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B cells regulate anti donor T cell reactivity in transplantation

Anna Valujskikh

Glickman Urological Institute and Department of Immunology, Cleveland Clinic, Cleveland, Ohio 44195, USA

Abstract

The analyses of indirect T cell responses in patients with antibody-mediated renal transplant injury by Shiu et al. emphasize the complex contribution of B cells in alloimmunity. The data suggest at least three distinct but potentially overlapping consequences of T/B cell interactions: antigen presentation by B cells, alloantibody production, and immune regulation. These multifaceted functions of B cells should be taken into consideration while developing diagnostic tools and therapeutic strategies.

Keywords

transplantation; lymphocytes; cytokines

Despite increasing interest in antibody-mediated renal allograft injury, the underlying immunological mechanisms of this process are not entirely understood. The activation of CD4 T cells recognizing donor antigens in the context of self MHC molecules (indirect allorecognition) is critical for providing helper signals to donor-reactive B cells and the generation of donor-specific alloantibody (DSA) (1, 2). The assumption has been made that while immunosuppression and/or immune regulation control relatively low frequencies of indirectly primed helper T cells early after transplantation, eventual loss of regulation leads to gradual accumulation of pathogenic DSA and chronic graft tissue injury. The manuscript by Shiu and colleagues explores this possibility by comparing T cell IFNγ production in recipients with stable renal transplants, biopsy-proven AMR and non-immune related graft dysfunction (3). The use of donor cell protein preparation rather than intact cells as stimulating antigens allowed the authors to focus on T cells (presumably $CD4^+$) responding through the indirect pathway. To test for potential immune regulation, the responder peripheral blood mononuclear cells (PBMCs) were depleted either of $CD4^+CD25^+$ or $CD19^+$ cells. The data revealed that in contrast to the prevailing hypothesis, the immune modulation of anti-donor indirect T cell responses by $CD4^+CD25^+$ T cells and/or by B cells is not restricted to recipients with stable grafts but is rather a common feature of ongoing alloresponses. Interestingly, although non-immune mediated pathology, such as calcineurin

Corresponding Author: Anna Valujskikh, Cleveland Clinic, Lerner Research Institute, NB30, 9500 Euclid Avenue, Cleveland, Ohio 44195, Telephone: (216) 445-5452, Fax: (216) 444-8372, valujsa@ccf.org.

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inhibitor toxicity, was associated with indirect alloreactivity (perhaps through increased antigen release and presentation), the immune regulation in these recipients was minimal.

From the immunological perspective, the most intriguing findings of the study is the complex roles played by B cells during indirect T cell alloresponses (Figure 1). On one hand, indirect T cell allorecognition and cognate interactions with the donor peptide/self MHC complexes on recipient B cells is essential for B cell activation and differentiation leading to the production of pathogenic DSA (4). CD40/CD154 costimulatory pathway plays a central role in this process, while the cytokines secreted by T cells regulate immunoglobulin class switch recombination and determine the isotype of resulting antibodies (5). However, the helper signals for alloantibody generation are not the only consequence of T/B cell interactions. Recent studies suggest that B cells can influence T cell responses via antigen presentation, providing costimjulatory signals and secretion of pro- or anti-inflammatory cytokines (6). Supporting this concept, Shiu et al. report that the depletion of $CD19^+$ cell reduced IFNγ production through the indirect pathway in patients with detected anti-donor T cell reactivity. This is not surprising as B cells are major antigen presenting cell population within PBMCs. However, the short term ELISPOT assay measures the frequencies of previously activated effector/memory T cells, and the ability of B cells to indirectly present alloantigen *in vitro* does not necessarily reflect the mechanism of initial *in vivo* T cell priming. Furthermore, the fact that total B cell depletion restores indirect alloreactivity in low responders demonstrates that B cells are dispensable for antigen presentation during short term in vitro assay. The exact contribution of B cells to indirect anti-donor T cell reactivity and the roles of B cell-derived cytokines following transplantation need to be tested more rigorously.

The study convincingly demonstrates that in addition to acting as APCs, circulating B cells can suppress *in vitro* indirect responses by T cells. Consistent with previous reports on B cell regulation, the data suggest that the balance between “stimulatory” and “regulatory” B cells can be reflected in their ability to produce IFNγ versus IL-10 (7, 8). However, more complex regulatory patterns are revealed by experiments depleting $CD25^+$ T cells and/or B cells and many questions remain to be addressed. For example, as regulation appears to be donor antigen specific, what is the role of indirect pathway and B cells in Treg development and responses? Are there potential interactions between Tregs and B cells with regulatory phenotype? How does T cell regulation influence B cell activation and alloantibody generation? What is the influence of T and B cell regulation on direct alloresponses and cellular rejection? Most relevant to clinical transplantation and immune monitoring of transplant patients, the results raise a possibility that the analyses of alloresponses by unseparated PBMC may significantly underestimate the frequencies of donor antigen-reactive T cells.

Unexpectedly, the involvement of B cells in T cell indirect alloreactivity was not correlated with serum DSA levels. For instance, B cell suppression was detected in patients with high serum DSA titers. Such findings suggest that the cognate interactions between indirectly primed CD4 T cells and B cells may elicit IFNγ secretion by T cells but do not necessarily lead to productive B cell activation and humoral immunity. Another implication is that B cells secreting IFNγ and supporting indirect responses by CD4 T cells and B cells

differentiating into DSA secreting cells represent two distinct subsets (as in Figure 1). Temporal analyses of various B cell subsets and their functional profiles would be instrumental in addressing these possibilities.

The authors acknowledge several limitations of the study, including low patient numbers in some groups and the lack of cell separation experiments due to small sample size. In addition, one can argue that the analyses of peripheral blood cells may not be truly representative of processes within secondary lymphoid organs or transplanted tissue. Despite these drawbacks, the manuscript brings forth several interesting possibilities and justifies future mechanistic investigations in well-characterized animal models. Understanding intricate patterns of T/B cell interactions caused by transplantation may eventually provide more informative diagnostic tools and identify novel therapeutic targets to improve allograft outcomes.

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References

1. Clatworthy MR. B cell responses to allograft--more common than we thought? American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2013; 13:1629–1630.
2. Colvin RB, Smith RN. Antibody-mediated organ-allograft rejection. Nature reviews. Immunology. 2005; 5:807–817.
3. Shiu KY, McLaughlin L, Rebollo Mesa I, Zhao J, Semik V, Cook T, Roufosse C, Brookes P, Bowers R, Galliford J, Taube D, Lechler R, Hernandez Fuentes M, Dorling A. B lymphocytes support and regulate indirect T cell alloreactivity in individual patients with chronic antibody-mediated rejection. Kidney International. current issue.
4. Heeger PS. T-cell allorecognition and transplant rejection: a summary and update. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2003; 3:525–533.
5. Bishop GA, Hostager BS. B lymphocyte activation by contact-mediated interactions with T lymphocytes. Current opinion in immunology. 2001; 13:278–285. [PubMed: 11406358]
6. Lund FE, Randall TD. Effector and regulatory B cells: modulators of CD4+ T cell immunity. Nature reviews. Immunology. 2010; 10:236–247.
7. Cherukuri A, Rothstein DM, Clark B, Carter CR, Davison A, Hernandez-Fuentes M, Hewitt E, Salama AD, Baker RJ. Immunologic human renal allograft injury associates with an altered IL-10/TNF-alpha expression ratio in regulatory B cells. Journal of the American Society of Nephrology : JASN. 2014; 25:1575–1585. [PubMed: 24610932]
8. Mauri C, Bosma A. Immune regulatory function of B cells. Annual review of immunology. 2012; 30:221–241.

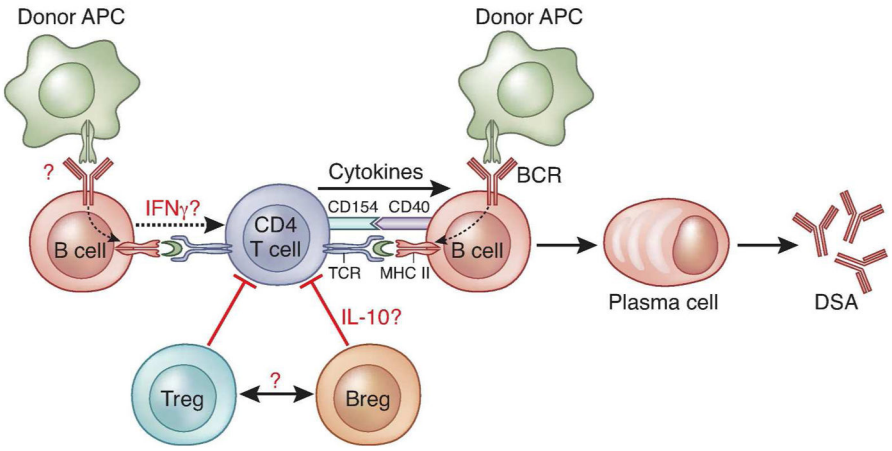

Figure 1.
Multiple functions of B cells during indirect T cell alloresponses