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Shaoping Deng, Daniel J. Moore, Xiaolun Huang, Moh-Moh Lian, Muhammad Mohiuddin, Ergun Veledeoglu, Major K. Lee IV, Samsher Sonawane, James Kim, Jing Wang, Haiying Chen, Steven A. Corfe, Christopher Paige, Mark Shlomchik, Andrew Caton and James F. Markmann

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Cutting Edge: Transplant Tolerance Induced by Anti-CD45RB Requires B Lymphocytes


Selective interference with the CD45RB isoform by mAb (anti-CD45RB) reliably induces donor-specific tolerance. Although previous studies suggest participation of regulatory T cells, a mechanistic understanding of anti-CD45RB-induced tolerance is lacking. We report herein the unexpected finding that tolerance induced by this agent is not established in B cell-deficient mice but can be recovered by preemptive B lymphocyte transfer to B cell-deficient hosts. Using B cells from genetically modified donors to reconstitute B cell-deficient recipients, we evaluate the role of B lymphocyte-expressed CD45RB, T cell costimulatory molecules, and the production of Abs in this novel tolerance mechanism. Our data document an Ab-induced tolerance regimen that is uniquely B lymphocyte-dependent and suggest mechanistic contributions to tolerance development from the B cell compartment through interactions with T cells. The Journal of Immunology, 2007, 178: 6028–6032.

The CD45 is a family of transmembrane protein tyrosine phosphatases critically involved in lymphocyte development and activation (1). Through its protein tyrosine phosphatase activity, CD45 can operate as a positive as well as a negative regulator of Src-family kinases for signal transduction through Ag receptors in both T and B cells (2, 3). Thus, CD45 serves as a rheostat that determines the overall sensitivity of the adaptive immune system to antigenic stimulation. Given its crucial role in lymphocyte activation, CD45 has been targeted with therapies that have emerged as potent immunosuppressive agents in both autoimmune and transplant models (4, 5).

Investigation of the mechanism of tolerance induction by anti-CD45RB initially focused on alteration of the T cell response due to T lymphocyte expression of CD45RB and their central role in transplant rejection. Recent studies correlated the effect of anti-CD45RB with up-regulation of CTLA-4 on T cells (6, 7). Because CTLA-4 can deliver negative signals in T cell activation and may be expressed by regulatory T cells (Tregs),6 anti-CD45RB-induced up-regulation of CTLA-4 may play an important role in deactivation of graft-reactive lymphocytes (8, 9). In addition, induction of T cell anergy and formation of Th2 or Treg cells have been suggested in previous studies (4, 10).

The emergence of Treg function as a critical aspect of the tolerance mechanism has also stimulated investigation into the APC population because modulation of T cell-APC interactions may enhance Treg formation (11). Initial studies indicated a role of tolerogenic dendritic cells in this model (12). In addition, we have recently studied the effect of anti-CD45RB therapy in NOD mice and found that NOD mice are resistant to anti-CD45RB-induced transplant tolerance, even in the absence of autoimmunity (13). Because of the critical role played by B lymphocytes as APCs in autoimmune disease (14), we hypothesized that B cells may play a requisite role in tolerance induced by anti-CD45RB. In the current work, we demonstrate that B cells are absolutely required for development of anti-CD45RB-induced tolerance and that they function through direct cell interaction with T cells via costimulatory molecules.

Materials and Methods

Mice

Wild-type C57BL/6 (B6, H2b), B cell-deficient C57BL/6 (μko-B6, H2b), C3H (H2f), BALB/c (H2b), and C57BL/6J mice with specific gene knockouts (B7-1/B7-2, CD40) were purchased from The Jackson Laboratory. TS1 and HA104 mice were bred internally and have been described for use in transplantation.  

*Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA 19104; †Institute of Organ Transplantation, Sichuan Provincial People’s Hospital/Academy of Medical Sciences of Sichuan, Chengdu, China; ‡Ontario Cancer Institute and Department of Immunology, University of Toronto, Ontario, Canada; §Department of Laboratory Medicine and Section of Immunology, Yale University School of Medicine, New Haven, CT 06520; and ¶The Wistar Institute, Philadelphia, PA 19104

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2 S.D. and D.J.M. contributed equally to this study.

3 Address correspondence and reprint requests to Dr. Shaoping Deng, University of Pennsylvania, 313 Stemmler Hall, Philadelphia, PA 19104; E-mail address: deng@ mail.med.upenn.edu or Dr. James F. Markmann, Department of Surgery, Hospital of the University of Pennsylvania, 36th and Hamilton Walk, Philadelphia, PA 19104; E-mail address: james.markmann@uphs.upenn.edu

4 Current address: Department of Pediatrics, Vanderbilt University, Nashville, TN 37232.

5 Current address: National Institutes of Health/National Heart, Lung, and Blood Institute.

6 Abbreviations used in this paper: Treg, regulatory T cell; mIgM, membrane IgM; HA, hemagglutinin; MST, median survival time.

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studies (15). Membrane IgM (mIgM) mice on a BALB/c background (16) were bred at Yale University School of Medicine under specific pathogen-free conditions. CD45-deficient animals were provided by C.P. (University of Toronto, Ontario, Canada). All mice were housed under specific pathogen-free barrier conditions at the University of Pennsylvania.

Heart transplantation

Experiments were performed according to a protocol approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania. Transplantation was performed according to the Oso-Lindsey (4, 17) model as adapted for mice and described previously.

Anti-CD45RB therapy

Animals were treated with i.p. injection of 100 μg of rat anti-mouse CD45RB Ab (clone, MB23G2; American Type Culture Collection) on days 0, 1, 3, 5, and 7 following transplantation.

Reconstitution model

B cell-deficient mice were reconstituted with mature syngeneic B cells by i.v. injection of 5 × 10⁶ splenocytes or purified B cells (negative selection via MACS) from normal or gene knockout mice.

Flow cytometry

One million cells were suspended in biotin-free RPMI 1640 containing 0.1% azide and 3% FCS and surface stained in 96-well plates with the appropriate mAbs (BD Pharmingen). Biotin-conjugated mAbs were subsequently stained with streptavidin-RED670 (Invitrogen Life Technologies). All samples were analyzed on a FACSCalibur flow cytometer (BD Biosciences) using CellQuest software (BD Biosciences).

MACS

B cells were enriched by negative selection of splenocytes with ferritin-conjugated Thy1.2 and anti-CD11b-biotin followed by streptavidin-conjugated MACS beads (Miltenyi Biotec). All depletions yielded >95% efficiency in negative selection of the targeted population.

Statistical analysis

All data are presented as mean ± SD. Statistical analysis was done by ANOVA using n-1 custom hypotheses tests as appropriate. Survival curves were generated by the Kaplan-Meier method and analyzed by the log-rank test.

Results

Anti-CD45RB treatment promotes cellular proliferation and phenotypic alterations in the B cell compartment

Because anti-CD45RB treatment induces robust tolerance in both the allogeneic C3H to B6 and the BALB-derived transgenic HA104 (hemagglutinin (HA) expressing) to TS1 (HA-specific TCR) combinations (4), we investigated the cellular mechanisms underlying tolerance. We initially evaluated B and T cell-expressed surface molecules for changes in their expression in the draining para-aortic lymph nodes of cardiac-grafted mice. Controls included mice grafted without Ab treatment and naive mice. T lymphocytes from mice treated with anti-CD45RB demonstrated down-regulation of CD4, CD45RB, and CD62L (data not shown). Phenotypic changes were also noted within the B cell compartment where molecules involved in B cell signal transduction, activation, and T cell costimulation were assessed. Most noticeable among these alterations were an increase in CD54 and MHC class II and a decrease in the levels of CD19, features suggesting a B cell that had been stimulated and was now prepared for T cell engagement (Fig. 1). Only a minor change was noted in the expression of B7.1, B7.2, and CD40 molecules (data not shown). As a confirmation of the anti-CD45RB effect on these cells, we performed in vitro MLR in the presence or absence of anti-CD45RB. Anti-CD45RB enhanced proliferation in CD4 and CD8 T cells and B cells in the presence of allogeneic stimulators (data not shown).

Anti-CD45RB-induced tolerance requires B lymphocytes

Because anti-CD45RB enhances the B cell response during allogeneic stimulation, we assessed the requirement for host B lymphocytes during anti-CD45RB-induced tolerance by using the μMT−/− knockout mice generated by Kitamura et al. (18). These mice maintained on the B6 background have no mature B cells and no detectable Ab production. Transplantation of C3H heart grafts to untreated B6 hosts resulted in prompt rejection, documenting that neither B cells nor Ab are required for rejection in this model (Fig. 2A). However, anti-CD45RB treatment failed to induce tolerance when C3H hearts were grafted to B6μMT−/− hosts. In the absence of B cells, not only did tolerance not develop, but the immunosuppressive effects of the agent were lost as indicated by a prolongation of survival to only 14 days from 9 days in controls. This finding directly implicates host B cells in the tolerance pathway and in the immunosuppressive properties of anti-CD45RB. Because B cell-deficient mice may have other immunologic deficits or tolerance resistance secondary to the development of their immune system in the absence of B cells, we confirmed the role of B cells in this model by reconstituting our recipients with mature syngeneic B cells by i.v. injection of 5 × 10⁶ splenocytes or with the same number of MACS-purified B cells from normal B6 mice on the day before transplantation. When these mice were transplanted, anti-CD45RB therapy induced permanent graft survival (median survival time (MST) >90 days; n = 9; p < 0.001).

To confirm the generality of this finding, we extended this analysis to the TS1 transgenic model and developed a line of B cell-deficient TS1 mice (BALB/c background) by interbreeding our TS1 mice with the BALB/c Jh−/− line (19). The Jh−/− line does not develop mature B cells or produce Ab. We tested the ability of CD45RB to induce tolerance in TS1-Jh−/− mice. We
survival was only slightly prolonged by anti-CD45 in the cells and assessed for susceptibility to tolerance induction by anti-CD45RB immunotherapy. For the tolerogenic and immunosuppressive actions of anti-CD45RB, modified B cell function.

Collectively, these data demonstrate that B cells are necessary for anti-CD45RB-induced tolerance, we questioned whether there was a requisite role for B lymphocytes in anti-CD45RB therapy, but all grafts were rejected in the CD45−/− splenocyte-reconstituted μ ko mice (n = 7) treated with the same anti-CD45RB regimen (p = 0.001).

B cell-mediated anti-CD45RB-induced tolerance requires CD40 and CD80/86 but not secreted Ab

We also assessed the effector mechanisms that could be used by B cells to promote tolerance. In this regard, we investigated both the necessity of B cell-mediated Ab production and the role of B cell-expressed costimulatory molecules. To address the role of Ab, we used the B cell reconstitution model together with B cells that are incapable of secreting Ig as developed by Hannum et al. (16). These B cells, denoted mlgM and maintained on the Jh−/− BALB/c background, have a specific mutation in the Ig exons required for secretion of Ig. We transplanted cardiac allografts into B cell-deficient Ts1/Jh−/− mice that received splenocytes from mlgM mice. Similar to the wild-type transplant model, long-term survival of cardiac allografts (n = 4; >100 days) was achieved in anti-CD45RB-treated B cell-deficient mice reconstituted with B cells unable to secrete Ab (Fig. 4A). These data indicate that B cell-dependent CD45+/- Splenocytes, anti-CD45

Anti-CD45RB-induced tolerance requires B cell expression of the CD45 molecule

Having demonstrated a requisite role for B lymphocytes in anti-CD45RB-induced tolerance, we questioned whether there was interaction of the Ab with CD45RB expressed by B cells. To test this thesis, we used CD45−/− mice produced by targeted disruption of exon 9 of the CD45 gene as a source of B cells lacking CD45 in our reconstitution model (20). Again, B6μMT−/− recipients were reconstituted with CD45−/−B cells and assessed for susceptibility to tolerance induction by anti-CD45RB. Although long-term graft survival (MST >100 days; n = 5) was observed in anti-CD45RB-treated B6μMT−/− mice that had received CD45+/- splenocytes, all grafts (MST = 21–30 days; n = 7) were rejected in the anti-CD45RB-treated B6μMT−/− mice that received CD45−/− splenocytes (Fig. 3). These data indicate that the tolerogenic mechanism of anti-CD45RB acts, at least in part, directly through CD45RB expressed on B cells and suggests that the Ab modifies B cell function.

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transplant tolerance in this model is not mediated through Abs. To assess the role of B-T interactions through costimulatory molecules, cardiac allografts were transplanted to B cell-deficient mice reconstituted with splenocytes from knockout mice with deficiency for the costimulatory molecule CD40 or the combination B7-1/B7-2. As shown in Fig. 4B, long-term survival was not obtained in anti-CD45RB-treated B cell-deficient mice reconstituted with B cells lacking either the CD40 molecule or B7-1/2 molecules, whereas long-term survival (MST > 100 days; n = 9) was readily achievable in B cell-deficient mice reconstituted with wild-type B cells. These data indicate the importance of costimulatory signaling in B cell-mediated transplantation tolerance following anti-CD45RB therapy and implicate a direct T-B interaction in the tolerogenic pathway.

Discussion

The current work adds to our understanding of tolerance induced by anti-CD45RB by demonstrating the obligate role of B cells. This function requires their expression of CD45 and the costimulatory molecules B7 and CD40 but is not dependent on Ab. Collectively, these findings suggest a model in which B cells interact directly with T cells to foster tolerance and identify previously uncharacterized B cell-dependent pathways of allograft tolerance induction.

We have also reported that anti-CD45RB therapy has separable effects in the peripheral and central immune compartments (4). Specifically, tolerance induced by anti-CD45RB administration requires the presence of an intact thymus to generate donor Ag-specific Tregs. However, in the absence of a thymus (and tolerance), anti-CD45RB still exhibits marked peripheral immunosuppressive activity, as revealed by the demonstration here, is lost in the absence of B cells (MST = 56 days vs MST = 14 days in μ μ mice). Thus, we conclude that the peripheral interaction of B cells with T cells in anti-CD45RB-treated hosts is responsible for the peripheral immunosuppressive effects of the agent and suggest that this effect is needed to render the periphery receptive to Treg-mediated donor-specific tolerance perhaps by favorably altering the ratio of Tregs to effectors in favor of tolerance.

The mechanism by which anti-CD45RB induces peripheral B cell-mediated attenuation of T cell alloreactivity remains to be defined. However, because CD45RB treatment acts through T cell CTLA4 up-regulation (7–9), our finding that B7-deficient B cells cannot mediate anti-CD45RB-induced tolerance suggests that B cells, as the most prevalent APC population, provide critical B7 ligands for CTLA4 triggering in the model. The requirement for CD40 may also contribute to this pathway because CD40 signaling couples to NFκB, which may control surface expression of the B7 molecules during T cell engagement. In addition to a potential interaction with CTLA4-4-expressing regulatory cells, our preliminary studies (data not shown) indicate that anti-CD45RB-activated B cells enhance activation-induced T cell death, which may eliminate alloreactive T cells in the periphery. Thus, B cells may positively affect the balance between regulatory and effector cells. In addition to a role for Treg development, B cells may interact directly with T cell subsets other than CD4+CD25+ Tregs to inhibit immune activation in the periphery. In a transgenic model of T cell activation, Knoechel et al. (21) have demonstrated the ability of B cells to inhibit the proliferation of autoreactive T cells and prevent disease progression. In a TCR diverse model of colitis, Wei et al. (22) have found similar results. In their model, B cells played a critical role in the prevention of autoimmune colitis. Investigation of the cellular mechanism indicated a role for interactions with both NKT cells as well as CD8 cells.

Finally, our observation raises interesting questions regarding the use of anti-B cell therapy in clinical approaches to generate tolerance. Recently, interest has grown in the use of B cell-depleting agents such as anti-CD20 in transplantation, with the rationale that B cells may serve as critical APCs or produce deleterious alloantibody. The current data suggest a contrary role for B cells in the setting of anti-CD45RB therapy because they are essential components of tolerance induction. Whether other tolerance regimens rely on B cells or would benefit from their depletion will require further study.

In summary, short-term administration of anti-CD45RB Ab effectively prevents cardiac allograft rejection and induces T cell tolerance to donor alloantigens. The tolerogenic efficacy of anti-CD45RB therapy requires host B cells that mediate anti-CD45RB-induced tolerance through the interaction of costimulatory molecules on B cells with T cells. Because Treg formation in the thymus is also required, it is tempting to hypothesize that enhanced activation of peripheral host B cells contributes to render peripheral T cells unresponsive and receptive to suppression by donor-specific thymic-derived Tregs, thereby giving rise to a state of stable and long-lived tolerance. Overall, this study reveals the contribution of previously unrecognized cellular pathways to permanent donor-specific tolerance following a mAb therapy and suggests a unique role for B cells in tolerance induction to alloantigens.

Acknowledgments

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Disclosures

The authors have no financial conflict of interest.

References


