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The Paradoxical Functions of B Cells and Antibodies in Transplantation

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Scarcely anyone would dispute that donor-specific B cells and the Abs that they produce can cause rejection of transplants. Less clear and more controversial, however, is the possibility that donor-specific B cells and the Abs that they produce are one or more means by which transplants can be protected from injury. In this article, we review and discuss this possibility and consider how less well-known functions of B cells and Abs might impact on the design of therapeutics and the management of transplant recipients.

Impact of Abs on transplants

The impact of Abs on transplants depends to the greatest extent on the origin of the blood vessels feeding those transplants (8, 9). Organ transplants have donor-derived blood vessels that can be targeted directly by donor-specific Abs. Binding of Abs to foreign blood vessels generates hyperacute, Ab-mediated acute and chronic rejection, as well as accommodation (9).

However, cell and tissue grafts are fed mainly by blood vessels of the recipient that grow into the grafts. These blood vessels are not targeted by donor-specific Abs and, indeed, in the absence of inflammation, the blood vessels block ready access of Abs to the graft (9). Accordingly, cell and tissue grafts are not generally subject to hyperacute, Ab-mediated acute, or chronic rejection (9). However, because activated T cells migrate efficiently through vessels, cell and tissue grafts are susceptible, and some believe more susceptible, to cellular rejection. Before the importance of anti-donor Abs in the outcome of grafts was understood, donor-specific Abs were sometimes considered of little or no importance in transplantation immunity. In classic reports, Mitchison (10) showed that transfer of donor-specific Abs had little impact on allogeneic tumor grafts, and Snell et al. (11) found that these Abs can actually “enhance” the growth of these grafts. However, one happy by-product of this incomplete understanding was the emergence (some would say re-emergence) of the appreciation of cells as effectors of immunity (10).

If Abs are now appreciated as effectors of organ transplant rejection (6), the availability of these Abs and, hence, the susceptibility of a graft to Ab-mediated rejection, is sometimes underestimated. Large organs, such as kidney and heart, absorb huge amounts of anti-donor Abs (12-15) and in this way can clear the blood of all or nearly all of the Abs as long as perfusion of the graft is unimpaired. Thus, the level of these Abs in the blood increases dramatically following removal of an organ transplant (16) or severe graft injury (17, 18). Hence, although new technologies facilitate assay of donor-specific Abs (19), and although these assays are gaining wide application for analysis of pre- and posttransplant risk, one might exercise caution, if not skepticism, because after organ transplantation the Abs of highest affinity and perhaps highest biological import will be absorbed in preference to Abs of lower affinity (20). Also, because MHC class I is expressed in grafts more widely than is MHC class II and, hence, Abs against MHC class I might be more fully absorbed than Abs against MHC class II, one should exercise caution when interpreting reports that associate anti-MHC class II Abs with graft rejection.

Accommodation and enhancement

Abs against a transplant can protect the transplant from immunological injury by inducing accommodation, acquired
resistance to immune and inflammatory injury (21–23); or enhancement, humoral suppression of cellular immunity (11). Accommodation, although still a subject of controversy, has been the subject of recent critical reviews (23). Enhancement, although reviewed critically (7) and possibly less controversial, has been ignored in recent decades. Both merit consideration because the processes challenge the notion that B cell responses invariably harm transplants.

Accommodation was first observed in the 1980s when some ABO-incompatible kidney transplants were found to function normally and suffer little or no injury in the face of high levels of circulating Abs against the donor blood group (21). Accommodation is associated with heightened expression of complement regulatory proteins and cytoprotective genes in the transplant (24–29). Whether either or both of these mediate accommodation is yet unclear, although the absence of either dramatically heights the susceptibility of tissues to injury of every type (30, 31). The original reports of accommodation used donor-specific Abs as markers (8); however, because organ transplants can absorb vast amounts of Ab, these markers lack sensitivity. Expression of cytoprotective genes appears to mark accommodation, but the high levels of expression found in rejecting organs undermine the specificity of these markers (31). The presence of C4d in normally functioning organ grafts might help to identify accommodation in recipients having little or no donor-specific Abs in the blood. Still more sensitive might be donor-specific B cell responses, which we recently detected in many transplants (R.J. Lynch, I.A. Silva, J.B. Chen, J.D. Punch, M. Cascalho, and J.L. Platt, submitted for publication). If confirmed, the high prevalence of donor-specific B cell responses would suggest that accommodation is the most common outcome of organ transplantation.

The possibility that donor-specific Abs might suppress transplant immunity was first reported by Snell et al. (11), who observed that administration of tumor vaccines sometimes “enhanced,” rather than retarded, cancer growth. Kaliss (32), who studied the phenomenon most extensively, showed that Abs mediate enhancement, because they can be used in lieu of vaccines, and do so by “blocking” immunological recognition (7). One might expect that any suppressive properties of donor-specific Abs would be eclipsed by the humoral injury that they cause to organ transplants. However, the survival of experimental and clinical organ transplants is sometimes improved and alloimmunity is sometimes suppressed by evoking or administering anti-donor Abs (7, 33, 34).

It is far from clear how anti-donor B cell responses and anti-donor Abs suppress immunity. Early investigations seemed to implicate the blockade of Ag recognition, and this mechanism has not been excluded. However, apart from the Abs that they produce, B cells can suppress immunity by secreting IL-10; this function can control alloimmunity in mice (discussed below). Enhancement might also reflect Ab-dependent suppression of cellular immunity, which De Groot et al. (35) ascribed to activation of FOXP3+ T regulatory cells by IgG-derived peptides associated with HLA class II. Regardless of the mechanism, enhancement might account for the paradoxical intensification of cellular immunity associated with depletion of B cells in transplant recipients (36). That these mechanisms have not been implicated in enhancement probably reflects neglect of that subject rather than contrary evidence.

Ab-dependent T cell responses

Abs enhance Ag presentation to T cells. Binding of Abs can concentrate Ag and direct it to sites of Ag presentation. IgM captures Ag in blood, transports it to the spleen, and retains it in marginal zones (37). The Ag receptor of marginal zone B cells captures Ag and transports it to follicular dendritic cells in lymphoid follicles (38). In addition to facilitating Ag presentation, Ig can directly promote cellular immunity. Peptides originating from Ig variable regions can associate with MHC and stimulate cellular immunity directed against IgG idiotypes originating from VH germline and mutated variants (39). T cells also can recognize peptides derived from mutated λ2 light chains (40), and recognition can generate delayed-type hypersensitivity (41). Because transplants adsorb and process large amounts of donor-specific Ab, this mechanism may explain why recipients producing such Abs have a high incidence and greater severity of cellular rejection.

However, humoral immunity does not always enhance cellular immunity, it can also eradicate or regulate it. Thus, expression of a transgenic Ig κ L chain caused deletion of κ L chain peptide–specific CD4+ T cells (42), T cell tolerance to an Ig idiotype prevented disease otherwise caused by Ig idiotype-specific T cells (43), and induction of tolerance to an Ig idiotype prevented lupus in NZB/NZW F1 mice (44). In addition to causing deletion of idiotype-specific T cells, Ig can induce regulation of those T cells (35). It is not known whether and/or to what extent peptides from donor-specific Abs underlie regulation of T cell responses to transplants, but the emergence of B cell therapeutics heightens the importance of this subject.

B cell—“dependent” T cell responses

Following the seminal observations of Mitchison (10) establishing that immune cells, rather than Abs, reject transplants, Szenberg and Warner (45) and Miller (46) showed that offending cells originate in the thymus and not in the bursa. Thus, cell and tissue transplants were clearly subject to cellular and not Ab-mediated rejection, as transplants in B cell–deficient mice confirmed (47).

However, the relationship between B cell functions and the outcome of transplantation would prove more complex than these results would suggest. First, as discussed above, it became apparent that rejection of organ transplants, including cell-mediated rejection, could, in some circumstances, be promoted by B cells and/or Abs, whereas in other cases, it could be suppressed. Organ transplant recipients with donor-specific Abs more often experience cellular-mediated rejection rather than Ab-mediated rejection (48). Although no one disputes that the incidence of cellular-mediated rejection in recipients with donor-specific Abs might simply reflect prior sensitization, it is also possible that Abs (and/or the B cells that produce the Abs) facilitate cellular immune responses. Consistent with that concept, Sarwal et al. (49), Huppen et al. (50), Tsai et al. (51), and Zarkhin et al. (52) showed CD20+ B cell clusters in C4d− biopsies of acutely rejecting kidney allografts, suggesting that B cells may promote rejection, perhaps by facilitating cellular immune responses. However, it is not known whether B cells in rejecting kidneys contribute to or merely mark rejection.

Depletion of B cells should offer clues to their function in transplantation. Abs against CD20, which is expressed on
B cells but not on plasma cells, decrease the levels of donor-specific Abs (53), improve outcomes of transplants in clinical transplant recipients (54, 55), improve survival of islet allografts (56), and attenuate allograft vasculopathy in nonhuman primates (57). These findings might suggest that pathogenic Abs against MHC originate with partly differentiated plasma cells or memory B cells. Still, the failure of anti-CD20 to reduce or eliminate anti-HLA Abs (58) suggests that other functions of B cells (59) and/or other sources of anti-HLA (plasma cells) might have a greater impact on transplant outcome.

Although the impact of B cell depletion on Ab-mediated and chronic rejection has been studied in detail (60), the impact on cellular immunity and cellular rejection has not. Depletion of B cells at the time of transplantation in sensitized individuals decreased the frequency and severity of cellular rejection (53). Work in mice suggests that at least some of this benefit might reflect hindered Ag presentation (61), although an impact on anti-graft Abs was not fully excluded. In contrast, B cell depletion can also heighten the risk for and severity of cellular rejection. Five of six renal allograft recipients treated with anti-CD20 as an induction therapy developed acute cellular rejection (36). Memory B cells promoted unresponsiveness to costimulation blockade, enhancing cellular rejection of heart allografts in mice (62), and depletion of B cells in mice accelerated rejection of minor histocompatibility–discordant skin grafts and major histocompatibility–discordant kidney allografts (63).

How B cells control cellular immunity

B cells establish the microenvironments of lymphoid tissues that enable the mounting of cellular immunity and function of adoptively transferred T cells. By providing lymphotoxicin, B cells promote lymphoid organogenesis (64), differentiation of follicular dendritic cells (64), development of B cell follicles (65) and T cell zones in spleen (66), and differentiation of M cells in the gut-associated lymphoid organs (67). The architecture of lymphoid tissues not only supports effector responses, it also supports regulation of cellular immune responses, as established from the study of transplants in mice (68). As only one example, Abs against CD62L, which impair T cell migration into lymph nodes, prevent establishment of transplant tolerance in mice with cardiac allografts (69). It is unknown whether depletion of B cells by agents such as anti-CD20 disrupts lymphoid architecture and, in this way, cellular immunity or regulation in the context of transplantation.

It is generally accepted that B cells present Ags. However, it is not known whether the type of T cell responses initiated by B cell Ag presentation is distinct from those initiated by conventional APCs. B cells present Ags like conventional APCs following Ag phagocytosis or pinocytosis, and they may do so more efficiently than previously thought (70, 71). B cells also present Ag by a novel “cognate” pathway that might have particular importance in transplantation. Lanzavecchia (72) showed that B cells can, via their BCR, take up Ag, which is then processed and presented to MHC class II–restricted T cells. B cell cognate Ag presentation differs from conventional Ag presentation owing to the unique ability of B cells to take up Ag specifically through binding clonotypic BCRs, which, in turn, concentrates the presentation of peptides from one Ag (73). Also, in contrast to conventional APCs, which do not divide, B cells proliferate by forming clones, amplifying presentation of Ag uptake by the BCR. B cell cognate Ag presentation might be important in transplantation, because the nearly universal B cell response to MHC infers that every individual has some, perhaps many, B cells capable of cognate presentation of MHC and perhaps some minor Ags; it might also explain how cellular immunity and cellular rejection frequently occur, despite potent immunosuppression. The importance of cognate presentation in transplantation seems ripe for study, given the recent attention devoted to depletion of B cells.

In addition to establishing lymphoid microenvironments that nurture immune activation and regulation, B cells directly control immunity, including transplantation immunity. B cells control immunity, in part, by secreting IL-2, IL-4, IL-10, IL-13, IFN-γ, IL-12, and TNF-α (74, 75). B cells also promote the differentiation of regulatory T cells (76–78). Excellent reviews of the properties of regulatory B cells were published recently (75, 79). Consistent with a regulatory function for B cells in transplantation, B cell genes are expressed more frequently in tolerant, rather than in nontolerant, renal transplant recipients of renal allografts (80, 81); tolerant kidney transplant recipients have large numbers of B cells producing IL-10 (82); and tolerance to experimental cardiac allografts in rats can be transferred by a purified population of B cells (83). As mentioned above, an increased risk for acute cellular rejection following depletion of B cells prior to transplantation could be due to a loss of regulatory B cells (36).

In addition to regulating the response of T cells to transplantation and other stimuli, B cells, and particularly diverse Ig, expand the repertoire of T cells (84). This property of B cells may be particularly relevant in transplantation, because transplantation introduces powerful immunogens (like MHC) that cannot be cleared, inducing chronic immune activation and biasing the lymphocyte repertoire (85). Additionally, although rejection of transplants does not require T cell diversity (86), regulation of alloimmunity might (86).

Conclusions

Recent years have brought heightened appreciation that donor-specific B cells pose a key barrier to successful transplantation, especially of organs. This appreciation has naturally sparked interest in the development of agents for the depletion and suppression of B cells. Yet, this interest also heightens the importance, if not appreciation, of paradoxical functions of B cells in transplantation. No less important than effector B cell functions might be those B cell functions that prevent or suppress immunity against the graft or protect the graft against injury. Enhancement, accommodation, and tolerance all reflect functions of B cells, and all are potentially compromised by therapies aimed at B cells. That is not to say that B cell therapeutics should be put aside; rather, a broader view of the outcomes might be needed. We consider especially urgent the testing of whether anti-CD20 or other such agents modify lymphoid architecture or the numbers and functions of regulatory T cells. For example, B cell–depletion therapies may cause structural and/or functional defects in lymphoid tissue, which, in turn, may limit their efficacy or decrease immune responses to vaccines. Equally important would be investigating whether these agents impair accommodation, enhancement, and/or spontaneous tolerance. New, more sensitive assays for donor-specific Abs should allow more attention to be devoted to learning whether and how these Abs prevent graft injury.


