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New insights into the development of B cell responses: Implications for solid organ transplantation

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Abstract

A resurgent interest in the role of B cells following solid organ transplantation is being driven by clinical data suggesting that antibody mediated rejection (AMR) is a major cause of dysfunction and organ transplant failure. These observations suggest that, in a subset of patients, current immunotherapies are failing to control the development of alloantibody responses, or failing to reverse the production or the effects of alloantibodies. Quantification of donor-specific antibodies (DSA) has proven to be an imperfect predictor of AMR, and efforts to improve DSA quantification anticipate that this will result in improved predictive power. At the same time, attempts to control of ABMR have focused on the non-specific elimination of B cells, plasma cells (PCs) or circulating antibodies. In the past decade, there has been an improvement in our understanding of the processes that drive B cell differentiation into germinal center (GC)-dependent or GC-independent memory B cells and antibody-secreting PC. These insights are suggesting new ways to more specifically target the DSA response, which may lead to better long-term allograft survival outcomes while preserving protective immunity. In this review, new insights into processes that lead to antibody production upon primary and secondary antigen encounter are discussed, and the potential implications to DSA production and future areas of investigation to control AMR are discussed.

Introduction

Experimental data stemming from the early studies of skin graft rejection by Billingham and Medawar [1] set the stage for a paradigm underscoring a critical role of T cells and an unnecessary role for B cells and antibodies in allograft rejection [2]. In the past decade, clinical studies have challenged this T cell-centric paradigm, driven by seminal observations that the presence of preformed circulating donor-specific antibodies (DSA) is associated with high risk for acute rejection, and that *de novo* DSA generated after transplantation is associated with poor outcomes and vascular obliterative lesions [3]. Indeed, antibody mediated rejection (AMR), is now recognized as a significant, and possibly the major cause of chronic kidney transplant dysfunction and failure [4].

There has been an increase in the understanding of the mechanisms resulting in rapid antibody production following immunization of naïve and sensitized hosts. However, less is

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understood of the B cell responses that result in chronically sustained antibody production mediating chronic AMR and transplant failure. This review will summarize the processes that underlie the primary and recall phases of B cell activation and antibody production, and discuss how these insights made with model antigens or infections, may be applied to understanding the generation of DSA following solid organ transplantation.

Routes of antigen presentation to B cells

B cells have to encounter cognate antigen in order to start the process of differentiating into PCs producing high affinity antibody and memory B cells. While it has long been established that B cells can bind intact soluble antigen, there is increasing evidence suggest that optimal B cell activation occurs when the B cell receptor (BCR) engages intact antigen displayed on FDCs, B cells or macrophages (reviewed in [5]). Several strategies exist to increase the opportunities for B cells to encounter soluble and membrane-bound antigen in the draining lymph nodes (reviewed in [5; 6]; Figure 1). Mature B cells circulate though the lymph nodes approximately every 24 hours, by leaving the vascular system and entering the lymph nodes through specialized high endothelial venules (HEV), migrating along processes extending from follicular dendritic cell (FDCs) and following the chemokine CXCL13 gradient established by FDCs and fibroblastic reticular cells (FRCs). Eventually these B cells congregate within the cortical region near the subcapsular sinus where they may encounter soluble or particulate antigens that enter the draining lymph node via multiple routes depending on antigen size, the presence of circulating antigen-specific antibodies, and the deposition of complement on the antigen by the classical or alternative pathways. In addition, there may be additional contribution by migratory DCs that acquire antigen at the tissue site and transport them into the lymph node.

The humoral response can also arise from the spleen, which is divided into two distinct compartments: the red pulp comprising a network of venous sinuses that traps old or damaged erythrocytes by red pulp macrophages, and the white pulp involved in the initiation of immune responses (reviewed in [7]; Figure 1). The white pulp is comprised of the T cell zone (also referred to as the periarteriolar lymphoid sheath; PALS), B cell follicles and marginal zone (MZ), which is strategically situated at the interface of the red and white pulp. The MZ contains a large reservoir of resident cells that participate in capturing and shuttling the antigen to FDCs within the B cell follicles and cells that are capable of processing and presenting the antigen to T cells. The routes for antigen delivery to B cells in the spleen and lymph nodes, identified through the study of model antigens or pathogens, are applicable to antigens derived from solid organ transplantation.

Small soluble proteins (≤14 kD), such as those secreted by the transplanted organs, may gain direct access to the B cell via passive flow through FRC conduits or gaps in the sinus floor of the lymph node or in the marginal sinus in the spleen (reviewed in [5; 6], [8]). These FRC conduits intersect with FDCs and thus provide direct connection for soluble antigen to be captured and presented on the FDC surface. In addition, natural polyreactive antibodies and DSA in naïve and sensitized recipients, respectively, can bind to soluble antigens and activate complement. These opsonized antigens are captured by complement receptor 3 (CR3; CD11b/CD18) expressed by subcapsular sinus macrophages (SSM) in draining lymph

nodes. The localization of these $CD169^{+}CD11c^{lo}CD11b^{+}MOMA\text{-}1^{+}$ SSMs, lining the sinus region of afferent lymphatic vessels, is dependent on lymphotoxin. Opsonized antigens captured and displayed by the SSM are relayed to non-antigen-specific naïve B cells in the underlying follicles via the complement receptors, CD21 (CR2) and CD35 (CR1), or FcRγIIB receptors. These B cells then transport opsonized antigens to FDCs that capture the immune complexes by CR1 binding C3b or C4d [9]. Likewise, opsonins draining into the spleen are captured in a C3d/CR2-dependent manner by MZ macrophages or B cells located just underneath the marginal sinus, which are then delivered to FDCs [5; 10].

Antigens not bound by antibodies can bind to macrophages and DCs located in the lymph nodes, via innate recognition proteins such as natural IgM; C-type lectins such as MBL (mannose binding lectin) and ficolins; and pentraxins, including C-reactive protein. These DCs and macrophages in the lymph node, together with $CD8^{-}$ DCs, MZ metallophilic macrophages and MZ macrophages in the spleen capture antigens via SIGLEC1, SIGNR1, TLR, type 1 scavenger receptor MARCO and C-type lectin, SIGNR1 (reviewed [7; 11]). Antigens displayed on the surface of these cells activate complement, and then follow the route of opsonized antigen delivery to CR1 on FDCs.

In addition to antigens secreted and shed from the allograft, a new type of alloantigen delivery has become increasingly appreciated ([12], reviewed [13; 14]). Donor-derived intact MHC complexes carried by extracellular vesicles or exosomes released by the allograft can accumulate in the draining lymph node and spleen. These exosomes are then captured by $SIGN\text{-}R1^{+}$ MZ macrophages, $F4/80^{+}$ macrophages in the red pulp of the spleen, SCS macrophages and DCs. Alternatively, a relatively limited number of donor DCs migrate from the graft into draining lymph nodes or spleen, where they deliver exosome to resident DCs. Donor MHC delivered by exosomes to recipient DCs, results in cross-dressed DCs that have the ability to stimulate recipient $CD8^{+}$ T cells via the direct pathway [15; 16]. Curiously, recipient APCs cross-dressed with donor MHC II cannot prime efficiently $CD4^{+}$ T cells [17]. The exosome surface also bears numerous glycoproteins decorated with sialic acid that allow their capture by sialoadhesin (CD169) expressed on SSM and MZ macrophages [18]. These macrophages then deliver exosomes bearing intact donor MHC to FDCs within the B cell zone [19].

Early B cell activation and the extrafollicular T/B cell interaction

When the BCR binds to antigen displayed on FDCs, SSMs or non-antigen-specific B cells, it triggers B cell activation, the upregulation of CCR7 and migration to the T/B border (reviewed in [5; 6]). Concurrently, B cells internalize the BCR-bound antigen, process and present the peptides derived from the antigen on MHC Class II molecules, in preparation for interaction with antigen-specific T cell receptors on $CD4^{+}$ T cells. It is notable that while alloreactive T cells can directly recognize intact donor MHC or indirectly recognize processed donor MHC presented on recipient MHC, only $CD4^{+}$ T cells that have indirect specificity for donor-derived antigens presented by the MHC molecules expressed by recipient B cells are capable of driving the differentiation of recipient B cells into PCs producing DSA [20]. This cognate interaction between T and B cells initiates the T-dependent DSA response.

T cells in the lymph node exit via HEVs located in the cortical ridge, and migrate along a network of reticular fibers to a gradient of CCL19 and CCL2 to localize in the T cell zone. Likewise, a FRC network exist within the PALS and connects the PALS to specific regions (bridging channels) of the MZ; T cells exiting the blood into the spleen use these FRC networks to enter the PALS [21; 22]. The activation of T cells requires an initial encounter with migratory DCs that had acquired antigen from the allograft and migrated via afferent lymph and along the same FRC network in the lymph node or spleen to reach the T cell zone. These DCs arrive between 12–18 hours to 5 days after antigen encounter in the tissues, and it has been argued that such delivery would be asynchronous to the more rapid delivery of antigen to FDCs and B cell activation, and that there has to be another more rapid route of antigen delivery to DCs in the T cell zone. Indeed, small antigens can gain rapid access to lymph node and spleen resident DCs within minutes of subcutaneous injection [8], via lymph and through FRC conduits that provide an efficient network for delivering small antigens, cytokine and chemokines to resident DCs that are localized along the FRC conduits in the T cell area. The FRC conduits have an outer diameter of 1–2 μm, are composed of tightly packed type I collagen fibers with spacing of 5–8 nm, resulting in a size exclusion of proteins over 60–70 kDa. For larger antigens, Gerner et al. [23] reported that strategically localized $CD11b^+$DCs within the lymphatic sinus endothelium scan the lymph with motile dendrites, and capture particulate vaccine antigens, pathogens and potentially, allograft-derived exosomes and membrane fragments. These DCs process and present captured antigens to T cells, thereby inducing T cell responses more rapidly than, and independently of, migratory DCs.

The initial encounter of T cells with cognate antigen presented on DCs result in a subset acquiring T follicular helper (Tfh) cell properties [24; 25; 26] (Figure 2). How $CD4^+$ T cell fates are determined has been the subject of a number of investigations and remains incompletely resolved. Fazilleau et al. [27] and Tubo et al. [28] independently concluded that increasing T cell receptor (TCR) strength results in more Tfh at the expense of Th1 cells, consistent with our findings that optimum Tfh responses were elicited by higher doses of T cell epitopes compared to Th1/Th2 responses [29]. In contrast, Keck et al. [30] reported that antigen affinity significantly controlled Th1 accumulation whereas Tfh cells were less affected by affinity. Krishnamoorty et al. [31] reported that low-affinity TCR signaling, resulting in lower levels of IRF4 were linked preferentially to a Tfh over Th1 gene program; findings recently corroborated by Snook et al. [32]. The reasons for the conflicting impact of TCR signaling strength are unclear; nevertheless, it is clear that the differentiation into Tfh cells require specific signals derived from the TCR, co-stimulation and inflammatory milieu that are distinct from those facilitating differentiation into the other $CD4^+$ T effector cell lineages. Understanding these differences may lead to the identification ways to more precisely prevent and treat AMR versus T cell-mediated rejection.

Tfh cells can be divided into two subsets: early extrafollicular mantel Tfh and GC Tfh cells [33]. Both Tfh subsets are characterized by the upregulated expression of CXCR5 and the transcription factor, Bcl-6. CXCR5 together with the G-protein-coupled receptor EBI2 promotes the initial localization of mantel Tfh cells towards the B cell follicle and T zone (T/B) interface [34] [35], where they interact with specialized activated DCs expressing inducible co-stimulator (ICOS) ligand and CD25. Membrane and soluble CD25 quench T

cell-derived IL-2, together with ICOS engagement and IL-21 produced by Tfh cells, promote Bcl-6-dependent Tfh cell differentiation [36] [37].

B cell priming at the T/B interface results in the generation of early PCs, memory B cells as well as B cells that are destined to migrate back to the follicle to initiate GC responses (Reviewed in [38]). These pre-GC responses tend to generate PCs that are of lower affinity than post-GC PCs, but can be class-switched [39]. Ballesteros-Tato et al. [37] reported that bcl-6-expression in T cells is essential for the extrafollicular production of IgG1 in response to 2 different model antigens, and of IgG2 specific to *Salmonella enterica*. This early antibody production has been shown to be critical for constraining infection, while waiting for the higher affinity post-GC antibody response to develop. The relative importance of the pre-GC response to DSA production following solid organ transplantation, and the contribution of this response to AMR, has not been delineated.

Germinal center response

When extrafollicular B cells receive costimulation from extrafollicular Tfh cells, they down-regulate EBI2 EBI2, which releases T cells from the outer follicle, and increase expression of the chemorepulsive receptor S1PR2, which repels cells from the S1P-rich lymph in the subcapsular sinus toward the follicle center [40; 41]. In addition, the retention of Tfh cells in the GC is regulated by contact-dependent repulsion by Ephrin B1-expressing GC B cells, which may additionally prevent Tfh cell exhaustion by providing respite from interacting with GC B cells and preserving the ability of the GC-Tfh cells to secrete IL-12 [42]. The GC-Tfh cells express higher levels of Cxcr5, Pdcd1 and IL-21 compared to extrafollicular Tfh.

The GC is divided into the light zone comprising stroma-derived FDCs and Tfh cells and the dark zone, which is devoid of FDCs. Light zone B cells express the activation markers, CD86 and CD83 [43; 44] and gene signatures associated with signaling from the BCR, CD40 and Myc. These B cells engage immobilized antigen presented on FDCs, and receive survival signals from GC-Tfh cells (reviewed in [38; 45]). Survival signals include those provided by the interaction between costimulatory molecules, CD28-B7, CD40-CD154 and ICOS-ICOSL, by cytokines such as IL-21 and BAFF, and signals downstream of SAP-SLAM intracellular interactions. Positively selected B cells upregulate CXCR4 and migrate into the dark zone to undergo cell proliferation and BCR diversification mediated by activation-induced cytidine deaminase (AID) [44; 46], [33; 47]. In the absence of T cell survival signals, B cells undergo apoptosis in the light zone, while B cells with damaged BCR genes as a result of AID activity also undergo apoptosis in the dark zone. Dark zone B cells with intact BCR downregulate CXCR4 and reenter the light zone where their newly generated BCR are tested for binding to antigen and access to T cell help [47]. Within each GC, and following the selection for B cells with high affinity BCR for antigens presented by the FDCs, post-GC B cells emerge as PCs (PC) that are ultimately responsible for persistent circulating antibodies, or as quiescent memory B cells that are responsible for the recall antibody response upon antigen reencounter (reviewed in [38]).

We, and others, have used MHC Class I and Class II tetramers to track the fate of alloreactive B cells in mice immunized with donor spleen cells or following heart allograft transplantation [48; 49; 50; 51; 52] (Figure 2). Within 7 days, donor-specific B cells acquire an activated phenotype (downregulated IgD and upregulated Class II and CD86), and differentiate into GC B cells or PC. The importance of CD40:CD154 interactions between B cells and T cells in the initial activation of T cells and in the maintenance of the GC response is well documented [53; 54]. In contrast, the necessity of CD28:B7 interactions in sustaining the GC response was less clear. Because there is currently no FDA approved drug that targets the CD40:CD154 interaction, while CTLA-4Ig is an FDA approved immunosuppressive agent for preventing kidney rejection, it was important to test the effect of CTLA-4Ig on established B cell responses. Additionally, observations that CTLA-4 on Tfr limited the expansion of antigen-specific Tfh cells and reduce antigen-specific antibody responses raised the possibility that CTLA-4Ig may in fact, promote humoral responses [55; 56]. Chen et al. [49] compared the ability of anti-CD154 and of CTLA-4Ig to reverse established GC response in mice. Both anti-CD154 and CTLA-4Ig administered at day 7 post-immunization comparably collapsed established GC B cell responses and prevented further DSA increase. Furthermore, delayed treatment with CTLA-4Ig significantly diminished the frequency of memory alloreactive B cells generated, and the recall DSA response upon re-immunization in the absence CTLA-4Ig [50]. The efficacy of CTLA-4Ig in controlling ongoing GC B cell responses and memory B cells in experimental models are congruent with reports of belatacept, a high affinity mutant of CTLA-4Ig, preventing DSA development in kidney transplant recipients despite high rates of acute rejection [57] [58]. Indeed, Leibler et al. [59] reported that belatacept was able to control humoral responses in humans by inhibiting B cell-Tfh interactions, thereby preventing B cell differentiation into PC. Whether this superiority of belatacept in controlling humoral responses compared to cyclosporine, will be maintained when compared to tacrolimus, which is currently more extensively used for kidney transplant recipients, requires further investigation.

Germinal Center responses to multiple complex antigens

For most part, the events shaping affinity maturation within the GC is based on the analysis following immunization with single haptens or small proteins, however most organ transplantation involves multiple MHC and non-MHC antigen incompatibilities. Therefore, it is critical that we understand how the B cell and antibody repertoire is shaped following the simultaneous introduction of multiple complex antigens. For select pathogens such as malaria, most naïve individuals generate antibodies directed to a variety of epitopes, whereas for other pathogens such as dengue, the majority of antibodies target an immunodominant epitope [60; 61]. How the immune response responds to multiple antigens to culminate in these diametrically opposite outcomes remains unresolved, and could be due to accessibility of binding sites on the antigen, stochastic founding events, genetic predisposition affecting the helper T cell response, and chance mutations during affinity maturation. Childs et al. [62] used computational modeling approaches to explain how different patterns of antibody responses arise. Their study suggested that upon initial antigen encounter, B cell clones with different antigenic specificity and affinity compete for stimulation during rounds of somatic hypermutation within GCs. As a result, the presence of many antigenic epitopes tends to

reduce the relative breadth of the antibody repertoire. Their model also predicted that the initial affinity of the generated antibodies to multiple antigens would be reduced, due to a reduction in the number of GCs and B cells available for each epitope, which compromises affinity selection. When the initial repertoire of circulating antibodies is generated, these antibodies will bind to the same antigenic epitopes driving their production, resulting either in the selection of B cells with higher affinity than circulating antibodies, or in the selection of B cells with specificity for new epitopes. If there are no alternative immunogenic epitopes, the B cell response will terminate with a relatively restricted repertoire. Thus circulating antibodies may increase the avidity, but either increase or decrease the breadth of the antibody repertoire.

In the majority of kidney transplant recipients, recipient B cells will most likely encounter multiple complex antigens. Under current immunosuppression, approximately 15% of renal transplant recipients develop *de novo* DSA within 4.6 years of transplantation, with some patients responding with a limited DSA repertoire while others more broadly [63]). Using a computation method to evaluate HLA epitope mismatch, Wiebe et al. [64] reported that the development of antibodies directed at donor Class II was most frequent in renal transplantation recipients with a higher degree of HLA epitope mismatch. Understanding how the alloantibody repertoire is selected in response to multiple antigen-mismatched allografts, how this repertoire evolves over time, and the impact of immunosuppression on these process, will result in a better understanding of when pathogenic versus non-pathogenic DSA develops.

Regulating the germinal center response

A subset of $CD4^+$ T cells that express the regulatory T (Treg) cell master regulator Foxp3, and sharing many phenotypic characteristics of Tfh cells, has recently been described [65; 66; 67]. These T follicular regulatory (TFr) cells express CXCR5, PD-1, Bcl-6. Blimp-1, FoxP3, GITR, ICOS, CTLA-4 and IL-10, but not CD25, and function by controlling GC responses. Early studies utilizing adoptive transfer or mixed bone marrow chimeras showed that Tfr are located in the GC, and that they suppress self-reactive GC B cells that may have inadvertently arose during the GC response [66]. Using $Bcl6^{flox/flox}Foxp3^{cre}$ mice (where bcl6 is deleted in $FoxP3^+$ Tregs) that lack Tfr, Botta et al. [68] recently reported that Tfr cells expanded during the contraction phase of an anti-influenza response, when IL-2 levels were reduced. These Trf cells migrated to the B cell follicles, and suppressed self-reactive B inadvertently generated in GCs during infection [69]. In the absence of Tfr, these self-reactive B cells differentiated into PC that produced anti-histone and anti-nuclear antibodies. Interestingly, Tfr cells did not inhibit the expansion of influenza-specific B cells or their differentiation into PC, and had no significant effect on influenza-specific antibody responses. In contrast, other studies have reported that Tfr cells inhibit antigen-specific GC B cells and antibody production [65; 66; 67].

Using multiplexed quantitative imaging of human mesenteric lymph node, and functional assays, Sayin et al. [70] recently reported that the majority of $CD3^+FOXP3^+$ Tfr cells expressing CD25 but low levels of CD5, resided at the T/B or GC-mantle borders, with very few located in the GC. The median Tfh/Tfr ratio was 1.3:1; 2:1 and 24:1 at the T-B border, B

cell follicle and GC, respectively, leading the authors to suggest an alternative model wherein Tfr cells regulate antibody responses by preventing long-lived interactions at the T/B border. Inhibition at this early stage of B cell response, would prevent further activation of Tfh cells and entry into GCs, as well as B cell differentiation into GC B cells, and post-GC memory B cells or PCs. Suppression of B cells by Tfr was independent of PD-1 expression, and correlated with elevated expression of CD69, IL-10, CTLA-4, and GARP, a protein critical for the surface expression of latent TGF-ß [71]. These observations led the authors to speculate that TGF-ß production may be the mechanism by which Tfr inhibit B cell responses.

Generation of memory B cells and PCs

The appropriate and rapid generation of PCs is essential for the successful control of infection, and of memory cells and long-lived PCs for the protection against reinfection. Factors that determine the PC fate during primary antigen encounter have been extensively investigated, with critical roles for BCR affinity and Tfh (reviewed by [72]). Differentiation into PCs at the T:B border and within GCs is facilitated by high BCR affinity [73; 74; 75]. Sciammas and colleagues [76; 77; 78] reported that graded expression of interferon regulatory factor-4 (IRF4) is an early measure of BCR signaling intensity: high levels of IRF4 induced Blimp-1 expression, promoted the PC program and shut down the expression of Bach2 controlling GC B cell fate [78; 79], while modest levels of IRF4 promote differentiation into GC B cells [76; 78]. Within GCs, PC differentiation was induced in a discrete subset of high-affinity B cells residing within the light zone upon BCR engagement with antigen presented on FDC, while Tfh cells provided the subsequent signals essential for completing the PC differentiation and driving their migration out of the GC [80].

Memory B cells are also generated in two distinct phases: early pre-GC memory B cells with lower affinity and enriched for IgM, and later post-GC memory B cells with higher affinity and expressing IgM or IgG [54; 81]. Relative to PCs, memory B cells are derived from cells receiving lower-affinity BCR signaling and reduced T cell help, which in turn, induces reduced IRF-4 and higher Bach2, respectively [82]. Gitlin et al. [83] reported that class-switching to membrane IgG1, which signals more efficiently compared to IgM [84], biased the fate choice to PC over memory fate. Furthermore, GC B cells that lack CXCR4 and therefore failed to enter the DZ were more likely to enter the memory compartment, confirming that BCR-signaling and T cell help is sufficient to drive memory differentiation, without the need for further proliferation or somatic hypermutation [85]. These features of memory B cell versus plasma cell differentiation are consistent with memory B cells being preferentially generated in the pre-GC and early GC period, and long-lived PC emerging significantly later [86].

The differences in affinity and kinetics of memory B cell versus PC generation suggest that successful treatment of acute AMR and reduction of circulating DSA may not have prevented memory donor-specific B cell generation. Indeed, in a recent meeting report by the Sensitization in Transplantation: Assessment of Risk 2017 working group [87], a major finding was that the absence of donor-specific antibody does not equate to an absence of sensitization or of memory B cells. There may be other explanations for humoral

sensitization without detectable DSA in transplant recipients, including the absorption of DSA by the allograft, the loss of shorter-lived PC the generation of a repertoire of memory B cells that is not identical to the long-lived PC [88]. In the absence of a clinical test of donor-specific memory B cells, the STAR recommendation is that an accurate patient history be obtained, and only patients without DSA and also without HLA sensitizing events such as pregnancies, transfusions, previous transplantation and implants should be considered to be immunologically low risk for alloimmune memory.

Recall B cell responses

Memory B cells upon antigen reencounter will either differentiate directly into PCs, generating a faster, high-titer and class-switched recall antibody response compared to a primary response, or they will differentiate into GC B cells that generate new, higher-affinity and class-switched PCs. However, the rules that predict memory B cell fate in the recall response remain to be fully clarified. Dogan et al. [89] and Pape et al. [81] reported that IgM^+ memory B cells preferentially differentiated into GC cells, whereas the $IgG1^+$ memory B cells gave rise primarily to PCs. Furthermore, Pape et al. [81] reported that the IgG^+ memory B cells predominated over IgM^+ memory B cells in the presence of circulating antibodies, because these antibodies outcompeted the low-affinity IgM BCR for access to limiting amounts of antigens. Shlomchik and colleagues [90] reported that memory B cells that express CD80, PD-L2, and CD73 were mostly IgM^+ and were mostly likely to produce PC. Most recently, Krishnamurthy et al. [91] investigated the memory B cell responses in mice infected with the malaria parasite, *Plasmodium chabaudi*. Upon challenge with *P. Chabaudi*-infected red blood cells, high-affinity IgM^+ memory B cells rapidly differentiated (≤3 days) into IgM^+ and IgG^+ PC. Collectively these data suggest that the fate of memory B cells upon reencounter with antigens is dependent, in part, on how and type of memory B cell was generated and the conditions of the antigen-reencounter.

When memory alloreactive B cells in sensitized murine recipients reencounter alloantigen following heart transplantation, they generate a recall DSA response that is largely dependent on the rapid differentiation into PC, with minimal GC responses [50] [48] (Figure 2). Nevertheless, the recall response remains dependent on T cell help, and co-stimulation blockade with CTLA-4Ig completely prevented memory B cell differentiation into PC and the recall DSA response. In addition, long-lived PC express CD28 that provides survival signals by engaging CD80/CD86 expressed by bone marrow stromal cells [92; 93; 94]. As a result, inhibition of the CD28-CD80/CD86 interaction with CTLA-4Ig may result in long-lived PC depletion and explain the recently described ability of belatacept to control and reverse DSA responses in sensitized recipients [95].

Conclusion

Despite an emerging appreciation of the limits of DSA in predicting ABMR and sensitization, the appearance *de novo* DSA remains a strong predictor of allograft loss [96; 97; 98]. In this review, we have provided a summary of the cellular processes that generate an antibody response, but for brevity, have avoided discussion of non-antibody producing roles of B cells, including their roles as antigen-presenting cells and as immune modulators

to T cell responses. Insights into the processes that lead to antibody production and humoral memory have arisen largely from the study of model antigens in reductionist mouse models, and how these processes are altered by the unique features of organ transplantation require further investigation. Following solid organ transplantation, the recipient is exposed to an enormous diversity of antigenic epitopes, large amounts of antigens that are persistent, as well as pharmacological immunosuppression. These factors will impact on the cellular responses that generate PCs, and the quality of the DSA they produce, as well as quality of memory donor-specific B cells, all of which remain formidable barriers to successful transplantation. Finally, defining the mechanistic differences between the immune responses to model antigens, pathogens and transplantation antigens may lead to new ways to control DSA production while preserving protective immunity.

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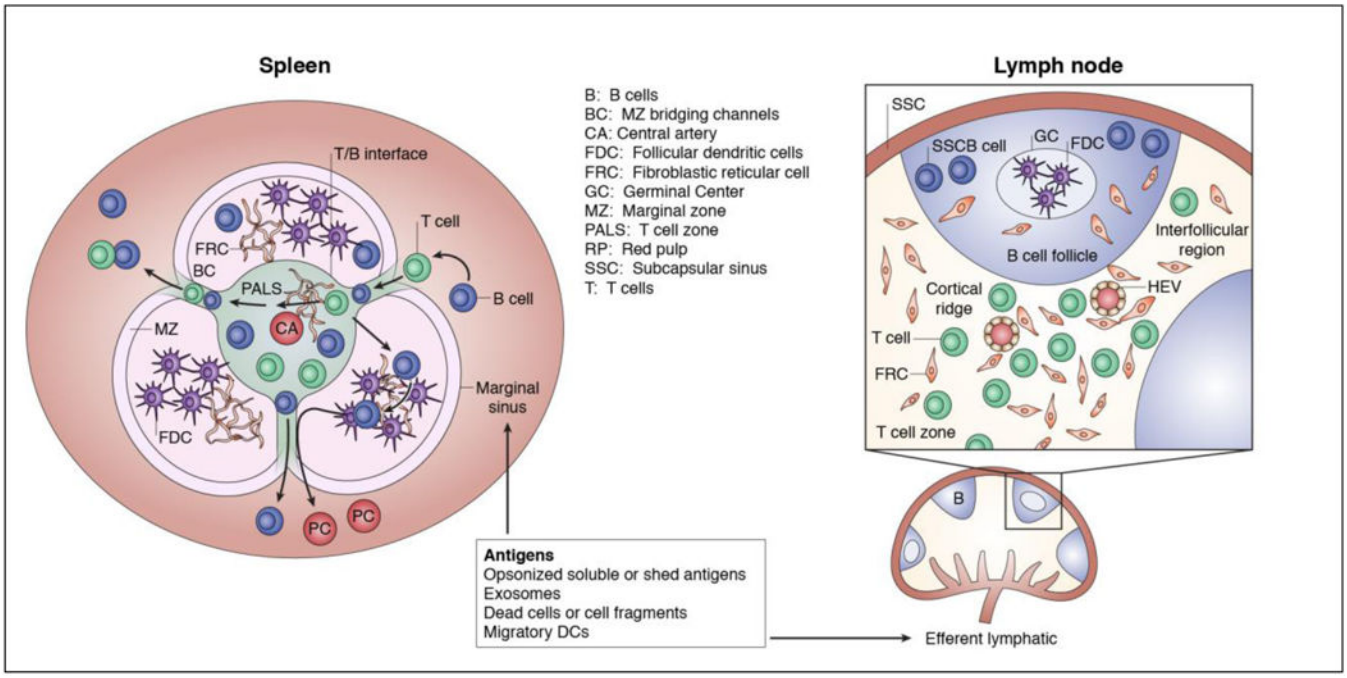

Figure 1:

Potential routes of antigen entry into the B and T cell zones in the lymph node and spleen. The FRC network guides soluble antigens, dendritic cells and macrophages bearing antigen, as well and T and B cells, into the correct anatomical location to optimize the likelihood of cognate antigen encounter.

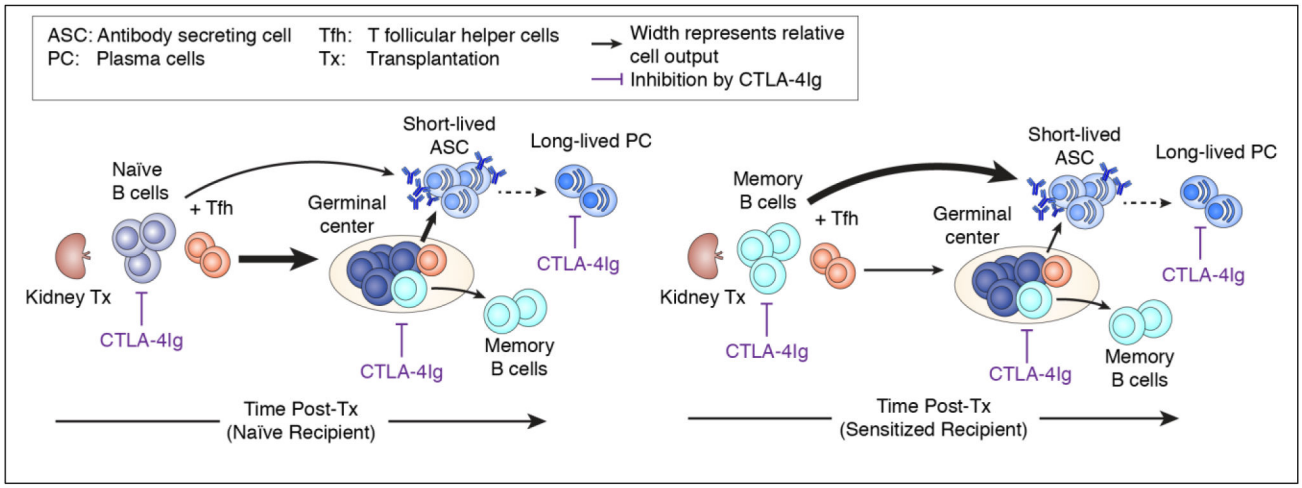

Figure 2.

B cell responses in naïve and sensitized recipients, and their control by CTLA-4Ig. Allografts transplanted into naïve recipients elicit a T cell-dependent B cell response that results in a germinal center (GC) reaction, whereas allografts in sensitized recipients elicit a T cell-dependent but GC-independent donor-specific antibody (DSA) response. CTLA-4Ig is inhibitory at multiple stages during primary and recall antibody responses.