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New insights into the functions of B cells

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Abstract

Organ transplants between genetically different individuals elicit powerful immune responses that invariably cause rejection in the absence of immune suppression. Among the immune responses elicited by organ allografts, B cell responses causing antibody-mediated rejection is one of the most vexing. However, recent advances in the field indicate that B cells and antibodies' contribution to immunity extends well beyond the traditional functions ascribed to antibodies. Here we review "non-humoral" functions of B cells and the implications of these functions to transplantation.

B cell responses in transplantation

After transplantation, B cells might be activated by one of three pathways. The pathway used is determined by how antigen engages receptors on B cells. The first pathway that may lead to B cell activation is called T cell dependent and is thought to be evoked by antigen plus activated T cells. Antibodies produced in response to proteins such as HLA typically arise by T cell dependent responses. These responses require ligation of the immunoglobulin receptor on B cells plus the delivery of T cell help. T cell help is typically delivered through cell-cell interactions, through engagement of CD40 on B cells by CD40-ligand on T cells for example, and also by cytokine and other soluble mediators secreted by activated T cells (1).

The second and third pathways that may lead to B cell activation occur independently of T cell help and are called T-independent Type 1 and T-independent Type 2 B cell activation. In the second pathway, B cell activation involves toll-like receptors (TLR). Since B cells respond to TLR stimuli in the absence of T cells, this pathway is referred to as T cell-independent type 1 B cell activation. Because most B cells bearing diverse immunoglobulin receptors express the TLR4 receptor (2), stimulation with endotoxin gives rise to polyclonal B cell activation (and thus it is not antigen specific) (3). In the non-transplant setting this pathway is typically engaged by endotoxin (produced by most gram-negative bacteria) binding to TLR4. Under conditions of transplantation, endotoxin is not introduced in sufficient amounts to stimulate this pathway; however, other TLR4 ligands could still contribute to B cell activation through this pathway. For example, we have shown that the break-down products of heparan sulfate (a normal component of the basement membrane) can stimulate TLR4 (4) and these break-down products can be released by grafts owing to ischemia following transplantation (5). In addition to the polyclonal stimulation by TLR4, the saccharide moiety of endotoxin also engages the B cell receptor specifically producing endotoxin-specific antibodies (6).

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In the third pathway, B cell activation follows cross-linking of the B cell receptors (BCR, the immunoglobulin expressed at the surface of every B cell). Cross-linking of the BCR is facilitated by molecules bearing repetitive epitopes such as polysaccharides, like those forming the capsule of *streptococcus pneumoniae*. Like the responses to TLR4 ligands, B cell responses to polysaccharides may occur in the absence of T cells and are therefore referred to as T-independent type-2 B cell activation (1). The anti-blood group antibodies are thought to be produced by this mechanism (7). However, while blood group antigens lack extensive polymerization (they are oligosaccharides) needed to evoke type-2 T-independent B cell responses, muco-polysaccharides of the intestinal flora and in the gut generate the antibodies that cross-react with the anti-blood group antigens (8). Because the anti-blood group antigens are produced without deliberated immunization, they are called “natural antibodies” (9), Table 1.

Control of antibody responses

T-independent and T-dependent antibody responses are controlled differently and pose very different challenges in the context of organ transplantation. Persistent antibody responses to polysaccharides have been thought to require repeated differentiation from naïve B cells because polysaccharides may not promote the development of long-lived memory B cells or plasma cells. Since polysaccharide-responding cells are generally short lived, inhibiting *de novo* activation or inducing deletion or inactivation of newly produced polysaccharide-specific B cells would in principle abolish these responses (10). The concept that antibody responses to polysaccharides are short lived has been recently contested by two independent groups. Hsu et al. (11) showed sustained antibody responses to a TI-2 antigen in V(D)J recombination-deficient mice reconstituted with mature B cells and proposed that maintenance of TI-2 antibody responses does not require differentiation *de novo* from naïve B cells. Obukhanych and Nussenzweig (12) showed long-term persistence of antigen-specific B cells following TI-2 stimulation, suggesting that responses to TI-2 antigens generate B cell memory. Whether sustained antibody production or persistence of antigen-specific B cells identified in the studies above are “bona fide” memory, understood as a faster, more effective response causing survival advantage, is not yet clear.

Specific non-responsiveness (tolerance) to polysaccharide antigens may develop spontaneously. West et al. (13,14) found that children who received blood group-disparate cardiac grafts in infancy, before the development of blood group antibodies, developed B cell tolerance to the blood group antigen expressed by the cardiac graft. In contrast, transplantation across blood groups in adults and older children with high titers of anti-A and or anti-B antibodies requires depletion of those antibodies.

Most cases of acute humoral rejection are caused by anti-HLA antibodies. Despite effective control of cellular rejection by aggressive immunosuppressive regimens, transplant recipients often have anti-HLA antibodies (15). How these antibodies are produced in the presence of immune suppression is unclear. One possibility is that anti-HLA antibodies might be produced by memory B cells and long-lived plasma cells which require less or no T cell help to secrete antibodies (16). Another possibility might be that B cells interact directly with donor antigen-presenting cells (APC). The donor APCs in this case could provide co-stimulation to the host’s B cells while simultaneously providing the antigen bound to the membrane in a repetitive manner facilitating cross-linking the B cell receptor, thus mimicking the effect of a T-independent antigen. Alternatively, donor antigen may be presented along with toll-like receptor agonists shed from the graft such as heparan sulfate (4), which may overcome the need for specific T cell activation or perhaps suffice to activate the differentiation of memory B cells. Responses from memory B cells and long-lived plasma cells pose the most vexing hurdle in transplantation. This is because while available therapies effectively control cellular

rejection they do not control antibody production from memory B cells and long-lived plasma cells (16).

Production of antibodies to alloantigens may be controlled by means other than tolerance (specific non-response). Soluble, monomeric antigen alone shed by grafts or deliberately injected into recipients of transplantation suppresses B cell functions (17). Liver transplants, for example, are thought to shed soluble antigen, which may contribute to liver graft suppressive effects on allo-immune responses by inhibiting B cell responses. Additionally, immune complexes inhibit B cell responses by acting through Fc receptors, and this property may explain how intravenous immunoglobulin benefits transplant recipients. Complement may also inhibit B cell responses (18).

Recent reports suggest that T cells with regulatory properties (defined by CD4+, CD25+ expressing the transcription factor FoxP3) inhibit B cell proliferation in response to polyclonal stimulus (19,20). Regulatory T cells may also suppress B cell immunoglobulin class switch, decreasing Ig production (21,22). While several mechanisms may be involved, Zhao et al. (23) showed that T regulatory cells preferentially kill activated B lymphocytes by cell-cell contact involving perforin and granzymes.

The idea that regulatory T cells control B cell responses led Callaghan and colleagues (24) to explore whether these T cells may control alloantibody production. Although antigen-specific CD4 regulatory T cells were found to repress alloantibody-mediated rejection, other mechanisms were not excluded. The possibility that inducible T regulatory cells may control alloantibodies remains attractive as a means of regulating antibody-mediated rejection.

Accommodation

Under some conditions, allo-antibodies directed against alloantigens do not cause the rejection of organ grafts, but instead the grafts survive and maintain function in spite of alloantibody binding (25) (Table 1). First observed in ABO incompatible transplants, this condition is called “accommodation” (26). We have suggested that accommodation is the most common outcome of organ transplantation (27). The devising of optimal strategies for controlling humoral responses should consider the antagonistic functions of antibodies, inducing graft injury or accommodation. Allograft-specific antibodies damage the graft but also control new antibody production and induce resistance to injury (accommodation). Antibodies may also mediate a condition called “enhancement” in which antibodies bound to the graft may mask immunogenic properties, decreasing the graft’s susceptibility to rejection (28). Thus, procedures presently used to remove antibody or suppress complement may also impair control of humoral responses, graft resistance to injury and, as we will discuss next, may also impair B cell and antibody-mediated control of T cell responses.

Non-humoral functions of B cells with impact on transplantation

B cells may impact T cell responses independently of secreted antibodies (29). We call these functions non-humoral functions of B cells. We consider developmental functions of B cells which include lymphoid organogenesis (reviewed elsewhere (29)) and the establishment of the T cell repertoire. We will also discuss functions of B cells that promote or control T cell responses (such as B cell antigen presentation, cytokine production, and perhaps “regulation” of cellular immunity).

B cell-dependent T cell development

In studying mice with a defined B and T cell compartment, we made an unexpected observation (30). In these mice, the number of T cells in the thymus and in the periphery depended on

whether or not the mice had B cells (30). The dependence of T cell number on B cells suggested a role for B cells in the development and maintenance of T cells (31). Pursuing this suggestion in mice that could produce diverse T cells, we found that B cells and B cell products drive the diversification of the T cell repertoire in the thymus and contribute to diversity of the mature repertoire in the periphery (32). Although the mechanisms may be several, one mechanism was shown to involve the use of immunoglobulin (32). Immunoglobulin could be a source of diverse peptides to promote the development and/or survival of T cells or might act as a superantigen (that binds to the surface of the TCR outside the antigen binding site) in the selection and/or survival of T cells.

If B cells and Ig contribute mostly to the development of the T cell repertoire in the thymus as opposed to the maintenance of T cells in the periphery, defects in the B cell compartment manifested early in life ought to cause severe contractions of the T cell repertoire. If, on the other hand, B cells and Ig mostly contribute to the maintenance of a diverse T cell repertoire in the periphery then acquired B cell deficiencies, such as a consequence of immune-suppression or malignancy, may also contract the T cell compartment. How developmental or acquired contractions of the T cell repertoire will impact the responses of T cells to transplantation or in immune defense is not known. Below we summarize our findings.

Immunologists generally believe that T cell receptor diversity is needed for efficient cellular immunity (33). Contraction of the T cell receptor repertoire should thus perturb T cell function. Instead, we found that many T cell functions including rejection of male-to-female skin grafts were maintained in mice that have a contracted T cell repertoire up to 100-fold, owing to B cell defects (34). In fact, mice with more than 100-fold contracted T cell repertoires rejected male-to-female skin grafts faster than wild type mice (unpublished observations). In spite of the enhanced kinetics, secondary and tertiary grafts were not rejected faster than primary grafts, suggesting that the primary response had properties akin to memory. In accord with this possibility we found that mice with a contracted TCR repertoire had an increased proportion of T cells with phenotypic properties of memory (CD44**hi** and CD62L**lo**). Our results indicated that the T cell compartment “adapts” to developmental contractions of the T cell repertoire. The adaptation to decreased diversity may enhance certain functions of T cells but may impair others. For example, enhanced kinetics of male-to-female graft rejection could be owed to deficient regulation. In summary, our findings disclosed an unforeseen plasticity of the cellular immune compartment to contractions of the TCR repertoire. How much of the T cell compartment adaptation is in response to the primary B cell defect or to the contraction of the repertoire remains to be established.

The discovery that T cells adapt to extraordinary contractions of the TCR repertoire motivated the study of the immune system in children who were subjects of cardiac transplantation in infancy. Children receiving cardiac transplants suffer drastic T cell repertoire contraction, owing to thymectomy and T cell depletion prior to transplantation (31,35). We found that although these children have 100-fold contracted T cell repertoires they are not unusually susceptible to infections by viruses or opportunistic pathogens that depend on cellular immunity for their control (35). Instead, we found that the levels of endogenous viruses such as the herpes simplex 7 are elevated in the blood, albeit without causing clinical symptoms (35). In addition, children immunized with hepatitis B post-surgery show depressed IgG responses, suggesting a defect in the generation of B cell memory (35). These studies indicate that adaptation of the T cell compartment to contractions of the T cell repertoire are not unique to situations that occur with B cell deficiency but is instead a direct consequence of T cell repertoire contraction.

Given the high prevalence of allo-reactive T cells, we reasoned that T cell repertoire contractions may have much less impact on the fate of MHC-disparate grafts than on the fate

of grafts differing in minor histocompatibility antigens, but sharing the MHC of the host. This is because T cells with reactivity to allogeneic MHC are thought to be 5 to 10% of all peripheral T cells and at least 100-fold more frequent than T cells that respond to minor histocompatibility antigens (36–38). The high frequency of allo-MHC-reactive T cells is thought to be owed to "direct" recognition of the allogeneic MHC expressed by the graft cells and owed to "indirect" recognition of allogeneic MHC-derived peptides presented by the recipients' "self" MHC on the recipient antigen-presenting cells (39). How much T cells' direct or indirect recognition contribute to allograft rejection is a subject of controversy.

Testing the impact of TCR repertoire contraction in graft rejection, we found that extreme contractions of the T cell repertoire owing to B cell defects did not impair rejection of skin allografts but, surprisingly, did also not impair rejection of male-to-female skin grafts which differ from the host only in the male minor histocompatibility antigens. In fact, female mice with extreme T cell repertoire contractions rejected male grafts faster than wild type [AbuAttieh et al., manuscript in preparation]. These results indicated that, contrary to expectations, repertoire contractions may paradoxically enhance responses of T cells to transplantation and thus enhance rejection. It is, therefore, important to consider that T and B cell depletion manipulations designed to prevent rejection may also induce adaptation of the remaining T cells, causing a paradoxical enhancement of T cell responses to allografts.

Two recent clinical studies suggest that B cell depletion may promote regulation. Sfikakis et al. (40,41) and Vallerskog et al. (41) in independent studies, found that depletion of CD20-positive B cells with rituximab in patients with systemic lupus erythematosus was associated with an increase in regulatory T cells expressing FoxP3. Thus, at least in the setting of auto-immunity B cells may determine the frequency of T regulatory T cells. Further studies in experimental models will be necessary to address fundamental questions such as whether regulatory function does indeed depend on B cells and whether B cells modify the generation of T regulatory cells in the thymus or in the periphery.

B cells as antigen-presenting cells

Besides producing antibodies, B cells can present antigen quite effectively. B cells express on their surface MHC class II and peptide as well as the co-stimulatory CD80 and CD86 molecules enabling the delivery of signal 1 and signal 2 to T cells (42). In contrast to dendritic cells which take up antigen in a rather non-specific manner, B cells can endocytose antigens that bind to the B cell receptor. This specific uptake facilitates processing of antigen-specific peptides (43). Because binding of antigens to the BCR is specific, activated B cells are likely to display peptides enriched for the specific antigen internalized by the BCR facilitating the engagement of T cell receptors with specificity for those peptides, thus establishing a "cognate" link between T and B cells (44).

Under certain experimental conditions, B cells can prime T cells as effectively as dendritic cells (45–47). The cognate B-T interaction described above promotes B and T cell clonal expansion (46–48) and establishes both B (49) and T cell memory (50–52).

How much the cognate B cell and T cell interaction modifies responses to transplantation is still a matter of debate. Antigen presentation by B cells is not required for rejection of allografts across MHC barriers since mice that lack B cells or immunoglobulin (the JH-/- mice (34)) or mice that have a very severe B cell deficiency (the μMT-mice (53)) reject skin and/or organ grafts as quickly as their B cell-proficient counterparts (54). Responses to minor antigens that might be concentrated by cognate interaction of B and T cells are also not impaired in B cell-deficient mice (34). However, since B cell deficiency causes defective lymphoid organogenesis (29), antigen presentation is not the only variable being studied. Also, since B cells have been found to promote T cell receptor diversification (31,32) and T cell responses in B cell-deficient

mice reflect functional adaptations of T cells to the repertoire contraction (34), any contribution of B cell antigen presentation may be masked.

To avoid the indirect contributions of B cells in the development of lymphoid organs, some have studied adult chimeric mice reconstituted with B cells with defined properties. Noorchashm and colleagues (55) showed that chimeric mice with B cells defective in antigen presentation had prolonged cardiac allograft survival but normal skin allograft survival. The authors concluded that B cell-mediated antigen presentation was required for enhancing cardiac allograft rejection; however, the authors could not rule out lack of allo-antibodies as a cause of prolonged cardiac allograft survival. Because the chimeras generated in the studies by Noorchashm and colleagues (55) were lethally irradiated, both B cells and T cells had to be reconstituted from bone marrow precursors. Given the contribution of B cells in the development of T cells (31), the T cell compartment of mice reconstituted with B cells deficient in antigen-presentation may be abnormal. If that were to be the case then prolonged graft rejection may not be a direct consequence of deficient B cell antigen presentation.

Closing remarks

The functions of B cells extend well beyond antibody production and include lymphoid organogenesis, generation and maintenance of T cell receptor diversity, and antigen presentation. In the setting of transplantation, implementation of B cell ablative therapies may thus impact the function of other immune cells. Of particular interest is the possibility that B cells may contribute to immune regulation and tolerance (Table 1).

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Table 1

B cells in transplantation
Humoral Functions: Induce graft rejection or accommodation:
1. Anti-polysaccharide antibodies (e.g., anti-blood group, generally produced in a T cell-independent manner)
2. Anti-protein antibodies (e.g., anti-HLA antigens or anti-minor histocompatibility antigens, generally produced in a T cell-dependent manner)
Non-humoral functions: Induce graft rejection or tolerance
1. Lymphoid organogenesis
2. T cell repertoire development and/or maintenance
3. Regulation
4. Antigen presentation