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Editorial

B cells as organizers of immunity in transplantation

This issue of Human Immunology provides a collection of papers concerning B cell biology in transplantation and related fields. Readers of Human Immunology have devised and applied the most sophisticated tools for identifying and weighing immune responses, especially the responses of B cells to transplantation. Indeed, readers of Human Immunology have used the products of those B cell responses to forge the fields of immunogenetics and histocompatibility and to generate many key discoveries in transplantation immunology. The guest editor and authors would not presume to summarize current knowledge or portray the forefronts of these fields. However, investigation of B cell biology has brought some advances that have yet to enter the daily practice of transplantation immunology but might eventually prove pertinent if not essential. Some of these advances (e.g. benefits B cells might confer on transplants) contradict common understanding, some (e.g. regulatory properties) could fuel new therapies, and some suggest B cells could have distinct impact on various types of transplants.

Experiments of nature led to key discoveries in many fields, perhaps especially in immunology. It is therefore fitting that this special issue begins with a review of primary B cell immunodeficiencies by Tukisa Smith and Charlotte Cunningham-Rundles [1]. Their review provides a synopsis of how B cell defects impair immunity and, perhaps more importantly, how certain B cell deficiencies impair immune regulation. Thus, certain B cell defects that hinder antibody production also cause auto-immunity and lymphoproliferation. While defective antibody synthesis can be repaired by administration of gammaglobulin, the lymphoproliferation and autoimmunity associated with B cell-deficiencies has no effective treatment. Whether, and in what circumstances, immune regulation by B cells determines the outcome of transplants remains a matter of urgent inquiry and debate as new therapeutics offer more effective means for depleting B cells or suppressing B cell functions. Such concerns draw support from the observations of DiLillo et al. [2] that B cell depletion prior to certain experimental transplants intensifies cell-mediated rejection, an observation appearing to confirm Clatworthy's alarming experience with B cell depleting induction therapies [3].

The studies that identified antigen specificity-independent B cell functions helped to shift the attention away from the cognate-specific B cell and immunoglobulin functions but were limited by exclusive focusing on a single non-cognate function, regulatory function of B cells as an example. The non-cognate B cell functions are multiple and include lymphoid organogenesis, to some extent antigen presentation, secretion of growth factors and cytokines, control of complement activation, diversification of the T cell repertoire, and regulation of immune responses. The non-cognate functions of B cells transform B cells into central organizers of immunity, coordinating innate immunity cues with antigen availability and cellular networks needed for productive responses or for their extinction. These multiple functions confound efforts to determine how individual functions contribute to certain outcomes. In this issue, Jeffrey Platt and I [4] review the non-canonical functions of B cells and offer our perspective on how those functions converge in the development and governance of immunity, particularly immunity to transplants, and hurdles to advancing understanding of B cell functions in transplantation.

Anita Chong [5] reviews how antigens evoke cognate B cell responses. Her article focuses on how antigens find their way to activate specific B cells and how the encounter between antigens and B cells generates plasma cells and memory B cells that perpetuate responses to the triggering antigen. Properties of antigens determine how they evoke immune responses; these include size, immunoglobulin and/or complement opsonization, or particulate nature (exosomes). But the chance combination of antigen and antigen-specific T cells and B cells by itself does not generate immunity – rather, immunity arises when antigens and immune cells meet in the specialized microenvironment of lymphoid tissues. How lymphoid tissues organize the cellular elements of the immune system to orchestrate and govern alloimmune responses is incompletely known, because, as Chong points out, nearly all work on this subject has been pursued using model antigens present only transiently. Conversely, clinical and most experimental transplants introduce large amounts of antigen and availability of that antigen continues for the life of the graft. The quantity and persistence of transplant antigen fuels what Chong argues may be the greatest hurdle to using indices of transplant immunity to predict or diagnose rejection – transplant immunity often occurs in the absence of measurable donor-specific antibodies, and donor-specific antibodies are often detected in the absence of rejection. These concepts highlight the complex ways in which antibodies interact with the graft: sometimes protecting, sometimes damaging. The findings also shift the scope of observation from the antibodies to the donor-specific B cells that, as the repositories of the immunological history, may predict transplant outcomes better than DSA and indicate the way to personalized therapies.

It is clear that B cells and the antibodies they produce determine most outcomes in solid organ transplantation, good [6] and bad [7,8]. It is not so clear, however, how (and if) anti-donor B cell responses determine graft fate in cellular transplants and vascularized composite allotransplantation (VCA). The differences in the impact of B cell responses to the various transplants can be in part explained by the origin of the blood vessels that feed the graft: donor origin in solid organ transplants, recipient in cellular transplants. However, the origin of the blood vessel supply does not explain why VCA, which are fed by donor blood vessels, are relatively inure to antibody mediated rejection. To begin the discussion of these topics we include in this issue reviews on B cell responses to stem cell transplantation and to VCA.

The role of B cell immunity in the outcome of vascularized composite allotransplantation (VCA) is discussed by Kaufman et al. [9].

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VCA provide a reconstructive option for patients who have suffered catastrophic tissue loss. Because VCA include anastomoses between donor and recipient blood vessels, the management of clinical VCA has been modeled on the management of solid organ transplants. However, in contrast to recipients of solid organ transplants and in spite of robust anti-donor antibody responses, recipients of clinical VCA only occasionally exhibit significant vascular disease and suffer less acute or chronic antibody-mediated rejection. Although recipients of VCA are sometimes found to have DSA in their blood, VCA in adequately immunosuppressed patients are rarely destroyed as a consequence. The review discusses why VCA recipients are relatively spared from antibody-mediated rejection hoping that we will learn from these studies how to induce resistance to antibody-mediated disease in recipients of solid organ transplantation.

Allo-hematopoietic stem cell transplantation (HSCT) is a therapy of choice for the treatment of hematologic malignancies and other diseases. Allo-HSCT results in graft versus host disease (GVHD) and whether or not the outcome of the GVHD depends on functions of B cells has been controversial. Stefanie Sarantopoulos and colleagues [10] review the mechanisms contributing to B cell dysfunction in chronic GVHD and discuss the merits of targeting B cell signaling pathways to ameliorate this condition. In a separate paper, the subject of immunotherapies to treat B cell acute lymphoblastic leukemia is taken up by Richard Bram and Kirk Wyatt [11]. These authors discuss the new therapies that engage the immune system of the patient to treat B cell malignancies and the consequences of inducing B cell deficiency in the context of hematologic malignancy.

The reviews in this issue highlight the many unanswered questions regarding how B cells eventuate outcomes in transplantation. Other outstanding questions that would merit an issue all on their own have not been considered for lack of space. For example, the observation that development of tolerance is rare in transplantation even in well immunosuppressed individuals is at odds with fundamental concepts supporting the development of B cell tolerance when T cell help is deficient. Other questions that need investigation are: How do T-dependent B cell responses occur in the presence of effective immunosuppression? How are B cell responses regulated in immunosuppressed recipients of transplants?

Overall, we hope the reviews in this issue will illustrate how far we have come in our understanding of how B cells shape immune responses and influence transplantation outcomes with the hope to inspire novel B cell targeted approaches to emphasize protective responses over non-protective ones.

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