Immune Network
DOI 10.4110/in.2010.10.3.81
pISSN 1598-2629 eISSN 2092-6685
REVIEW ARTICLE

The Role of B Cells in Transplantation and Immunopathic Diseases

*A. Basten**
Garvan Institute, Sydney, Australia

B cells, by virtue of their diverse roles in immune responses to foreign and self antigens, have become of increasing interest to the clinician as well as the basic immunologist. In particular, it is now apparent that the development of B cell unresponsiveness in antibody and T cell mediated autoimmune disorders and the transplant setting is both worthwhile and achievable. **[Immune Network 2010;10(3):81-84]**

INTRODUCTION

The development of the B cell repertoire in humans and rodents occurs in two stages: during the first VDJ gene recombination within primary lymphoid tissue (eg bone marrow (BM)) leads to expression of specific antigen receptors (BCRs) on immature B cells which can then recognise their cognate antigens as they undergo further differentiation in peripheral lymphoid tissue. The second stage takes place largely within germinal centres (GCs) where B cells undergoing somatic hypermutation are positively selected for increasing affinity, but negatively selected against self (1). Due to the random nature of these processes self-reactive B cells are generated as well as B cells with useful anti-foreign specificities. Consequently there is a need for regulatory mechanisms to operate at multiple checkpoints throughout B cell differentiation in the BM and peripheral lymphoid tissue (2-4).

SPECTRUM OF B CELL FUNCTIONS

It has become apparent in the past 5 years that B cells, like T cells have a broad range of functional capabilities. Not only do they produce antibodies, but they can transfer antigen in peripheral lymphoid tissue (5), act as antigen presenting cells (APC) and secrete pro- and anti-inflammatory cytokines and chemokines. Thus, depending on the circumstances they behave as either effector or regulatory cells (6-8). Moreover, it appears that in both mouse (9) and man (10) there is a discrete subset of IL-10 secreting B cells with regulatory properties (Bregs) which can switch off T as well as B cell mediated immune responses. The indirect effects of B cell dependent suppression on the T cell compartment include deletion, induction of anergy and selective expansion of Tregs (9). This range of presentation-related functions is now being exploited to treat a variety of immunopathic conditions involving both T cells and antibodies. For example, Bregs are being engineered by transfecting naïve B cells with the antigen in question (eg self antigens like factor VIII in models of haemophilia where allo-antibodies have been generated) coupled to an IgG heavy chain scaffold (11).

ROLE OF B CELLS IN AUTOIMMUNE DISEASE

Pathogenesis

The precise role of B cells in pathogenesis of autoimmune diseases has been studied in two main ways. The first involves crossing autoimmune prone mice with B cell deficient (eg muMT or anti-CD20 antibody treated) mice and determining whether disease still occurs or not. For example, type-1 diabetes prone NOD mice lacking B cells fail to develop clinical disease due to a failure in activation of self-reactive effec-

Received on June 4, 2010. Accepted on June 11, 2010.

*Corresponding Author. E-mail: a.basten@garvan.org.au

Keywords: B cells, Transplantation, Immunopathic diseases

tor T cells (12). Likewise Aire deficient mice the organs of which are heavily infiltrated with B cells lose their susceptibility to multiple autoimmune disorders when bred on to a B cell deficient background or after being treated with anti-CD20 antibody (13). In this model as well as the NOD mouse, B cells exert their pathogenic effect through presentation of self-antigen and possibly release of proinflammatory cytokines. The second approach involves studying human neonates for development of autoimmunity. Since the great majority of autoantibodies belong to the IgG class and therefore can cross the placenta, development of transient autoimmune disease post-natally is a neat way of proving that autoantibodies per se and not other B cell activities are responsible. Examples include Graves disease, myasthenia gravis, ITP, certain bullous skin diseases and Lupus associated congenital heart block. In some other instances autoantibodies even though not directly pathogenic can be valuable diagnostic and/or prognostic markers, for instance, islet cell antibodies in type 1 diabetes and antibodies to mitochondria or smooth muscle in autoimmune liver disease. By contrast the principle role of B cells in diseases like multiple sclerosis, rheumatoid arthritis and the chronic inflammatory demyelinating neuropathies (in addition to type 1 diabetes (see above)) is probably as APCs. Interestingly deposition of autoantibody containing immune complexes in tissues is no longer considered to be a primary event in autoimmune states, but rather on of the pathogenic pathways that contribute downstream to tissue destruction once self-tolerance has been broken.

Anti-B cell therapy

Over the past five years B cell depletion particularly with anti-CD20 antibodies has become an accepted second line modality of therapy for patients with refractory autoimmune diseases (14). Thus promising results have been obtained with anti-CD20 antibodies in patients with seropositive rheumatoid arthritis who have failed therapy with the combination of TNF inhibitors and methotrexate (15-17). Less impressive responses have been obtained in patients with moderate to severe lupus (18), although some promise has been shown in relapsing remitting multiple sclerosis (19). What is of clinical importance, however, is that depletion of circulating B cells is not associated with an increased incidence of serious infection, presumably due to the sparing of long-lived anti-foreign plasma cells in the bone marrow (20,21). Inhibition of BAFF with a BCMA fusion protein was shown to be efficacious in preventing the onset of Type 1 diabetes in the NOD model, this effect being due not only to B cell depletion, but to alterations in effector and regulatory T cell subsets (22). Moreover, the use of anti-CD20 in patients with recent onset TID appeared to be associated with lower insulin requirements and higher C peptide levels (23). Due to their widespread applications, B cell depletion techniques are shedding significant light on the positive and negative functions of mature B cell subsets (24).

ROLE OF B CELLS IN TRANSPLANTATION

B cells as opposed to T cells have received relatively little attention in a transplant setting until recently. Nevertheless it comes as no surprise that B cells are becoming of much greater interest in this field given their regulatory as well as effector functions.

Hemopoietic stem cell transplantation

The major residual clinical challenge in allogeneic stem cell transplantation remains acute and chronic graft versus host disease (GVHD) and their control while retaining the beneficial effects of the graft versus leukemia effect. In acute GVHD there is minimal evidence of a role for B cells; consequently B cell depletion with anti-CD20 antibodies is ineffective except if given pre-transplant when it may cause a slight reduction in cumulative incidence of rejections (25). By contrast, B cells have clearly been shown to be important in chronic GVHD (25). Thus this syndrome is characterised by high circulating levels of BAFF and development of associated autoantibody mediated autoimmune diseases (eg ITP and glomerulonephritis). Moreover there is a correlation between anti-HY antibodies and chronic GVHD. Predictably therefore B cell depletion with anti-CD20 antibody is beneficial (25). Interestingly infusion of pooled intravenous immunoglobulin given pre- or post transplantation does not ameliorate either acute or chronic GVHD despite its potent anti-inflammatory activity, whereas it remains an accepted form of therapy in solid organ (eg renal) transplants (26).

Solid organ transplantation

The role of B cells in *hyperacute graft rejection* is well established. In the case of xenografts, hyperacute rejection is mediated by 'natural' anti- glycolipid antibodies derived from B1 cells, while pre-existing antibodies to ABO blood group antigens or HLA are responsible for the same process in allog-

raft recipients (27). The only clinical situation where human allografts (eg cardiac) have been successfully transplanted across an ABO or full HLA mismatch is in the neonatal period where it is possible to capitalise on the relative immaturity of the infant's immune system (28). Success in humans with xenografts remains an important challenge given the chronic shortage of human organ donors. It is therefore encouraging that promising results are being obtained in experimental models involving creation of mixed xenogeneic bone marrow chimeras (29). These models depend on ablating the recipient's immune system before transplantation in order to capitalise on the sensitivity of immature B cells to tolerance induction during reconstitution with BM precursors.

With respect to *acute allograft rejection*, conventional dogma has it that T cells are the primary effectors. However, two lines of evidence have emerged that point to a role for B cells as well. First, significant numbers of B cells and plasma cells have been demonstrated in the cellular infiltrate of rejecting renal allografts (30). Secondly and based on these data anti-CD20 antibody, when added to anti -T cell and cytotoxic drug therapy, has been shown to reduce the rejection rate of human renal allografts (31) and primate islet cell grafts in an experimental model (32).

As was the case with certain types of autoimmune disease (see above), the primary contribution of B cells to allograft responses, other than hyperacute rejection is likely to be due to their role in antigen presentation to T cells. Support for this contention comes from the demonstration by Terasaki's group that antibodies to HLA and non-HLA antigens are predictive of renal allograft rejection in only about 50% of cases (33). On the other hand, the proportion of B lineage cells in grafts does not appear to be a reliable indicator of graft survival versus loss (30,34). Interestingly the same conclusion has been reached concerning infiltrating Tregs (34) which is in striking contrast to their well established prognostic role in human tumours (35-37).

CONCLUSIONS

B cells in addition to producing antibodies secrete pro- and anti- inflammatory cytokines and chemokines, transport antigens and present them to T cells. Their capacity to act as regulatory as well as effector cells under both normal and pathological conditions means that their role in autoimmunity and transplantation has become not only more complex, but now offers intriguing new opportunities for therapy using B cell depletion or tolerance induction in the B cell compartment.

ACKNOWLEDGEMENTS

I am grateful to Terri Faroe for her assistance with preparation of the manuscript. Our research is supported by a Program Grant from the National Health and Medical Research Council of Australia.

CONFLICTS OF INTEREST

The author have no financial conflict of interest.

REFERENCES

1. Basten A, Brink R. Tolerance and Autoimmunity: B cells. In: Rose NR, Mackay IR, editors. The Autoimmune Diseases. 4th ed. St. Louis: Academic Press; p167-177, 2006
2. Goodnow CC: Multistep pathogenesis of autoimmune disease. Cell 130:25-35, 2007
3. von Boehmer H, Melchers F: Checkpoints in lymphocyte development and autoimmune disease. Nat Immunol 11:14-20, 2010
4. Wardemann H, Nussenzweig MC: B-cell self-tolerance in humans. Adv Immunol 95:83-110, 2007
5. Phan TG, Gray EE, Cyster JG: The microanatomy of B cell activation. Curr Opin Immunol 21:258-265, 2009
6. Cox SL, Silveira PA: Emerging roles for B lymphocytes in Type 1 diabetes. Expert Rev Clin Immu 5:311-324, 2009
7. Singh A, Carson WF 1th, Secor ER Jr, Guernsey LA, Flavell RA, Clark RB, Thrall RS, Schramm CM: Regulatory role of B cells in a murine model of allergic airway disease. J Immunol 180:7318-7326, 2008
8. Yanaba K, Bouaziz JD, Matsushita T, Magro CM, St Clair EW, Tedder TF: B-lymphocyte contributions to human autoimmune disease. Immunol Rev 223:284-299, 2008
9. DiLillo DJ, Matsushita T, Tedder TF: B10 cells and regulatory B cells balance immune responses during inflammation, autoimmunity, and cancer. Ann N Y Acad Sci 1183:38-57, 2010
10. Blair PA, Norena LY, Flores-Borja F, Rawlings DJ, Isenberg DA, Ehrenstein MR, Mauri C: CD19(+)CD24(hi)CD38(hi) B cells exhibit regulatory capacity in healthy individuals but are functionally impaired in systemic Lupus Erythematosus patients. Immunity 32:129-140, 2010
11. Skupsky J, Zhang AH, Su Y, Scott DW: B-cell-delivered gene therapy induces functional T regulatory cells and leads to a loss of antigen-specific effector cells. Mol Ther 2010 [Epub ahead of print]
12. Silveira PA, Dombrowsky J, Johnson E, Chapman HD, Nemazee D, Serreze DV: B cell selection defects underlie the development of diabetogenic APCs in nonobese diabetic mice. J Immunol 172:5086-5094, 2004
13. Gavanescu I, Benoist C, Mathis D: B cells are required for

Aire-deficient mice to develop multi-organ autoinflammation: a therapeutic approach for APECED patients. Pro Natl Acad Sci U S A 105:13009-13014, 2008
14. Browning JL: B cells move to centre stage: novel opportunities for autoimmune disease treatment. Nat Rev Drug Discov 5:564-576, 2006
15. Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, Stevens RM, Shaw T: Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N EnglJ Med 350:2572-2581, 2004
16. Jacobi AM, Dörner T: Current aspects of anti-CD20 therapy in rheumatoid arthritis. Curr Opin Pharmacol 2010 [Epub ahead of print]
17. Lee YH, Bae SC, Song GG: The efficacy and safety of rituximab for the treatment of active rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials. Rheumatol Int 2010 [Epub ahead of print]
18. Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, Utset TO, Gordon C, Isenberg DA, Hsieh HJ, Zhang D, Brunetta PG: Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum 62:222-233, 2010
19. Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, Bar-Or A, Panzara M, Sarkar N, Agarwal S, Langer-Gould A, Smith CH, HERMES Trial Group: B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med 358:676-688, 2008
20. Bingham CO 3rd, Looney RJ, Deodhar A, Halsey N, Greenwald M, Codding C, Trzaskoma B, Martin F, Agarwal S, Kelman A: Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum 62:64-74, 2010
21. Kessel A, Rosner I, Toubi E: Rituximab: beyond simple B cell depletion. Clin Rev Allergy Immunol 34:74-79, 2008
22. Marino E, Villanueva J, Walters S, Liuwantara D, Mackay F, Grey ST: CD4(+)CD25(+) T-cells control autoimmunity in the absence of B-cells. Diabetes 58:1568-1577, 2009
23. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, Becker DJ, Gitelman SE, Goland R, Gottlieb PA, Marks JB, McGee PF, Moran AM, Raskin P, Rodriguez H, Schatz DA, Wherrett D, Wilson DM, Lachin JM, Skyler JS, Type 1 Diabetes TrialNet Anti-CD20 Study Group: Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. N Eng J Med 361:2143-2152, 2009
24. Thaunat O, Morelon E, Defrance T: Am"B"valent: anti-CD20 antibodies unravel the dual role of B cells in immunopathogenesis. Blood 2010 [Epub ahead of print]
25. Ratanatharathorn V, Pavletic S, Uberti JP: Clinical applications of rituximab in allogeneic stem cell transplantation: anti-tumor and immunomodulatory effects. Cancer Treat Rev 35:653-661, 2009
26. Guidelines for clinical usage of intravenous immunoglobulin IVIg in Australia. National Blood Authority, Australia. pp 160-165, 2008
27. Parsons RF, Vivek K, Redfield RR, Migone TS, Cancro MP, Naji A, Noorchashm H: B-cell tolerance in transplantation: is repertoire remodeling the answer? Expert Rev Clin Immunol 5:703, 2009
28. Fan X, Ang A, Pollock-Barziv SM, Dipchand AI, Ruiz P, Wilson G, Platt JL, West LJ: Donor-specific B-cell tolerance after ABO-incompatible infant heart transplantation. Nat Med 10:1227-1233, 2004
29. Gibbons C, Sykes M: Manipulating the immune system for anti-tumor responses and transplant tolerance via mixed hematopoietic chimerism. Immunol Rev 223:334-360, 2008
30. Zarkhin V, Kambham N, Li L, Kwok S, Hsieh SC, Salvatierra O, Sarwal MM: Characterization of intra-graft B cells during renal allograft rejection. Kidney Int 74:664-673, 2008
31. Zarkhin V, Li L, Kambham N, Sigdel T, Salvatierra O, Sarwal MM: A randomized, prospective trial of rituximab for acute rejection in pediatric renal transplantation. Am J Transplant 8:2607-2617, 2008
32. Liu C, Noorchashm H, Sutter JA, Naji M, Prak EL, Boyer J, Green T, Rickels MR, Tomaszewski JE, Koeberlein B, Wang Z, Paessler ME, Velidedeoglu E, Rostami SY, Yu M, Barker CF, Naji A: B lymphocyte-directed immunotherapy promotes long-term islet allograft survival in nonhuman primates. Nat Med 13:1295-1298, 2007
33. Terasaki PI, Ozawa M, Castro R: Four-year follow-up of a prospective trial of HLA and MICA antibodies on kidney graft survival. Am J Transplant 7:408-415, 2007
34. Turka LA, Lechler RI: Towards the identification of biomarkers of transplantation tolerance. Nat Rev Immunol 9:521-526, 2009
35. Barnett JC, Bean SM, Whitaker RS, Kondoh E, Baba T, Fujii S, Marks JR, Dressman HK, Murphy SK, Berchuck A: Ovarian cancer tumor infiltrating T-regulatory (T(reg)) cells are associated with a metastatic phenotype. Gynecol Oncol 116: 556-562, 2010
36. Xu L, Xu W, Qiu S, Xiong S: Enrichment of CCR6+Foxp3+ regulatory T cells in the tumor mass correlates with impaired CD8+ T cell function and poor prognosis of breast cancer. Clin Immunol 135:466-475, 2010
37. Zhang HH, Mei MH, Fei R, Liao WJ, Wang XY, Qin LL, Wang JH, Wei L, Chen HS: Regulatory T cell depletion enhances tumor specific CD8 T-cell responses, elicited by tumor antigen NY-ESO-1b in hepatocellular carcinoma patients, in vitro. Int J Oncol 36:841-848, 2010