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Essential role for B cells in transplantation tolerance

Robert R Redfield III, Eduardo Rodriguez, Ronald Parsons, Kumar Vivek, Moiz M Mustafa, Hooman Noorchashm, and Ali Naji

Harrison Department of Surgical Research, University of Pennsylvania School of Medicine, Philadelphia, PA, United States

Abstract

T lymphocytes are the primary targets of immunotherapy in clinical transplantation. However, B lymphocytes are detrimental to graft survival by virtue of their capacity to present antigen to T cells via the indirect pathway of allorecognition and the generation of donor specific alloantibody. Furthermore, the long-term survival of organ allografts remains challenged by chronic rejection, a process in which activated B cells have been found to play a significant role. Therefore, the achievement of transplantation tolerance will likely require induction of both T and B cell tolerance to alloantigens. Moreover, human and animal investigations have shown that subsets of B cells, Transitional and Regulatory, are inherently tolerogenic. Developing therapeutic strategies that exploit these populations may be key to achieving transplantation tolerance. In this review we describe the current evidence for the essential role of B cells in transplant tolerance and discuss emerging B cell directed strategies to achieve allograft tolerance.

Introduction

Currently, the mainstay of immunotherapy in clinical transplantation is T cell directed which effectively prevents acute T-cell mediated allograft rejection. However, the long-term survival of organ allografts remains challenged by chronic rejection, a process in which activated B cells have been found to play a significant role [1].

In solid organ transplantation development of donor specific alloantibodies (DSA) are emerging as major mediators of allograft rejection. DSA can be acquired by prior organ transplantation, blood transfusion, pregnancy or generated *de novo* after transplantation.

It is well established that preexisting DSA in the prospective allograft recipient mediate hyperacute and acute-antibody-mediated rejection (AMR) leading to rapid demise of the allograft. There is now solid epidemiologic evidence that *de novo* emergence of DSA in recipients with seemingly normal allograft function compromise long-term graft survival [1,2]. Even DSA specific for non-HLA alloantigens are associated with worse outcomes [3]. DSA is a product of B cell activation, which is a multistep process that leads to the formation of antibody secreting cells (ASCs) or plasma cells (PCs).

In the present review we describe the current evidence for the essential role of B cells in transplant tolerance. However, the mechanism for the generation and maintenance of alloantibody is beyond the scope of this review and has recently been reviewed in this journal [4]. We will discuss the role of B cell mediated antigen presentation and activation of alloreactive CD4 T cells in transplantation which provides a logical argument for B cell depletion at the time of transplantation to impair T-cell mediated alloimmune responses. However, certain B cells, like Transitional and Regulatory B cells, are increasingly implicated as being tolerogenic, which could in fact serve as an argument against certain B cell directed therapies. Developing therapeutic strategies that exploit these tolerogenic B cell populations may be key to achieving transplantation tolerance.

B cells as antigen-presenting cells

B cells are by far the largest population of antigen-presenting cells (APCs) found *in vivo*. Although antigen-presenting dendritic cells are sufficient to activate CD4 T cells, B cells are particularly effective APCs [5]. It is important to note that in the context of alloreactivity B cells present alloantigenic peptides via the indirect pathway of allorecognition. The presence of dense intra-graft B cell infiltrates in renal allograft biopsies is associated with poor outcome [6]. In a murine model of cardiac transplantation in hosts deficient in B cell mediated antigen presentation, by virtue of selective absence of MHC class II expression, the tempo of acute rejection is significantly attenuated [7]. In confirmatory experiments it was also noted that CD8 and CD4 memory was impaired when the antigen-presenting function of B cells was absent [8]. These findings provide a cogent argument in favor for B cell depletion at the time of transplantation to impair T-cell mediated alloimmune responses. Preemptive B cell depletion (anti-CD20, Rituximab) is reported to prolong the survival of islet and cardiac allografts in non-human primates [9,10]. In humans, Rituximab induction has been shown to reduce the incidence of acute rejection in kidney recipients [11].

However, there is evidence implicating the role of B cell antigen presentation in tolerance, and strategies to deplete B cells could potentially eliminate this property. Antigens presented by naïve B cells have been shown to stimulate naïve T cells toward development into regulatory T cells [12]. B cells have also been shown to preferentially expand allogeneic FoxP3 + CD4 T cells [13]. This may explain classical observations that transferred naïve B cells have the capacity to promote the acceptance of murine skin allografts [14].

Further evidence for the tolerogenic effects of B cells in transplantation is reported by Deng *et al.* demonstrating that transplant tolerance induced by treatment with antibody to CD45RB required the presence of B cells [15]. The mechanism by which anti-CD45RB induces peripheral B cell-mediated attenuation of T cell alloreactivity remains to be defined.

These above studies demonstrate that B cells as APCs can impact T cell function both in a positive as well as a negative manner, leading to either T cell activation or tolerance. What renders these same cells immunogenic under some circumstances but tolerogenic under others is not entirely clear. However recent evidence suggests that part of the answer may be linked to the nature of the antigen presented by B cells. Specific cognate BCR mediated antigen uptake and presentation to CD4 T cells tends to promote immunity, whereas,

nonspecific antigens derived from endogenous or pinocytosed antigens presented by B cells promotes T cell tolerance [16]. These dual and opposing roles of B cells in T cell responses may potentially pose a problem for B cell depletion strategies in induction of transplantation tolerance. DiLillo *et al.* have shown that anti-CD20 depletion hastens skin allograft rejection in mice [17]. In humans, Clatworthy *et al.* showed that depletion of B cells at the time of kidney transplantation seemed to enhance acute T cell-mediated rejection [18]. These findings suggest that B cell depletion therapy may also eliminate a population of B cells with regulatory properties (B regulatory cells (Breg)), thus enhancing the T cell alloresponse. Further evidence to support this potential role of Breg can be found in the autoimmune setting where B cell depletion was associated with exacerbation of ulcerative colitis and precipitating vasculitis and psoriasis in some human patients [19]. However, the fact that most patients who receive anti-CD20 avoid dramatic disturbances in regulation, points to the predominant role of effector B cells [20]. Additionally, as noted above there is evidence that B cell depletion at the time of transplantation reduces the incidence of biopsy proven allograft rejection, which challenges the findings by Clatworthy *et al.* At present the mechanism(s) underlying these divergent findings are not entirely clear but may be related to different immunosuppressive regimens.

Transitional B Cell Signatures in Transplantation Tolerance

Not only will B cell depletion therapy impair T cell responses by eliminating B cell mediated antigen presentation, the reconstituting B cell repertoire may also provide a tolerogenic milieu. Interestingly, B cell depletion with Rituximab has been shown to expand the transitional (TR) B cell compartment upon reconstitution [21]. Non-human primates treated with T and B cell induction immunotherapy and Rapamycin maintenance enjoyed long-term islet allograft survival when immature and transitional B cells were predominant in the peripheral blood [9].

On the clinical front, Newell *et al.* showed that in operationally tolerant recipients (not on maintenance immunosuppression) of a kidney allograft, 22 of 30 genes found to have a 2-fold increase in expression in the tolerant versus non-tolerant group (still on maintenance immunosuppression) were B cell specific [22••]. Many of these genes are involved in B cell activation and differentiation, including genes encoding Ig heavy, light, and joining chains and HLA. The investigators narrowed down the signature to three genes that predicted, with 100% accuracy, tolerant from non-tolerant recipients. The three genes (IGKV4-1, IGLL1, and IGKV1D-13) are all expressed by TR B cells. They also observed significantly increased numbers of TR B cells in tolerant recipients, which was confirmed by a similar study [23]. These findings suggest that TR B cells are involved in the induction or maintenance of tolerance. The mechanisms governing the tolerogenic TR B cells may involve their poor APC and costimulatory function [24].

Transitional cells as B regulatory cells?

Additionally, there is evidence that the TR B cell compartment may be a source of Breg. Breg are found in both the B-1 and B-2 lineage B cells, and are currently defined by their ability to secrete IL-10 upon stimulation. The *in vivo* role of IL-10-producing B cells was

first demonstrated in a murine model of experimental autoimmune encephalomyelitis, were the consequence of a deficiency of IL-10-producing B cells was determined to be the cause of disease [25]. The involvement of Breg has been found to play a role in other autoimmune diseases including ulcerative colitis, lupus and arthritis [5,26–28].

In humans, the TR B cell subset (CD19 + CD24^{hi}CD38^{hi}) has been found to secrete the highest amount of IL-10 in response to CD40 stimulation, compared to other peripheral blood B cell subsets [29•]. Furthermore, in murine models, there is evidence that Breg increase the number of regulatory T cells (Treg) [30]. Whether those effects are mediated by IL-10 secretion, antigen processing/presentation or a combination of the two remains to be determined. Taking into consideration the TR B cell and Treg phenotype observed in operationally tolerant transplant patients as discussed above in Transitional B Cell Signatures in Transplantation Tolerance, one could argue that the increase in Treg observed in these patients may in fact be directly related to the subset of TR B cells that secrete IL-10 [22•,30]. Thus, moving forward, it will be important to assess the TR B cell compartment: as a potential candidate Breg population and as a catalyst for differentiation of Treg cells.

Humoral transplantation tolerance upon *de novo* emergence of B lymphocytes

Another potential advantage of B cell depletion therapy at the time of transplantation is that the emergence of the reconstituting B cell pool occurs in the presence of alloantigen provided by the transplanted organ. Whether this process recapitulates the ontogeny of B cell development and humoral tolerance is intriguing [31]. The experimental evidence in support of this view is reported by Parsons *et al.* demonstrating deletion of alloreactive B cells upon their *de novo* emergence in the presence of a transplanted cardiac allograft [32•] and Li *et al.* which observed clonal deletion of primary B cells in recipients of cardiac allografts after costimulation blockade [33].

In the clinical setting B cell tolerance has also been demonstrated in the developing immune system of infants. ABO-incompatible heart transplantation during infancy has been shown to result in development of B cell tolerance to donor blood group A and B antigens [34]. Tolerance in this setting has been found to occur by elimination of donor-reactive B cells and may be dependent upon persistence of some degree of antigen expression in the setting of B cell development. Further study has shown that generation of *de novo* anti-HLA antibodies following cardiac transplantation is clearly age dependent [35•]. These findings suggest that intentional exposure to non-self antigens to the developing B cell compartment can lead to tolerance in the clinical setting. These studies have led to the proposition that remodeling of the primary B cell repertoire at the time of organ transplantation may be required for establishment of robust humoral tolerance [36•].

Remodeling the primary B cell repertoire with B cell/BLyS directed immunotherapy

It is known that the susceptibility of transitional B cells to negative selection in the periphery is under the homeostatic control by the B cell survival factor BLyS [37] (Figure 1). BLyS deficiency is associated with arrest of further B cell development beyond the TR B cell stage [38] and excess BLyS rescues self-reactive B cells from peripheral deletion [39]. Therefore, transient depletion of the mature B-cell repertoire at the time of transplantation, and then permitting its reconstitution under BLyS-limiting conditions, is predicted to increase the stringency of negative selection of alloreactive clones [40]. It is also known that BLyS directed immunotherapy increases the ratio of transitional to follicular B cells [41], which has been identified as an important biomarker of a tolerant immune system [22••] (see Transitional B Cell Signatures in Transplantation Tolerance, above). In recipients of cardiac allograft in whom the B cell compartment was concomitantly depleted, allowing for the re-emergence of the B cell repertoire in the presence of the allograft and a BLyS deficient environment (achieved with anti-BLyS therapy), there was abrupt rejection of the cardiac allograft by the alloreactive T cells. However there was an absence of DSA, suggesting the elimination of alloreactive B cell clones, while the alloantibody response to a third party donor was preserved (Noorchashm *et al.*, unpublished). However, in one study islet allografts were accepted indefinitely in mice over expressing BLyS [42•]. This may be explained by the expansion of B cells due to excess BLyS (including tolerogenic B cells) and not intrinsic to T cell function.

The allo-sensitized patient

The opportunities for the induction of B cell tolerance in non-sensitized hosts may not apply to the alloantigen experienced patient. Following alloantigen exposure, long-lived alloantibody secreting PCs reside in the bone marrow where they rely on different and currently unknown survival signals than the naïve B cell pool in the periphery [43,44]. Understanding the survival factor(s) that govern plasma cell persistence will be critical to developing successful therapies to desensitize patients with preformed alloantibodies (Figure 2). Current therapies involving IVIG, plasmapheresis and Rituximab have had limited success in consistently lowering alloantibody levels in sensitized patients, likely as a result of their lack of specificity to target PCs [45]. Berek and colleagues made the recent discovery that eosinophils are required for the maintenance of PCs [46••]. Desensitization protocols targeting eosinophils have not been investigated and eosinophil directed immunotherapy may be a potential desensitization strategy. Furthermore, in mice TACI-Ig decreases PC numbers substantially by sequestering both BLyS and APRIL, and could be translated into a novel desensitization strategy as well [47]. The 26S proteasome inhibitor, Bortezomib, has been shown to eliminate both short and long-lived PCs by activating the unfolded protein response [48]. Reduction of alloantibody titers, but not their elimination, has been achieved with limited treatment with Bortezomib in human recipients awaiting kidney transplantation [49]. Without the targeted elimination of immunologic memory, DSA cannot be expected to be fully eliminated in the sensitized recipient and will continue to challenge long-term allograft survival.

Conclusions

B cells by virtue of their BCR specificity are potent APCs for activation of alloreactive CD4 T cells. Therefore, therapeutic strategies targeting B cells have the capacity to interrupt B–T collaboration and impede effector T cell alloimmune responses. However, there is compelling evidence that the impact of B cells on T cell activation is bimodal, promoting robust immunity or tolerogenic signals. Their tolerogenic signals appear to facilitate the generation of Treg, possibly through the production of IL-10 or suboptimal costimulatory signals dependent on their developmental stage. Moving forward rational strategies to target B cells need to maximize the tolerogenic capacity of B cells while minimizing their immunostimulatory effects. One logical approach is to harnesses the natural developmental tendency of the B cell compartment toward tolerance, thus eliminating the probability of an alloantigen specific germinal center response [32•,36•,40]. Remodeling the primary B cell repertoire to an allo-tolerant state could possibly be accomplished using B cell depletion therapy followed by re-emergence of the primary repertoire under BLyS-limiting conditions in the presence of transplanted alloantigen. Such ‘rebooting’ of the primary B cell repertoire to promote deletion of alloreactive clones may be a critical step in curtailing DSA mediated insults to transplanted organs.

Lastly, in the alloantigen experienced patient, without the targeted elimination of immunologic memory, B cell tolerance is unlikely to be achieved, and will continue to challenge long-term allograft survival. As the mediators of plasma cell survival become known, novel therapies will need to be evaluated to combat the specific alloreactive plasma cell pool in the alloantigen experienced patient. Therefore, transplantation tolerance will ultimately require induction of both T and B cell tolerance to alloantigens.

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Fig. 1.

B cell development and selection checkpoints. **(a)** Immature B cells have successfully rearranged their heavy and light chain immunoglobulin genes. During the BCR checkpoint, immature B cells that are engaged by high avidity antigens are induced to die, while those who do not, transit to the periphery and become transitional cells. The continued survival of transitional B cells in the periphery is dictated by the availability of BLyS and relative BCR tonic signaling. In instances when excess BLyS available it has been shown that the frequency of autoreactive cells entering the peripheral pool is increased. **(b)** The frequency of developing B cell survival is depicted here as development progresses across the BCR and peripheral selection checkpoint.

Fig. 2.

Novel approaches to directed plasma cell therapy. As the survival factors required for plasma cell (PC) persistence become known, new and more targeted approaches to elimination of alloantibody secreting cells will become available. Atacicept binds both BLyS and APRIL. PCs are known to rely heavily on APRIL production and there sequestration has been shown to reduce PCs. Mepoluzimab binds IL-5, which is known to be a critical eosinophil survival factor. Eosinophils are known to be one of the major sources of APRIL for PCs and could be a novel target for desensitization. The 26S proteasome inhibitor Bortezomib has been shown to reduce alloantibody and is somewhat selective for PCs. Rank-L has been shown to be a marker of long-lived plasma cells, and its blockade with Denosumab could be an additional target for desensitization.