irradiation and chemotherapy, and, with a few exceptions (intestinal and liver transplantation), the donor organ grafts do not typically contain large T cell loads. Moreover, organ transplants, in contrast to HCT, are most commonly performed across HLA barriers. Finally, unlike the situation in HCT, in which prophylactic immunosuppressive therapy can be discontinued after a time if GVHD does not develop or is controlled, organ transplantation requires life-long immunosuppressive therapy. This difference relates in part to the extensive T cell depletion of the recipient resulting from conditioning for HCT and/or destruction of residual host lymphoctyes by GVH-reactive donor lymphocytes. In addition, engrafted donor hematopoietic cell transplants have the capacity to educate newly developing T cells to regard the donor as self, due to the contribution of hematopoietic cells to negative selection in the thymus. In isolated organ transplantation, in contrast, there is no wholesale replacement of the T cell compartment and no donor hematopoietic graft to educate newly developing T cells to treat the donor as “self”.

Because of these major differences between HCT and organ transplantation and because the clinical specialties of the physicians managing both types of patients are completely different, the two fields have had minimal interchange over the years. Recently, however, several factors have contributed to a new convergence of HCT and organ transplantation. One factor is the explosion in technology, including advanced flow cytometry, multiplex assays for proteins and RNA species, microarrays and high throughput sequencing that have provided knowledge in human transplant recipients at a new level. These developments have led to the inescapable conclusion that GVHD, GVL, graft rejection and tolerance involve immune mechanisms and therapies that can be applied in both areas. Equally important, however, has been the development of less toxic, more specifically targeted approaches to

host conditioning for HCT that has finally opened up the possibility of using it in a situation that is not strictly life-saving, namely for the induction of allograft tolerance. Allograft tolerance induction has long been the “holy grail” in the field of organ transplantation, since the need for lifelong immunosuppressive therapy to prevent allograft rejection is associated with many complications, including malignancies and infections due to the non-specific immunosuppression, as well as metabolic and other side effects that necessitate treatment with many additional drugs and often result in end organ damage that may even result in the need for another transplant to replace recipient kidneys damaged in this way. Many approaches to achieving allograft tolerance have been developed in rodents, but very few have been successfully applied in oubred large animals or humans. As is discussed in both the reviews by Wood and colleagues(12), Chong and Alegre(13) and Turka and colleagues(14), many of these tolerance regimens in rodents have proved to involve a regulatory T cell response that prevails when various forms of temporary immunosuppression are used. The greater difficulty in achieving similar outcomes in outbred large animals and humans may relate to the lack of control of innate stimuli from microbes present outside of a controlled laboratory environment and from ischemia-reperfusion injury and conditioning therapy, as is reviewed by Goldstein and colleagues as well as by Chong and Alegre in this issue(13) and discussed in several other reviews(15, 16). Additionally, individuals in the real world are exposed to numerous pathogens and the immune responses to these may result in a memory T cell response that cross-reacts to alloantigens and that is particularly resistant to immunosuppressive, T cell-depleting and tolerance-inducing approaches, as discussed in the reviews by Rosenblum and Kirk(17), Farber and colleagues(16), Chong and Alegre(13) and Goldstein and colleagues(18).

Thus, there have so far been very few successful approaches to tolerance induction in non-human primates or humans. One approach that has enjoyed greater success in liver transplantation than kidneys is the gradual weaning of immunosuppressive drugs in a select group of recipients who have been stable with no rejection episodes for a number of years. This approach appears to be more successful in children than adults, but follow-up is still relatively short(19–21). The second approach is HCT, which has proved to be very robust in animal models, succeeding with highly immunogenic skin and intestinal grafts where other approaches have failed, and being successfully translated up the chain into large animals, including non-human primates (reviewed in (22, 23)). This approach, involving HCT for organ allograft tolerance induction, has begun to be evaluated in humans, as discussed in several reviews in this issue(10, 13, 24). While the potential of HCT to be used in this capacity was established nearly 60 years ago by Main and Prehn in rodents receiving lethal total body irradiation (TBI)(25), it has only been in the last 15 years that specific, non-myeloablative conditioning and HCT have been added to organ transplants for the purpose of tolerance induction. The first such studies were done in patients with renal failure due to multiple myeloma, so that the HCT offered the potential for cure of their malignancy while inducing allograft tolerance (26–28). The success of these initial patients, some of whom have now shown tolerance for as long as 15 years even with the achievement of only transient chimerism(29), justified subsequent trials involving conditioning and HCT solely for the purpose of organ allograft tolerance in patients without malignant disease(30–32). The outcomes and remaining challenges of these studies are discussed in the article by

Fuchs(10) and the potential of the approach to overcome the organ shortage by allowing tolerance to be achieved to xenografts is discussed in the article by Griesemer et al(24).

As our understanding of the immunologic underpinnings of events in both HCT and organ transplantation have advanced, some common themes have emerged. One that is mentioned above- innate immunity- has proven to be a clear-cut barrier to the success of both types of transplant, because of its role in inducing GVHD in the HCT setting and because of the impediment it presents to tolerance induction, as is discussed in the reviews by Goldstein and colleagues(18) and by Chong and Alegre(13). The article by Oberbarnscheidt and Lakkis(15) describes the role that a novel, incompletely understood form of innate allorecognition by monocytes may play in triggering and even mediating allograft rejection. The article of Jeffrey Miller and colleagues(33) reviews the complex biology of inhibitory and activating receptors on another innate immune subset, NK cells, that impact their ability to promote GVL effects and anti-infectious immunity and hence improve outcomes following HCT. Finally, the review of xenotransplantation by Greisemer and colleagues(24) discusses the particular importance of innate immunity, including natural antibodies, NK cells and macrophages, in rejecting both solid organ xenografts and preventing engraftment of xenogeneic hematopoietic cells which, once engrafted, have the capacity to tolerize not only the adaptive (T and B cell) immune system, but also components of the innate immune response, including natural antibodies and NK cells.

The importance of another relatively recent player in the immune system, regulatory T cells (Tregs), is being increasingly understood in both HCT and organ transplantation. The review by Turka and colleagues(14) details our emerging understanding of the signals and pathways that drive the development of Tregs, both in the thymus and in the periphery, and in their functional maintenance and homeostasis. The role of costimulation, the PI3 kinase pathway and related metabolic pathways is discussed. The articles by Wang and Yang(9) and Wood et al(12) discuss the important role that the IFN-γ pathway plays in Treg biology in HCT and solid organ transplant models, respectively. Tregs have shown considerable importance in rodent models of allograft tolerance induction, and these studies as well as recently-begun efforts to exploit expanded Tregs and other regulatory cell populations to achieve allograft tolerance in humans are discussed in the review by Wood and colleagues(12). Clinical trials of cellular therapy with expanded donor Tregs in an effort to inhibit GHVD have already been reported(34). The potential impact of induction and immunosuppressive therapies that may deplete or enrich Tregs on outcomes of organ transplantation and HCT is discussed in the article by Rosenblum and Kirk(17). The theme of cell-based therapy recurs in other contexts, as advances in our ability to select and expand desired T cell populations and engineer them under defined GMP-level conditions have made possible the exciting new approaches to fighting infections, as discussed in the review by Brenner and colleagues(11). This approach has also been used in solid organ transplant recipients and may have considerable potential in the treatment of intractable post-transplant lymphoproliferative disease, CMV reactivation and other opportunistic infections in immunosuppressed patients.

Another area where understanding is just beginning to move from the exclusive realm of animal models into human transplantation is that of T cell homeostasis. Recent studies in a humanized mouse model documented the ability of human T cells to undergo lymphopenia-

driven expansion, demonstrating the important role of autologous APCs in driving this process, as well as the conversion of naïve human T cells to effector/memory-type cells in T cell-deficient hosts(35). For obvious reasons such studies cannot be performed directly in humans, but as is reviewed by Rosenblum and Kirk(17), much can be learned by observing the impact of various selective or global T cell depleting agents on the distribution and recovery of immune cell subsets. This article discusses how constriction of the T cell repertoire and enrichment for memory-type T cells may impact transplant outcomes and infectious immunity. Donna Farber and colleagues review a newly-emerging understanding of the compartmentalization of human naïve and memory T cell populations throughout the body, including the possible impact of tissue-resident memory cells on infectious immunity following transplantation(16). Both of these articles reflect the increasing sophistication of our ability to analyze immunity directly in human beings.

The importance of alloantibodies in causing acute humoral and chronic rejection in human organ transplant recipients has been a growing concern as increasing numbers of patients in need of retransplantation are highly presensitized to many potential donors. The review by Zachary and Leffell(36) summarizes what is known about the impact of these antibodies, advances in methods of detecting them, and the latest methodologies for reducing their levels and “desensitizing” patients so that they may receive organ transplants from donors to whom they have alloantibodies. The potential mechanisms by which antibody responses may be tolerized or become less destructive following transplantation from such a donor or an ABO-incompatible donor are discussed. The theme of B cell tolerance is further discussed by Chong and Alegre(13) and in the context of mixed chimerism by Griesemer et al(24) in this issue. The article by Zachary and Leffell(36) discusses the emerging recognition that alloantibodies also impede engraftment of hematopoietic cell grafts, an area of increasing concern as HLA-mismatched HCT is more frequently performed.

The need for non-invasive biomarkers to diagnose rejection and predict outcomes without the need for a biopsy has driven a number of recent studies. The use of rare patients who successfully wean themselves from immunosuppression without rejecting their allografts to identify markers and predictors of this tolerant state is reviewed in this issue by Sophie Brouard and colleagues(37). These “operationally tolerant” patients show immune phenotypes that differ markedly from patients with chronic rejection and strikingly, but not completely, resemble those of healthy volunteers. The question of whether the more “normal” immune profile in these patients is the cause of the ability to achieve tolerance or an effect of the lack of immunosuppressive therapy is currently unanswered and awaits additional study. The article by Suthanthiran and colleagues reviews the development and validation of a PCR signature for acute renal allograft rejection using urinary RNA and discusses the development of a different signature for interstitial fibrosis/tubular atrophy using the same approach(38). These advances in diagnosis and outcome prediction have the potential to drive therapeutic decision-making without the need for invasive biopsies in the future.

The reviews in this issue are ordered to lead the reader through the challenges as well as advances in knowledge and immunotherapies in HCT (articles by Brenner et al(11), Wang and Yang(9), Miller and colleagues(33) and Fuchs(10)) through the application of HCT for

organ allograft tolerance (articles by Fuchs(10), Chong and Alegre(13),Griesemer et al(24)). Other approaches to tolerance induction, with considerable focus on regulatory T cells (reviews by Wood and colleagues(12), Turka and colleagues(14), Chong and Alegre(13)) and B cells (reviews by Wood and colleagues(12),Chong and Alegre(13), Brouard and colleagues(37)) are considered. The theme of innate immunity, induced both by infections and endogenous inflammatory stimuli, as a trigger of graft rejection and barrier to tolerance induction (articles by Goldstein and colleagues(18), Oberbarnscheidt and Lakkis(15), Chong and Alegre(13)) recurs in several different contexts. These are followed by discussions of T cell memory and homeostasis in the context of biological therapies used in transplantation in the reviews by Farber and colleagues(16) and Rosenblum and Kirk(17). The role of preformed antibodies and desensitization procedures in organ transplantation and HCT is then reviewed by Zachary and Leffell(36). Advancements in human transplant immunology are highlighted in these reviews and this theme is developed further in the context of biomarkers of tolerance and rejection in the reviews by Brouard(37) and Suthanthiran(38). The final article, by Griesemer, Yamada and myself(24), reviews a solution to the major limitation in organ transplantation imposed by the inadequate organ supply, namely xenotransplantation. Many of the themes encompassed in the other reviews, including innate immunity and tolerance induction, are of particular importance in this final subject area, which, in part due to the improved ability to engineer and thereby optimize pigs as source animals, may ultimately allow the transplant field to meet its full potential to improve and prolong human life in the not-too-distant future.

It is my hope that any immunologist reading this issue will come away with an understanding of the many challenges still faced by both HCT and organ transplantation and a perspective on how our rapidly advancing ability to study and manipulate the human immune system is informing and building our armamentarium for facing these challenges. I also hope that both basic and applied immunologists in all disciplines will see the importance of cross-talk between the disciplines, since they all depend on understanding and controlling (augmenting in the case of infection and cancer and suppressing in the case of autoimmunity, rejection and GVHD) the same human immune system. Finally, I hope that clinicians and scientists in both the HCT and organ transplant fields will come away with a better understanding of each other’s disciplines and that this issue will thereby contribute to an ongoing and long-overdue convergence of these two areas of applied immunology.

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