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B cells in transplantation

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Abstract

B cell responses underlie the most vexing immunological barriers to organ transplantation. Much has been learned about the molecular mechanisms of B cell responses to antigen and new therapeutic agents that specifically target B cells or suppress their functions are available. Yet, despite recent advances, there remains an incomplete understanding about how B cell functions determine the fate of organ transplants and how, whether or when potent new therapeutics should optimally be used. This gap in understanding reflects in part the realization that besides producing antibodies, B cells can also regulate cellular immunity, contribute to the genesis of tolerance and induce accommodation. Whether non-specific depletion of B cells, their progeny or suppression of their functions would undermine these non-cognate functions and whether graft outcome would suffer as a result is unknown. These questions were discussed at a symposium on “B cells in transplantation” at the 2015 ISHLT annual meeting. Those discussions are summarized here and a new perspective is offered.

Keywords

B lymphocytes; antibodies; accommodation; tolerance; rejection

B-cell responses underlie the most vexing immunologic barriers to organ transplantation. Much has been learned about the molecular mechanisms of B-cell responses to antigen, and new therapeutic agents that specifically target B cells or suppress their functions are

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available. Yet, despite recent advances, how B-cell functions determine the fate of organ transplants and how, whether, or when potent new therapeutics should optimally be used are not completely understood. This gap in understanding reflects in part the realization that besides producing antibodies, B cells can also regulate cellular immunity, contribute to the genesis of tolerance, and induce accommodation. Whether non-specific depletion of B cells or their progeny or suppression of their functions would undermine these non-cognate functions and whether graft outcome would be negatively affected as a result is unknown. These questions were discussed at a symposium on “B Cells in Transplantation” at the 2015 International Society for Heart and Lung Transplantation Annual Meeting. Those discussions are summarized here, and a new perspective is offered.

Humoral immunity has been considered the preeminent immune barrier to transplantation for many decades. Gorer[1,2] first recognized that allotransplantation evokes production of donor-specific antibodies (DSAs) and that a genetic locus (the major histocompatibility complex [MHC] of genes), the products of which, in humans, include the human leukocyte antigen (HLA) proteins, plays a major role. This genetic locus was shown to govern acceptance and rejection of transplants.[3] For several decades, and to some extent still today, the question of whether antibodies against histocompatibility antigens, such as HLA in humans or H-2 in mice, merely signify or actually cause rejection of transplants has remained controversial, as some grafts appear indifferent to the presence of DSAs in blood, whereas others are rapidly destroyed.

The complicated relationship between antibodies and graft outcome became still more complex by the observations of Mitchison,[4] who showed that administration of cytotoxic antibodies even in large quantities failed to cause rejection, whereas transfer of cells led to rejection. Finally, around the time of Gorer’s death, Szenberg and Warner[5] reported that rejection of grafts was sometimes caused by cells associated with the thymus, later called T cells, and that antibodies arise from cells arising from a distinct origin, ultimately called B cells.

What could not be imagined, then, was that the allelic complexity and extraordinary diversity of the loci encoding the antigen receptors of mature T cells and B cells, generating repertoires exceeding 10^9 different antigen receptors,[6] makes it impossible to predict the exact composition of an immune response even if the antigens are fully known. Just as difficult to imagine perhaps is that although T cells and B cells are anatomically, phenotypically, and genetically distinct, their development, survival, and functions are to a large extent inextricable.[7] Besides producing antibodies, B cells enable lymphoid organogenesis.[8] B cells promote the development of dendritic cells, which serve as antigen-presenting cells, in secondary lymphoid tissues.[9] T cells have long been known to provide help for B cells, but only more recently has it been apparent that B cells reciprocate—they enable thymocytes to diversify[10] and to mature into T cells. B cells provide survival signals for maintaining T cells in the periphery and regulate T-cell functions in ways that are not yet fully understood.[7] B cells present antigen and facilitate activation of T cells and contribute to T-cell tolerance and to accommodation that protects target tissues when tolerance fails.[11] Given the manifold and complex interactions between B cells and T cells, there is uncertainty about how best to weigh the impact of B-cell responses on an organ graft at a

given point in time and what short-term and especially long-term impact can be expected as new B cell–directed therapies emerge.

Although all transplants might cause DSAs to be produced (unless inhibited by immunosuppression), only organ grafts (and not cellular grafts) are susceptible to antibody-mediated damage. Antibodies and complement mainly attack endothelial cells of organ transplants because antibodies and complement are found predominantly inside blood vessels. Although antibodies and complement can penetrate blood vessel walls, they do so only slowly, and parenchymal cells and cellular transplants are relatively unaffected by DSAs. The impact of complement on living cells has also been found to depend on the kinetics of activation, rather than on the amount activated or "fixed," because, over time, cells acquire resistance to complement-mediated injury. Therefore, when antibody and complement are fixed acutely, they might induce cell death and rejection, but, over time, they might induce resistance to cell death and accommodation.[12] Bound antibody can facilitate cellular immunity and cellular rejection, and it can block or suppress cellular immunity and rejection in tumor transplants (i.e., enhancement).[13]

Today, humoral immunity, detected by assay of DSAs in blood, predicts increased risk of acute and chronic rejection, although few transplant physicians would treat a recipient with DSAs but no change in graft function or biopsy. However, the assays for DSAs in common use, based on binding to antigen on beads, do not represent all potential antigens or polymorphisms in a given recipient and do not model steric factors that might limit binding to the antigens that are displayed.[14]

The immune response of transplant recipients is usually assayed by testing the blood for the presence and concentration of DSAs and by evaluating graft function. DSAs are generally understood to refer to antibodies specific for HLA of the donor; however, DSAs might also refer to antibodies against donor blood groups. Graft recipients are often found to produce antibodies specific for HLA not present in the donor, but some of these anti-HLA antibodies cross-react with donor HLA. Furthermore, some methods (solid phase assays in particular) commonly used for detecting DSAs and anti-HLA antibodies might suggest that antibodies recognize donor antigens when in fact they do not (because standard antigens rather than donor-derived antigens are used, as reviewed by Tait et al[14]).

Because changes in graft function are not specific and are sometimes detected only after a graft has incurred substantial injury and because the presence of DSAs is associated with worsened graft outcome,[15] there has been increasing enthusiasm for use of DSAs as a tool to predict immunologic challenges the graft will face and as the earliest measure of the immune response. However, as the predictive and diagnostic value of DSAs gained currency, clinical and basic investigations were revealing new B-cell functions. Some of these functions, such as immune regulation and accommodation, would contradict the concept that B-cell responses are entirely detrimental to the graft. The International Society for Heart and Lung Transplantation sponsored a symposium at the 2015 Annual Meeting entitled "B Cells in Transplantation," at which experts discussed B-cell responses to transplantation from basic and clinical perspectives. We offer the authors' perspectives in this report.

B-cell activation and differentiation (Esme Dijke)

Dr. Dijke reviewed the basic biology of B-cell activation and differentiation in response to transplant antigens. B cells respond differently to foreign polysaccharides, such as blood group antigens, and to foreign proteins, such as MHC antigens. B-cell responses to some polysaccharides, such as blood groups, are generated continuously from newly activated B cells and do not generally become more effective with repeated exposure. These responses do not require T-cell help, and accordingly they are called T independent. Individuals normally produce “natural” antibodies to non-self blood group antigens, presumably as a result of immunologic cross reaction to similar antigenic determinants on enteric flora.[16,17] Delayed ontogeny of antibody formation to blood group antigens early in life allows for safe ABO-incompatible heart transplantation in infants, resulting in the development of donor-specific B-cell tolerance rather than immunity.[18–20]

In contrast, B-cell responses to protein antigens require T-cell help, which requires activation of T cells responding to peptides associated with MHC class II. The activation of T cells and the recruiting of T-cell help is sometimes consolidated if B cells recognize a foreign protein via the antigen receptor, engulf the protein, and present peptides to T cells. In contrast to B-cell responses to polysaccharides, B-cell responses to proteins manifest both memory of and progressive increase in affinity of the B-cell receptor to the antigen. This increase in affinity depends on the introduction of mutations in the variable regions of immunoglobulin genes followed by selection and survival of the mutated B cells that compete more effectively for antigen and T-cell help. The evolution of B cells in this way is called affinity maturation, and it reflects successive rounds of mutation and selection. The B cells that survive each round of mutation and selection form memory B cells, which persist quiescently until they meet antigen again. Memory B cells can be repeatedly engaged and, with time, form cellular lineages, a subset of which differentiates into plasma cells producing antibodies with increasing affinity and/or avidity to the transplant antigens. The molecular and cellular mechanisms of plasma cell generation have been recently reviewed.[21] The fact that production of high-affinity antibodies to allogeneic HLA is not subverted by immunosuppressive therapy in some transplant recipients suggests that T-dependent B-cell responses are resilient under current immunosuppressive regimens.

Accommodation and tolerance in transplantation (Jeffrey Platt)

Dr. Platt presented recent observations made in collaboration with Dr. Cascalho on tolerance and accommodation. Dr. Platt originally defined accommodation as a condition in which a graft seemingly acquires resistance to immune-mediated injury. Accommodation was identified in the setting of ABO-incompatible transplantation when recipients of kidney transplants with normal function were found to have DSAs in their blood.[12] Although the absence of acute rejection characteristic of accommodation might resemble tolerance, tolerance is characterized by donor-specific immune non-responsiveness, whereas accommodation is characterized by donor-specific immunity.

Dr. Platt suggested that we consider changing the way we identify accommodation because relying on detection of DSAs probably underestimates the prevalence of that condition. For

example, a study of kidney transplants in recipients with a positive crossmatch revealed that 50% developed appreciable levels of DSA but had stable graft function for months (although chronic changes did eventually develop in many).[22] Moreover, up to 30% of recipients who are not pre-sensitized develop de novo DSAs without manifesting acute rejection.[23,24] The idea that accommodation might be common was also drawn from observations that all or nearly all recipients of organ transplants exhibit a B-cell response specific for their donor.[25] This response, always IgM and sometimes IgG, is not often appreciated because anti-donor antibodies can be absorbed from the blood by functioning grafts.[25,26]

Monitoring DSAs, serial biopsies, and function of experimental kidney and cardiac allografts often reveals that substantial graft injury and functional deterioration precedes the appearance of DSAs in blood, even when antibodies cause rejection. In the clinical setting, DSAs are often detected for the first time after rather than before significant graft injury and rejection have occurred[14,27,28] and are thought to reflect the absorption of many DSAs produced before the graft loses function or blood flow declines. Thus, DSAs might provide an insensitive index of B-cell responses to the donor and accommodation and might turn out to be a more sensitive index of graft injury.

Some authors have suggested that expression of cytoprotective genes might be taken as an index of accommodation. However, Dr. Platt and others have found these genes expressed in transplants undergoing rejection.[29,30] Rather, the presence of donor-specific B-cell responses in recipients with undiminished graft function might constitute the first and most sensitive index of accommodation. Because most transplant recipients have B-cell responses to their donor, accommodation is probably the most common outcome of organ transplantation, regardless of whether DSAs are detected.

Dr. Platt presented preliminary work on the nature of B-cell responses to transplantation in recipients with normal function over periods exceeding 1 year and recipients with rejection. Although still preliminary, the work suggests that somatic hypermutation and clonality of donor-specific B cells might distinguish recipients who will soon experience rejection from recipients who maintain normal graft function who might also have distinct donor-specific B-cell responses.

B-cell regulatory functions (Paul Blair)

Dr. Blair discussed how B cells regulate immune responses to transplantation. Some B cells exhibit distinct properties that enable them to suppress immune responses, and these are called regulatory B cells. Regulatory B cells exert their immunosuppressive effect at least in part, through the production of interleukin (IL)-10, IL-35, and transforming growth factor (TGF)-β.[31] The phenotype and ontogeny of regulatory B cells is controversial.[31] Regulatory B cells are thought to represent a stage of B-cell development before their differentiation into plasma cells.[32] Consistent with that concept, Maseda et al[33] suggested that regulatory B cells could rapidly convert to plasmablasts on activation. Shen et al[34] and Matsumoto et al[35] showed that plasmablasts expressing IL-10 are found in the lymph nodes that drain the lesions in mice with experimental autoimmune encephalomyelitis. These findings suggest that B cells acquire regulatory functions as they differentiate, and the authors concluded that

IL-10 limits autoimmune inflammation and decreases severity of the disease. Although functions of regulatory B cells can be evoked in experimental conditions[36] and prolong skin graft survival in mice,[37] whether regulatory B cells control alloimmunity in solid-organ transplantation is uncertain at best.

Control of plasma cell function (Menna Clatworthy)

Dr. Clatworthy considered critically the potential for and the challenges of therapeutics directed specifically at B and plasma cells. Although B-cell responses to foreign protein antigens are T cell dependent and current immunosuppressive agents that disrupt cellular immunity to the transplant donor are relatively successful, as measured by the relative infrequency of unremitting cellular rejection, T cell–dependent B-cell alloresponses still occur and pose a significant immunologic challenge. Accordingly, intense interest has focused on the development of therapeutic regimens to disrupt B-cell and plasma cell responses. Activated B cells may differentiate into extrafollicular plasmablasts that secrete low-affinity antibodies or may undergo class switching and somatic hypermutation during germinal center responses, forming long-lived plasma cells that produce the preponderance of antibodies, including antibodies directed against protein antigens such as HLA. However, the source of anti-HLA antibodies in transplantation, when patients receive immunosuppression and have ongoing expression of abundant antigen (in the graft), is unknown. Immune therapeutics such as anti-CD20 antibodies that deplete naïve B cells may fail to have an impact on antibody-mediated pathology because plasma cells lack CD20 expression and many other B-cell surface markers. The experience with anti-CD20 therapy in kidney transplant recipients has been the subject of more recent studies.[38–40] Hence, recent attention has been directed at devising and testing therapeutics that might inhibit or deplete plasma cells.

Some basic principles of plasma cell biology were considered that might inform potential therapeutic strategies.[41] B-cell activation generates a wave of short-lived plasma cells or plasmablasts that remain in secondary lymphoid organs and may continue to express some B-cell markers such as CD19. The germinal center reaction generates long-lived plasma cells that migrate to specific niches within the bone marrow. This process requires expression of chemokine receptor type 4 (CXCR4) by plasma cells and production in bone marrow of the corresponding ligand, C-X-C chemokine-12 (CXCL12) by stromal cells.[42] Interaction of chemokines with their receptors promotes phosphorylation of guanosine diphosphate nucleotides, ultimately increasing intracellular [Ca^{++}] and promoting cell migration. The transcription factor B lymphocyte induced maturation protein-1 (BLIMP-1), orchestrates the transformation of B cells into terminally differentiated, immunoglobulin-secreting plasma cells, in part by stimulating the expression of X-box binding protein-1 (XBP-1), a transcription factor required for the unfolded protein response that allows plasma cells to withstand the stress associated with the synthesis of large quantities of immunoglobulin.[43–45] Various cell types, including eosinophils, megakaryocytes, neutrophils, and macrophages,[46] have been shown to contribute to the plasma cell niche, producing survival factors including IL-6, B-cell activating factor (BAFF), A proliferation inducing ligand (APRIL), hyaluronic acid, and IL-5.

Based on knowledge of plasma cell biology, 3 strategies to target plasma cells have emerged. First, plasma cell formation might be blocked. Suppressing B-cell activation and inhibiting the germinal center reaction, for example, by blocking co-stimulatory pathways (such as those mediated by the interaction of CD40L on T cells with its cognate receptor, CD40, on B cells and other antigen-presenting cells) may prevent the formation of plasma cells.[47]

Second, plasma cells and/or plasmablasts might be depleted. Antibodies that bind to plasma cell surface molecules (e.g., anti-CD19 antibody) cause bone marrow plasma cell depletion in mouse models.[48] One limitation of this approach is that a fraction of plasma cells might not express the target of the depleting antibodies. Alternatively, therapies that inhibit the function of the proteasome (a cellular organelle used to degrade misfolded proteins) are toxic for plasma cells. One example is bortezomib, a proteasome inhibitor that has been tested and approved in the treatment of plasma cell dyscrasias, including multiple myeloma and mantle cell lymphoma, and appears potentially to benefit some patients with antibody-mediated rejection (AMR).[49–51] Use of bortezomib in patients with cancer has been limited by toxicity, in particular, peripheral neuropathy. The optimal indications and dosage of bortezomib, in conjunction with other therapeutics in transplantation, are under active investigation (discussed subsequently).

A third strategy to deplete plasma cells is to target their niche; this can be achieved by targeting known plasma cell survival factors or the cells that produce them. Thus, depletion of eosinophils had moderate success in reducing alloantibody,[52] and inhibiting eosinophil survival by IL-5 blockade has shown some success in experimental models.[53] Such agents are being investigated in clinical trials to treat asthma.[54] The use of BAFF and APRIL blockade with atacicept has also shown some promise in non-human primate models.[55]

Supposing that a therapeutic agent for plasma cells were to be developed, a key question would be whether ongoing treatment would be needed. This question stems from uncertainty about which plasma cells might be the most important effectors of AMR. On one hand, if long-lived plasma cells were of greatest importance, treatment at 1 point in time might suffice, and some measure of toxicity would be acceptable. On the other hand, if the key effector cells are short-lived plasma cells, repeatedly generated from memory B cells, a better strategy might be directed at memory B cells. In addition, because more recent data suggest that plasma cells are a major source of the cytokine IL-10, a cytokine with immunosuppressive functions,[34] pan-plasma cell depletion may be undesirable.

Therapeutics of AMR (Jignesh Patel)

AMR remains a considerable challenge, as current immunosuppressive regimens interfere mainly with T-cell signaling pathways.[56] As a result, AMR occurs in 10% to 20% of heart transplant recipients.[57] Furthermore, there has been little agreement about what constitutes AMR of heart allografts,[58,59] and therefore historical experience can be misleading. In lung transplantation as well, the definition of AMR is a great diagnostic challenge.

Approximately 33% of heart recipients are now sensitized at transplant, which has contributed to an increase in the frequency of AMR. The high frequency of sensitization is

due to increased mechanical circulatory support in patients awaiting transplantation.[60] Sensitization, referring to antibody responses specific to a panel of allogeneic HLA in existence before transplantation, results in a limited donor pool, often prohibitive waiting time on the transplant waitlist, and increased waitlist mortality.[60] When transplantation is possible, these patients are at increased risk of rejection, graft loss, and development of allograft vasculopathy.

Many strategies have been used historically to prevent and treat AMR. Immunoadsorption and plasmapheresis allow removal of circulating immunoglobulins. Data on efficacy as a single therapy are sparse, but plasmapheresis has been associated with improved survival in patients with AMR complicated by hemodynamic compromise.[61] Pooled intravenous immunoglobulin modulates antibody-mediated responses through pleiotropic mechanisms, including cytotoxicity; receptor, cytokine, and complement blockade; and modulation of dendritic and regulatory T cells. Intravenous immunoglobulin combined with plasmapheresis and rituximab (a monoclonal antibody targeting the pan-B cell marker CD20) for treatment of sensitized patients awaiting heart transplant was associated with 5-year post-transplant survival comparable to non-sensitized recipients, although there was a greater incidence of AMR at 1 year.[62] However, none of these therapies targets the plasma cells, which are responsible for the synthesis of most circulating antibody. Bortezomib, a proteasome inhibitor, is active against plasma cells. It has been shown to be effective in conjunction with plasmapheresis at reducing calculated PRA in highly sensitized patients awaiting heart transplantation who were previously refractory to plasmapheresis, intravenous immunoglobulin, and rituximab.[63] In data presented at these sessions from an extended cohort of 30 patients, plasmapheresis and bortezomib was able to achieve a decrease in calculated PRA in 51.7% of patients. For 22 patients who subsequently underwent transplant, 1-year actuarial survival was 95.5%, and 1-year actuarial freedom from any treated rejection was 73.9%. Treatment was generally well tolerated with 10% developing infection and 14% developing reversible neuropathy during treatment.[63]

Complement activation is the predominant final common pathway through which antibodies facilitate cytotoxic activity. Eculizumab is a humanized monoclonal antibody that prevents activation of complement component C5, preventing formation of anaphylotoxins and the membrane attack complex. It is approved in the United States for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. In an ongoing pilot study presented at the meeting, eculizumab used after transplantation in 10 highly sensitized patients (mean calculated panel reactive antibodies 93.7% ± 8.6) was associated with a 90% 1-year actuarial survival and 77.8% 1-year actuarial freedom from AMR. In this study, patients received an initial dose of eculizumab intravenously before release of cross clamp at transplant and 7 more doses over the next 60 days.

Post-transplant prophylactic photopheresis in sensitized patients has been associated with decreased antibody burden.[64] In renal transplantation, use of co-stimulatory blockade with belatacept (a selective T-cell co-stimulation blocker that binds CD80 and CD86, co-stimulatory molecules expressed by antigen-presenting cells that help in T-cell activation) was associated with a significant decrease in class I– and class II–specific antibodies.[65] In a retrospective case-match analysis, patients treated with cyclosporine were matched to

patients treated with belatacept from a phase II study. Kidney function remained superior 10 years after transplantation in patients treated with belatacept compared with the control group of patients treated with cyclosporine. Moreover, none of the patients treated with belatacept had donor-specific antibodies ≥10 years after transplantation compared with 38.5% of tested patients treated with cyclosporine ($p = 0.045$). Other emerging therapies (atacicept, belimumab, and briobacept) target signaling pathways that promote B-cell survival through BAFF and APRIL, but clinical studies in transplantation are pending.

T cell–mediated allograft rejection is generally well controlled and understood. However, B cell–mediated humoral immune responses are only now being recognized as a significant contributor of post-transplant morbidity and mortality (Figure 1). Many therapies controlling B-cell responses are emerging, and some, particularly when used in combination, appear to allow highly sensitized recipients to undergo heart transplantation with acceptable survival. However, large-scale controlled trials will be needed to determine their precise role in thoracic transplantation.

Conclusions

The speakers and the audience identified some questions of clinical and theoretical importance.

1. When does accommodation end and tolerance begin?

Much remains to be understood about how accommodation and tolerance come about in the context of transplantation. The frequencies of these conditions are uncertain in part for lack of appropriate measurements. If B-cell responses against the donor in recipients with healthy grafts are an indication of accommodation, could their extinction measure the development of tolerance?

2. Are DSAs always “bad”?

No consensus exists about the significance of DSAs. Although the presence of DSAs may indicate a greater risk of rejection, some patients with DSAs do not experience rejection, and many exhibit no evidence of rejection for months after DSAs are detected. Dr. Platt pointed out that in experimental models in which B-cell responses are known to occur, DSAs are effectively absorbed by healthy organ grafts and often not detected in the blood until substantial damage to graft has occurred. He suggested that the presence of DSAs might be taken to suggest underlying pathology, rather than the first of a series of events leading to rejection. Thus, no matter at what level, the reliance on DSAs to evaluate graft health may compromise timely delivery of therapy.

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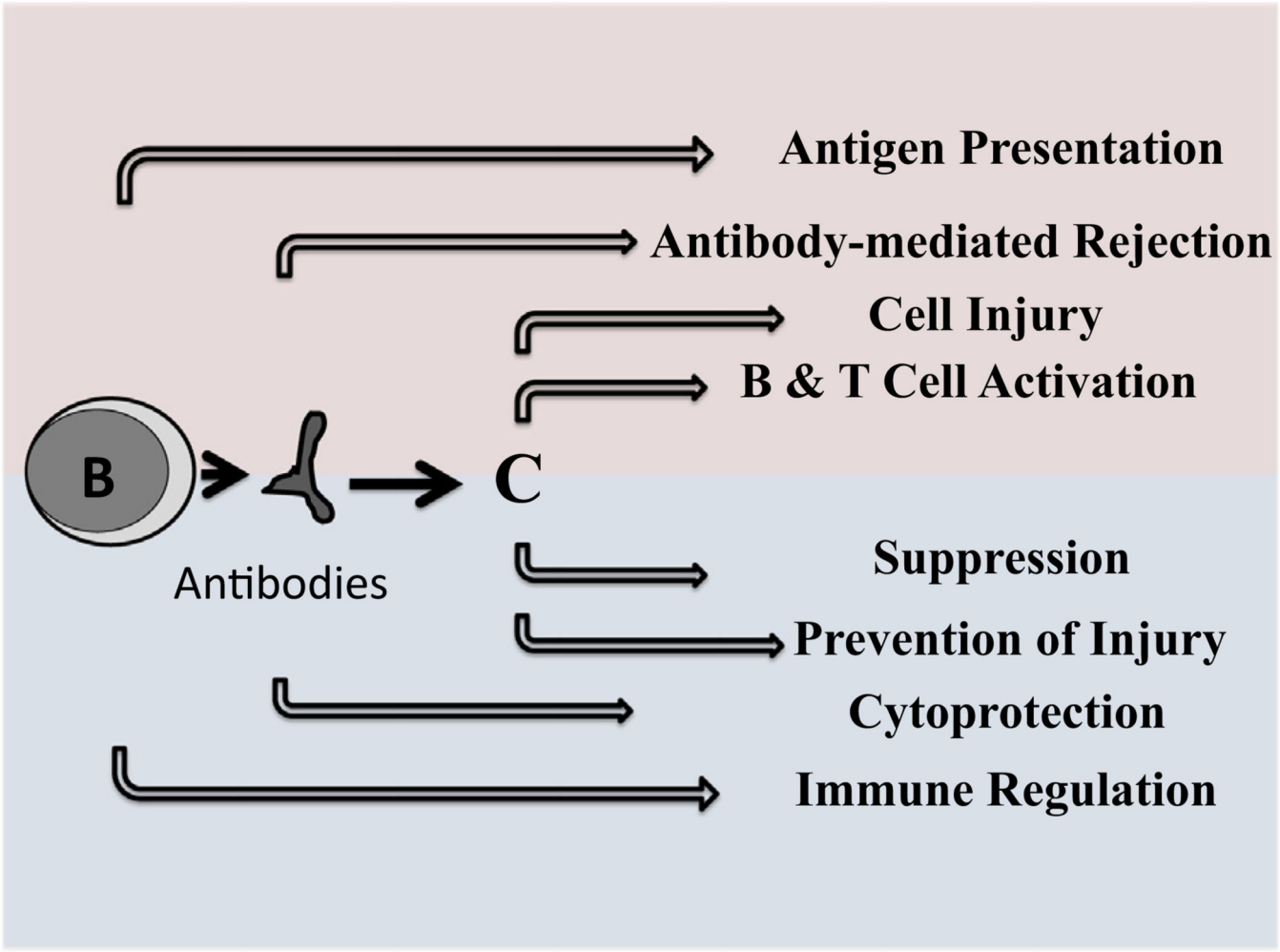

Figure 1.
Various functions of B cells in transplantation. Functions that protect the graft are in blue shaded area; functions that are deleterious to the graft are in red shaded area. B, B cells; C, complement.