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Migration of Antigen-Presenting B Cells from Peripheral to Mucosal Lymphoid Tissues May Induce Intestinal Antigen-Specific IgA Following Parenteral Immunization

Susan E. Coffin, Stephanie L. Clark, Nico A. Bos, Jeffery O. Brubaker, and Paul A. Offit

Parenterally administered immunizations have long been used to induce protection from mucosal pathogens such as Bordetella pertussis and influenza virus. We previously found that i.m. inoculation of mice with the intestinal pathogen, rotavirus, induced virus-specific Ab production by intestinal lymphocytes. We have now used adoptive transfer studies to identify the cell types responsible for the generation of virus-specific Ab production by gut-associated lymphoid tissue (GALT) after i.m. immunization. Three days after i.m. immunization with rotavirus, cells obtained from the draining peripheral lymph nodes of donor mice were transferred into naive recipient mice. We found that intestinal lymphocytes produced rotavirus-specific Igs (IgM, IgA, and IgG) 2 wk after transfer of either unfractionated cells, or unfractionated cells rendered incapable of cellular division by mitomycin C treatment. Additional studies demonstrated that rotavirus-specific IgA, but not IgG, was produced by intestinal lymphocytes after transfer of purified B cells. Ig allotype analysis revealed that rotavirus-specific IgA was produced by intestinal B cells of recipient origin, suggesting that migration of Ag-presenting B cells from peripheral lymphoid tissues to GALT may contribute to the generation of mucosal IgA responses after parenteral immunization. Strategies that promote Ag uptake and presentation by B cells may enhance mucosal IgA production following parenteral immunization.

We recently developed an animal model to examine the mechanisms by which mucosal Ab-secreting cells (ASC) are induced by nonmucosal immunization. Studies by several groups have shown that Ag-specific IgA-secreting cells that bear the mucosal homing receptor αββ can be detected in the circulation shortly after parenteral inoculation (8, 9). These findings demonstrate that nonmucosal immunizations can induce effector B cells capable of homing to mucosal tissues. However, how and where αββ-bearing ASC are induced by nonmucosal immunization remain obscure. Understanding the mechanisms by which nonmucosal immunizations induce IgA-secreting cells that bear mucosal homing receptors may allow for rational design of vaccines administered by the parenteral route.

Materials and Methods

Mice

Conventionally reared, 5- to 8-wk-old BALB/c (H-2d, Ighb), C.B-17 (H-2d, Ighb), or C57BL/6 (H-2d, Ighb) female mice (Taconic Breeding Laboratories, Germantown, NY), or C.B-17-SCID (H-2d) female mice (Wistar Institute, Philadelphia, PA) were housed in individual isolation units. Before inoculation, sera from these mice did not contain rotavirus-specific Abs as determined by ELISA.
Virus
Murine rotavirus strain EDIM was originally obtained from Richard Ward (Children’s Hospital of Cincinnati, Cincinnati, OH) and passaged in infant mice as previously described (10).

Immunization of donor mice
Adult BALB/c mice were inoculated i.m. bilaterally in the quadriceps femoris muscle with 200 μl per hind leg of EDIM. Mice were inoculated with 2.4 × 10^7 50% shedding dose (equivalent to 18 ng of viral Ag).

Experimental design
Three days after i.m. inoculation of donor mice, draining inguinal lymph nodes (ILN) were harvested and disrupted. Unfractionated or FACS-purified populations of cells were transferred either i.v. (via tail vein infusion) or i.p. in a volume of 200–300 μl to seronegative, adult recipient mice. Two or 6 wk after adoptive transfer, recipient mice were sacrificed and subjected to intestinal and nonintestinal lymphoid cultures were established. Supernatants from lymphoid cultures were subsequently tested for the presence of rotavirus-specific Abs by ELISA.

Isolation of cells
ILN were harvested and then disrupted with 21-gauge needles and 200-μm wire mesh (Small Parts, Miami Lakes, FL) in IMDM (Life Technologies, Grand Island, NY) with 10% FBS (Life Technologies). Cells were passed through a 125-μm cell sieve (Thomas Scientific, Swedesboro NJ), washed three times, and resuspended in IMDM with 10% FBS.

Cell preparation and sorting
Treatment of cells with mitomycin C to block cellular division. Unfractionated ILN cells were diluted to a concentration of 5 × 10^7 cells/ml in PBS and incubated with 50 μg/ml mitomycin C (Sigma, St. Louis, MO) for 20 min at 37°C. Cells were washed three times in IMDM with 10% FBS.

Purification of B cells. Unfractionated ILN cells were diluted to a concentration of 2 × 10^7 cells/ml and incubated for 30 min at room temperature (RT) with 4 μl/ml of mouse anti-mouse Thy1.2 (BioSource International, Camarillo, CA). Cells were washed with IMDM with 10% FBS, 0.3% (w/v) BSA (Sigma), and 20 mM HEPES buffer solution (Life Technologies) (lysis buffer). Cells were then resuspended in 900 μl lysis buffer and 100 μl Low-Tox rabbit complement (Accurate Chemical and Scientific, Westbury, NY) per 2 × 10^7 cells and incubated for 1 h at 37°C. Cells were placed on ice for 5 min, washed with cold lysis buffer, and resuspended in IMDM with 5% FBS. The remaining cells were incubated for 30 min at RT with PE-conjugated rat anti-mouse CD19 (PharMingen, San Diego, CA) at a concentration of 10 μg/10^6 cells. The cells were washed and resuspended in IMDM with 5% FBS. CD19^+ cells were purified by FACS using an EPICS Elite Flow Cytometer (Coulter, Hialeah, FL). This method yielded ≈99.9% CD19^+ cells.

Depletion of macrophages
Macrophages were stained by incubating unfractionated ILN cells with PE-conjugated rat anti-mouse CD11b (PharMingen) for 30 min at RT at a concentration of 2 μg/10^7 cells. Cells were washed and resuspended in IMDM with 5% FBS. Non-CD11b^+ cells were purified by FACS. This method yielded ≈99.8% non-CD11b^+ cells.

Depletion of dendritic cells
Dendritic cells were stained by incubating unfractionated ILN cells with biotin-conjugated mAb 33D1 (a kind gift of Dr. Ralph Steinman, Rockefeller University, New York, NY) (11) for 30 min at RT at a concentration of 2 μg/10^7 cells. The cells were washed and incubated with PE-conjugated streptavidin (PharMingen) for 15 min at RT at a concentration of 0.5 μg/10^7 cells. Cells were washed and resuspended in IMDM with 5% FBS. Non-33D1^+ cells were purified by FACS. This method yielded ≈99.9% non-33D1^+ cells.

Intestinal or nonintestinal lymphoid cultures
To assess the production of virus-specific Abs by intestinal or nonintestinal tissues of recipient mice, lymphoid cultures of ILN, PP, MLN, or small intestinal LP fragments were established 2 or 6 wk after adoptive transfer as previously described (12) with the following modifications. In brief, under sterile conditions ILN, PP, MLN, and small intestines were isolated. MLN, ILN, and PP were washed twice in IMDM containing 50 μg/ml of gentamicin (JRH Bioscience, Lenexa, KS). Segments of small intestine 5 cm in size were opened and washed twice in calcium- and magnesium-free HBSS (Life Technologies) containing 50 μg/ml of gentamicin and 25 mM Hepes (Mediatech, Washington, DC), once in HBSS with 0.05% EDTA to remove villous epithelial cells and intraepithelial lymphocytes, and twice in HBSS. Under a dissecting microscope (×30 magnification) fat, mesenteric, and connective tissue were removed from small intestinal segments. Eight 1 × 1 mm LP fragments from small intestinal segments of each animal were dissected. One LP fragment, MLN, PP, or ILN was placed in a well of a 48-well plate (Costar Scientific, Braintree, MA) containing 0.5 ml of GALT media (Kennet’s HY media (Life Technologies), 100 μg/ml of streptomycin (JRH Bioscience), 50 μg/ml of gentamicin and 0.25 μg/ml of amphotericin B (Fungizone, JRH Bioscience). Samples were incubated at 37°C in an atmosphere of 95% O2 and 5% CO2 for 5 days. Supernatant fluids were collected and tested for the presence of rotavirus-specific Igs (IgM, IgA, and IgG) by ELISA.

Detection of rotavirus-specific and total Igs by ELISA
Sera and supernatant fluids from intestinal and nonintestinal lymphoid cultures were tested for the presence of rotavirus-specific and total IgM, IgA, and IgG (13). Quantities of total IgM, IgA, and IgG were determined to assure the viability of the lymphoid cultures. To determine quantities of rotavirus-specific Abs, individual wells of 96-well, flat-bottom plates (Costar) were coated with either 100 μl PBS (Life Technologies) or 200 ng purified rotavirus diluted in 100 μl of PBS. To determine quantities of total Abs, individual wells of 96-well, flat-bottom plates were coated with either 100 μl PBS or 100 μl goat anti-mouse IgM, IgA, or IgG (Cappel, West Chester, PA) diluted in 1:1,000 in PBS. Plates were incubated for 18 h at 4°C in a humid chamber. Wells were washed 5 times with PBS plus 0.05% Tween-20 (Sigma), blocked with 300 μl of 1% BSA plus 0.025% Tween-20 (BSA-T), and incubated for 1 h at RT. Wells were washed again as above and 50 μl of sera or supernatant fluids diluted in BSA-T were added. Plates were gently rocked for 2 h at RT and washed as above. Fifty microliters of HRP-conjugated goat anti-mouse IgM, IgA, or IgG (Southern Biotechnology Associates, Birmingham, AL) diluted 1:2,000 in BSA-T were added to each well. Plates were incubated for 1 h at RT and washed as above. Fifty microliters of 0.04% tetramethylbenzidine peroxidase solution (Kirkegaard & Perry, Gaithersburg, MD) were added to each well and incubated for 30 min at RT. Wells were washed again as above and 50 μl of 30-mg/ml o-dianisidine dihydrochloride solution (Kirkegaard & Perry, Gaithersburg, MD) were added to each well. Plates were incubated for 1 h at 37°C. Cells were washed and resuspended in IMDM with 5% FBS. CD19^+ cells were purified by FACS using an EPICS Elite Flow Cytometer (Coulter, Hialeah, FL). This method yielded ≈99.9% CD19^+ cells.

Detection of allotype-specific, rotavirus-specific IgA by ELISA
Quantities of rotavirus-specific IgA^a or IgA^b were determined by ELISA using a modification of the technique described above. Following coating, blocking, and addition of sample as described above, 25 ng of biotinylated-mAb specific for mouse IgA^a (HY16) or IgA^b (HISM2) (14) diluted in 50 μl of BSA-T were added to each well and incubated for 1 h at RT. Wells were washed as above and 50 μl of streptavidin-HRP conjugate (Pharmingen) diluted 1:2,000 in BSA-T was added. Plates were developed, and quantities of Abs were determined as described above.

Results
Adaptive transfer of unfractionated cells from draining lymph nodes of i.m.-immunized mice induces rotavirus-specific Ab production by GALT of recipient mice
To determine whether cells resident in draining peripheral lymph nodes after i.m. immunization with rotavirus were capable of inducing mucosal humoral immune responses, 2 × 10^7 unfractionated cells harvested from draining ILN were transferred into naive syngeneic mice. Repeated analysis by flow cytometry demonstrated that unfractionated cell populations contained ~58–73%...
CD3+, 12–21% CD19+, 7–11% CD11b+, and <1% 33D1+ cells (data not shown). Two weeks after adoptive transfer, cultures of intestinal and nonintestinal lymphoid tissues from recipient mice were established. Supernatant fluids from these cultures were tested for the presence of virus-specific IgGs. Rotavirus-specific IgM, IgA, and IgG were present in GALT cultures 2 wk after unfractionated cells were transferred i.p. into naive recipient mice (Table I). Previously performed kinetic studies demonstrated that IgG detected in supernatant fluids of lymphoid cultures were generated in vitro and did not arise from passive transudation of serum-derived Abs (12, 15). Likewise, virus-specific IgA was not detected in sera from recipient animals (data not shown). Similar quantities of virus-specific IgM, IgA, and IgG were detected in GALT cultures following i.v. adoptive transfer of 2 × 10^7 unfractionated cells (data not shown). Virus-specific IgM and IgG were also produced by draining ILN. Virus-specific Abs were not produced by intestinal or nonintestinal lymphoid tissues from recipient mice inoculated i.p. with 2 × 10^7 cells harvested from immunized donor mice (data not shown).

To verify that free rotavirus was not transferred with unfractionated cells, mice were inoculated i.p. with 200 μl of supernatant fluids obtained from the first, second, or third cell washings. Two weeks after inoculation, rotavirus-specific Abs were not detected in sera or supernatant fluids from either intestinal or nonintestinal lymphoid tissues (data not shown).

**Production of rotavirus-specific IgM and IgA by intestinal lymphocytes is short-lived following adoptive transfer; conversely, production of virus-specific IgG persists for at least 6 wk**

To determine the duration of virus-specific Ab production by GALT after adoptive transfer, we established lymphoid cultures 6 wk after transfer of 2 × 10^7 unfractionated cells into naive recipient mice. Six weeks after cell transfer, virus-specific IgG was still produced by intestinal lymphocytes, although at reduced quantities than observed at 2 wk (Table II). However, neither virus-specific IgM nor IgA were produced by LP, PP, or MLN 6 wk after transfer.

**Rotavirus-specific Abs are produced by GALT lymphocytes after adoptive transfer of APCs**

To evaluate the role of APCs in the generation of intestinal humoral immunity following i.m. immunization, unfractionated ILN cells from recently i.m.-immunized BALB/c mice were treated with the radiomimetic agent, mitomycin C. Virus-specific IgG was produced by intestinal lymphocytes following adoptive transfer into naive BALB/c recipient mice (Table III). Similarly, no virus-specific IgA was produced by intestinal lymphoid tissues of SCID mice following adoptive transfer of 2 × 10^7 unfractionated cells harvested from the ILN of recently i.m.-immunized BALB/c mice (data not shown).

**Rotavirus-specific IgA, but not IgG, is produced by GALT lymphocytes after adoptive transfer of purified B cells**

To evaluate the contribution of adoptively transferred B cells to the generation of intestinal humoral immunity, 2 × 10^6 purified B cells derived from the ILN from i.m.-immunized donor mice were transferred into naive recipient mice. Two weeks after transfer, only virus-specific IgA was produced by PP, MLN and LP (Table IV). Rotavirus-specific IgM and IgG were not produced by intestinal lymphocytes.

**Ag-presenting B cells induce intestinal rotavirus-specific IgA production by GALT after i.m. immunization**

To determine whether adoptively transferred B cells were expanding and differentiating into virus-specific IgA-secreting cells or functioning as APCs, the following experiment was performed: 2 × 10^7 unfractionated cells from i.m.-immunized BALB/c mice were injected intraperitoneally into naive recipients, and supernatants were tested by ELISA for the presence of rotavirus-specific Abs. This experiment was performed twice with similar results.
notype), but not IgA a (donor phenotype), was produced by intestinal tissues after adoptive transfer, intestinal and nonintestinal lymphoid cultures from recipient mice were established. Supernatants were tested by ELISA for the presence of rotavirus-specific IgA a and IgA b. This table includes data from two consecutive experiments.

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<th>Site</th>
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a Draining peripheral lymph node cells were harvested from donor BALB/c mice 3 days after i.m. immunization with murine rotavirus strain EDIM. Unfractionated cells were incubated with mouse anti-mouse Thy1.2 and rabbit complement. The remaining cells were stained with PE-conjugated rat anti-mouse CD11b and CD19 cells were purified by FACS (purity >99.9%). A total of 2 × 10^6 cells per mouse were transferred i.p. to three naive, adult BALB/c mice. Two weeks after adoptive transfer, intestinal and nonintestinal lymphoid cultures from recipient mice were established. Supernatants were tested by ELISA for the presence of rotavirus-specific IgA a and IgA b. This table includes data from two consecutive experiments.

**Migratory pathways of virus-containing macrophages and dendritic cells**

Migration of virus-containing macrophages and dendritic cells may lead to the generation of rotavirus-specific IgG-secreting cells in GALT

To determine the contribution of macrophages or dendritic cells to the generation of intestinal humoral immune response after i.m. immunization, ILN cells from i.m.-immunized mice were depleted of either macrophages (CD11b-bearing cells) or dendritic cells (33D1-bearing cells) by FACS. A total of 1.7 × 10^6 non-CD11b- or 1.4 × 10^6 non-33D1-bearing cells were transferred into naive recipient mice, and 2 wk later lymphoid cultures were established. Virus-specific IgG was not detected after transfer of cells depleted of either macrophages (Table VII) or dendritic cells (Table VIII). However, small quantities of virus-specific IgA were produced by GALT of recipient mice despite depletion of either macrophages or dendritic cells from adoptively transferred cells.

**Discussion**

We found that adoptive transfer of cells from the draining peripheral lymph nodes of mice recently immunized i.m. with rotavirus induced virus-specific Ab production by intestinal lymphocytes of naive recipient mice. In addition, we demonstrated that populations of rotavirus-specific intestinal lymphocytes that produced virus-specific IgG...
IGA, as compared with IgG, were generated by different classes of APCs and had different life spans. Following i.m. immunization with murine rotavirus, B cells derived from peripheral lymph nodes functioned as APCs and stimulated a short-lived virus-specific IgA response in GALT. Conversely, either macrophages or dendritic cells or both appeared to induce a longer-lived intestinal IgG response.

The quantities of virus-specific IgGs produced by GALT following adoptive transfer of purified cell populations were less than those produced following transfer of unfraccionated cells. Likewise, smaller quantities of virus-specific Abs were produced following adoptive transfer of mitomycin C-treated, as compared to untreated, cells. These findings suggest that multiple cell types may be responsible for the generation of mucosal virus-specific IgA following i.m. immunization. Although we have shown that adoptively transferred B cells harvested from donor lymph nodes three days after i.m. immunization can function as APCs and induce intestinal IgA production, the time of cell harvest may have biased against identification of activated B cells that were also capable of inducing mucosal IgA responses. We are currently exploring the contributions of donor-derived CD4+ T cells and activated B cells in this system.

Using IgA-allotype-specific reagents we found that intestinal rotavirus-specific IgA responses were induced by Ag-presenting B cells present in adoptively transferred cells. Following adoptive transfer of congenic purified B cells, virus-specific IgA produced by intestinal tissues was of the recipient, not donor, phenotype. In addition, adoptive transfer of MHC-incompatible B cells failed to induce production of virus-specific Abs, indicating that rotavirus does not bind nonspecifically to murine B cells. In this system, B cells resident in draining peripheral lymph nodes 3 days after primary i.m. immunization, appeared to be capable of virus uptake, processing, and presentation to naive CD4+ T cells. To be effective APCs, B cells must meet three requirements: uptake of Ag, presentation of peptide in the context of MHC molecules, and expression of costimulatory molecules. Although the efficiency of Ag presentation by Ag-primed B cells has been described (16–20), naive B cells may also function as APCs (21). Naive B cells may take up Ag either specifically, by endocytosis of Ag bound to membrane Ig (mIg), or nonspecifically, by pinocytosis. Although in a naive animal the B cell precursor frequency for a given Ag may be presumed to be low, Milich et al (21) found that less than 3 x 10^3 activated, or 2 x 10^4 resting, splenic B cells were capable of activating hepatitis B core Ag-specific T cell hybridomas in the presence of hepatitis B core Ag. Low-affinity binding of multivalent Ag to mIg may explain the unexpectedly high frequency of Ag-presenting naive B cells observed (21). Similarly, recent work by DalPorto et al. (22) demonstrated that B cells with low-affinity mIg may bind Ag and participate in humoral immune responses. The mechanism by which rotavirus is taken up by naive B lymphocytes is unknown. Rotavirus is not known to infect lymphocytes. The redundant expression of two viral surface proteins on intact rotavirus capsids may facilitate virus uptake by mlg on non-immune B cells. Alternatively, Ag uptake by pinocytosis may occur. However, nonspecific uptake of Ag has been shown to be less efficient than receptor-mediated binding and internalization, and requires much higher concentrations of Ag and longer times for Ag uptake (21). Using limiting dilutions of B cells and virus, we are currently examining the mechanism by which naive B cells resident in peripheral lymph nodes take up rotavirus. In addition to providing cognate interaction between the TCR and surface MHC-peptide complexes, B cells must also express costimulatory molecules to activate naive CD4+ T cells and initiate T cell-dependent humoral immune responses (23). Expression of CD80 and CD86 by naive B cells has been shown to be induced by Ag-specific binding to mlg in vivo (17) and in vitro (21, 24, 25). Thus, i.m. immunization with rotavirus may induce expression of costimulatory molecules on naive B cells after binding and internalization of rotavirus through mlg. By adoptive transfer of B cells that do or do not express costimulatory molecules we hope to define the role of B7 expression in the induction of mucosal virus-specific IgA production in this system.

Our findings suggest that intestinal virus-specific ASC generation by i.m. immunization may be induced by Ag-bearing APCs that migrate from the draining peripheral lymph node to GALT. Once in intestinal inductive tissues, such as PP or MLN, these rotavirus-bearing APCs may participate in the activation of naive B and T cells with subsequent generation of virus-specific effector B cells that express the mucosal homing receptor α4β7. Kantele et al. (9) and Quiding-Jabrink et al. (8) demonstrated that Ag-specific α4β7-bearing IgA-secreting cells circulate 7–10 days after parental immunization. By isolating α4β7-bearing B cells from intestinal and nonintestinal tissues we hope to identify the site of origin of virus-specific IgA-secreting cells following i.m. immunization. Although B cells acting as APCs induced the production of virus-specific IgA in recipient mice, either macrophages or dendritic cells or both appeared to be responsible for the induction of intestinal virus-specific IgG production. At present we are unable to distinguish the relative contributions of highly purified populations of macrophages and dendritic cells; adoptive transfer of cell populations depleted of either CD11b+ or 33D1+ cells resulted in virtually identical profiles of intestinal rotavirus-specific Ab production. Because CD11b is expressed by a subpopulation of dendritic cells resident in peripheral lymph nodes (26), rotavirus-bearing dendritic cells may have been inadvertently excluded from our macrophage-depleted cell preparations.

The differential induction of virus-specific IgA or IgG by different types of APCs suggests that the profile of cytokines produced by individual naive CD4+ T cells may be influenced by APC type. Using in vitro models of APC-CD4+ interactions, several investigators found that Ag presentation by B cells induced production of Th2 effector cytokines such as IL-4 (27–31) but not Th1 cytokines such as IL-2 (32) or IFN-γ (30). Conversely, macrophages and dendritic cells may preferentially induce Th1 responses. T cell clones have been shown to be more responsive to stimulation from splenic macrophages and dendritic cells than B cells (27). However, numerous studies suggest that patterns of cytokine production by CD4+ T cells may not be predicted simply by the class of stimulating APC. First, factors such as the nature of the

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a Draining peripheral lymph node cells were harvested from donor BALB/c mice 3 days after i.m. immunization with murine rotavirus strain EDIM. Unfractionated cells were stained with biotinylated-αt anti-mouse 33D1. Non-33D1-bearing cells were purified by FACs (purity > 99.9%). A total of 1.4 x 10^7 cells per mouse were transferred i.p. to two naive, adult BALB/c mice. Two weeks after adoptive transfer, intestinal and nonintestinal lymphoid cultures from recipient mice were established. Supernatants were tested by ELISA for the presence of rotavirus-specific Abs.

b Mean quantity of Ab detected (in ng/ml) ± SEM.
Ag (16, 33, 34), dose of the Ag (35), route of Ag administration (35), and number of CD4+ T cell divisions stimulated by antigenic exposure (36) have all been shown to influence the T cell cytokine repertoire. Second, the anatomic source of dendritic cells (37, 38) may influence the outcome of APC-T cell interactions. Schrader et al. (39) demonstrated that both mucosally and systemically derived dendritic cells induced IgA production in vitro, whereas Spaulding et al. (40) found IgA production was preferentially supported by PP as compared with splenic dendritic cells. Finally, differences in cytokine profiles may be influenced by the anatomic site where APC-CD4+ interactions occur (39).

We found that production of intestinal rotavirus-specific IgA, as compared with IgG, was short-lived following adoptive transfer of unfractionated cells. Although controversial, persistence of Ag may be necessary to maintain Ag-specific, ASC populations (41, 42). Thus, the transient presence of intestinal virus-specific IgA-secreting B cells may reflect a relative inability of B cells displaying rotavirus peptide-MHC complexes to persist in intestinal lymphoid tissues as compared with either macrophages or dendritic cells. Although Ag-bearing dendritic cells have been shown to persist for over 100 days in germinal centers (43), the life span of Ag-presenting B cells is not known.

Pathogen-specific mucosal IgA plays a critical role in mucosal defense. Nonmucosal inoculation has previously been shown to induce mucosal IgA responses (11, 15, 44, 45). We have extended our understanding of how nonmucosal immunization induces mucosal immunity by demonstrating that intestinal IgA production can be induced by nonimmune, Ag-presenting B cells found in the draining peripheral node after i.m. immunization. However, the transient nature of Ag-specific, intestinal IgA induced by parental immunizations may explain a major shortcoming of these vaccines, namely the need for booster dosing to maintain mucosal protection. Strategies that increase the number of functional life span of Ag-presenting B cells may augment the magnitude and duration of mucosal IgA responses and thus enhance the efficacy of parenterally administered vaccines.

Acknowledgments

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References


