The Role of B Cells in Transplantation and Immunopathic Diseases

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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-

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A. Basten

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 auto-antibody 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 (e.g., 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). Second, 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.

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CONFLICTS OF INTEREST

The author have no financial conflict of interest.

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A. Basten

The Role of B Cells in Transplantation and Immunopathic Diseases

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