B Lymphocytes Regulate Dendritic Cell (DC)
Function In Vivo: Increased Interleukin 12
Production by DCs from B Cell–deficient Mice
Results in T Helper Cell Type 1 Deviation

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Abstract
Increasing evidence indicates that dendritic cells (DCs) are the antigen-presenting cells of the primary immune response. However, several reports suggest that B lymphocytes could be required for optimal T cell sensitization. We compared the immune responses of wild-type and B cell-deficient (μMT) mice, induced by antigen emulsified in adjuvant or pulsed on splenic dendritic cells. Our data show that lymph node cells from both control and μMT animals were primed, but each released distinct cytokine profiles. Lymph node T cells from control animals secreted interferon (IFN)-γ, interleukin (IL)-2, and IL-4, whereas those from μMT mice produced IFN-γ and IL-2 but no IL-4. To test whether B cells may influence the T helper cell type 1 (Th1)/Th2 balance by affecting the function of DCs, we immunized mice by transferring antigen-pulsed DCs from wild-type or mutant mice. Injection of control DCs induced the secretion of IL-4, IFN-γ, and IL-2, whereas administration of DCs from μMT animals failed to sensitize cells to produce IL-4. Analysis of IL-12 production revealed that DCs from μMT mice produce higher levels of IL-12p70 than do DCs from wild-type animals. These data suggest that B lymphocytes regulate the capacity of DCs to promote IL-4 secretion, possibly by downregulating their secretion of IL-12, thereby favoring the induction of a nonpolarized immune response.

Keywords: T helper cell type 1/type 2 balance • primary response • interleukin 4 • interleukin 10 • dendritic–B cell interaction

Introduction
The specificity, amplitude, and character of an immune response are determined early on, at the stage of antigen presentation. Among the population of APCs, which includes dendritic cells (DCs), B lymphocytes, and macrophages, DCs have the unique capacity to sensitize naive T cells (for review see reference 1) and are considered the sentinels that switch on the immune system at the appropriate "danger" signal. This property correlates with several unique features, including high expression of MHC and costimulatory molecules, motility, efficient antigen capture and processing, specialization of function over time, production of T cell–activating cytokines, etc.

Injection of splenic DCs pulsed extracorporeally with antigen, induces the development of Th cells secreting a large array of cytokines (IL-2, IFN-γ, IL-4, IL-5, and IL-10) in syngeneic animals. The capacity of DCs to direct the development of selected Th populations has been shown to be modulated by pathogens, cytokines, and other environmental factors (2). In particular, we have shown that DCs may induce the development of Th0 (or Th1 and Th2) lymphocytes in a neutral environment, and the differentiation of a polarized Th1 or Th2 population in the presence of IL-12 or IL-10, respectively (3).

The role of B cells (which represent the most abundant APC population) in T cell priming is still controversial. Several studies have revealed a critical role for B cells in the
T cell response in vivo (4–6). These results were challenged by reports showing that the absence of B cells had little impact on T cell responsiveness (7, 8). More recently, a few studies have suggested that B cells are not required for T cell sensitization but play an essential role in the induction of IL-4 gene expression by T lymphocytes (9, 10).

In this study, we compared the development of antigen-specific responses in B cell-deficient and wild-type mice. Our data demonstrate that the development of IL-4-secreting cells was impaired in the absence of B lymphocytes. We further determined that DCs from B cell-deficient mice had a reduced capacity to induce IL-4 production. These observations suggest that B lymphocytes regulate the Th1/Th2 polarized effector function of DCs in vivo.

Materials and Methods

Mice. C57BL/10, C57BL/6, and 10-lgh-6^{tm1Cgn} (B cell-deficient, or μMT, mice; reference 11) and C57BL/10-III^{tm1Cgn} (IL-10-deficient; reference 12) mice were purchased from The Jackson Laboratory. Some C57BL/6 mice were purchased from Charles River Laboratories. All animals were maintained in our pathogen-free facility and used at 8–12 wk of age.

Culture media. The medium used for the isolation of DCs was RPMI 1640 (Seromed; Biochem KG) supplemented with 2% HY (Utroser HY; Life Technologies) and additives Lympnh node cells from mice injected with KLH in CFA or KLH-pulsed DCs were cultured in Clik’s medium (Invirion Scientific) supplemented with 0.5% heat-inactivated FCS or mouse serum, respectively, and additives.

Antigen, Antibodies, and Cytokines. The antigen used was KLH from Calbiobiochem-Novoavibiochem. The following antibodies were used in this study: anti-Thy 1.2 (HOT134; American Type Culture Collection, or ATCC), anti-I-A^b (25.9.17; ATCC), anti-heat-stable antigen (anti-HSA; ATCC), anti-FcγR (2.4G2; ATCC), anti-CD45R/B220 (RA3-6B2; PharMingen), rat anti–IL-12 p40; provided by Dr. Presky, Hoffmann-LaRoche, Catholique de Louvain, Brussels, Belgium), 5D9 and 5C3 (rat mouse IgG2a (LO-MG2a-7; provided by H. Bazin, Université ATCC), anti-CD45R/B220 (RA3-6B2; PharMingen), rat anti–heat stable antigen (anti-HSA; ATCC), anti-FcγR, anti-CD45R/B220, and anti-IL-12 p40; provided by Dr. Presky, Hoffmann-LaRoche, Catholique de Louvain, Brussels, Belgium), 5D9 and 5C3 (rat mouse IgG2a (LO-MG2a-7; provided by H. Bazin, Université ATCC), anti-CD45R/B220 (RA3-6B2; PharMingen), rat anti–heat stable antigen (anti-HSA; ATCC), anti-FcγR, anti-CD45R/B220, and anti-IL-12 p40; provided by Dr. Presky, Hoffmann-LaRoche, Catholique de Louvain, Brussels, Belgium), 5D9 and 5C3 (rat mouse IgG2a (LO-MG2a-7; provided by H. Bazin, Université ATCC), anti-CD45R/B220 (RA3-6B2; PharMingen), rat anti–heat stable antigen (anti-HSA; ATCC), anti-FcγR, anti-CD45R/B220, and anti-IL-12 p40; provided by Dr. Presky, Hoffmann-LaRoche, Catholique de Louvain, Brussels, Belgium).

PCR Analysis of IL-10 Gene Expression. RNA was extracted from splenocytes from untreated C57BL/6, μMT, or anti-CD3-injected C57BL/6 mice, from B cell-enriched CD19^{+} C57BL/6 spleen cells, and from T cell hybridoma 3814.15 using the Trt type reagents (Boehringer). The CD19^{+} cells were enriched from spleen cells by incubation with anti-CD19-coupled microbeads and positive selection over a MACS column (Miltenyi Biotech). After preparation of CDNA, PCR was performed essentially as previously described (16). Reactions were incubated in a PerkinElmer Cetus DNA thermal cycler for 30 cycles for IL-10 gene expression and 24 cycles for housekeeping HPT gene expression (denaturation: 30 s, 94°; annealing: 1 min, 57°C; extension: 1 min, 72°C). Primers used were as follows: IL-10 sense primers: 5'-TCAAACAAAGGACCAGCTTGGACACATACTGC-3' and antisense 5'-CTGTCTAGGCCTGGGACAGCCACAGCT-CAA-3' (amplified fragment of 421 bp). HPT sense primer 5' -GGTGGATACACGGCAACAGCTTTTG-3' and antisense 5' -GAATTTCAACTTGCGCTCATCTTAGGC-3' (amplified fragment of 163 bp).

Production of IL-12 by DCs. Purified DCs (see above) were cultured in medium alone (RPMI 1640 supplemented with 5% FCS) or in the presence of 3T3 fibroblasts transfected or not with CD40L. The supernatants were assayed for IL-12 p40 after 48 h using a two-site ELISA (3). IL-12 p70 production was monitored on 72 h supernatants by a bioassay based on the ability of IL-12 to enhance and diversify the polarity of TH1 responses (denaturation: 30 s, 94°; annealing: 1 min, 57°C; extension: 1 min, 72°C). Primers used were as follows: IL-10 sense primers: 5'-TCAAACAAAGGACCAGCTTGGACACATACTGC-3' and antisense 5'-CTGTCTAGGCCTGGGACAGCCACAGCT-CAA-3' (amplified fragment of 421 bp). HPT sense primer 5'-GGTGGATACACGGCAACAGCTTTTG-3' and antisense 5'-GAATTTCAACTTGCGCTCATCTTAGGC-3' (amplified fragment of 163 bp).

Results

Responses of T Cells in B Cell–Deficient and B Cell–Sufficient Mice to KLH. We first compared the immune response of mice that are genetically deficient for B lymphocytes (μMT mice) and their control littermates, μMT and wild-type mice were injected in the footpads with KLH emulsified in CFA and the
draining lymph nodes were harvested 5 d later. The data in Fig. 1 indicate that KLH-specific T cells were primed in both groups of mice, as assessed by KLH-dependent proliferation in culture. Of note, the analysis of the cytokines released by lymph node cells revealed a differential T helper development in MT versus control mice. T lymphocytes from wild-type mice secreted IFN-γ and IL-4 when re-challenged with KLH in vitro, whereas T cells from MT mice produced higher levels of IFN-γ but no detectable IL-4 in the same conditions. These observations indicate that B lymphocytes are dispensable for T cell priming but are required for the development of IL-4–secreting cells.

Impaired Ability of DCs from MT Mice to Promote IL-4 Secretion. There is increasing evidence that the cell that presents the antigen to T cell may influence the Th1/Th2 balance in vivo. In particular, injection of splenic DCs has been shown to induce the activation of T cells that secrete a large array of cytokines (3, 17). Because DCs are the
production in addition to other cytokines. IL-4, whereas DCs from control mice prime for IL-4 production by T cells. The data in Fig. 3 show that DCs from wild-type and IL-10–deficient mice produce higher levels of IL-12 and have the capacity to promote Th2-type responses. We measured the level of IL-12 mRNA in unstimulated spleen cells from both strains of mice. The data in Table I show that the proportion of DC subsets is similar in both strains of mice.

Role of the Microenvironment. To test whether the microenvironment in which priming of T cells occurs may influence the character of the immune response, KLH-pulsed DCs from wild-type animals were transferred into control and B cell–deprived recipient mice. As shown in Fig. 5, immunization of μMT mice resulted in sensitization of cells producing high levels of IFN-γ and lower levels of IL-4, whereas priming of wild-type mice induced lower IFN-γ and higher IL-4 production. Evidence that T cells from μMT mice have the capacity to produce IL-4 is provided by the observation that injection of Th2-prone, IL-10–deficient DCs into μMT mice results in the development of IL-4–secreting cells (Table II).

Table I. Analysis of DC Subsets

| Wild-type mice | μMT mice |
|----------------|----------|
| CD8α− | CD8α+ | CD8α− | CD8α+ |
| 1 | 64.8 | 35.2 | 67.8 | 32.2 |
| 2 | 60.0 | 40.0 | 75.0 | 25.0 |
| 3 | 80.6 | 19.4 | 78.1 | 21.9 |
| 4 | 83.0 | 17.0 | 70.7 | 29.3 |

Low density spleen cells from FLT3L-injected (1 and 2) or untreated (3 and 4) mice were double stained for CD8α expression using PE-conjugated anti-CD8α mAb and for CD11c expression using FITC-conjugated N418. The data represent the percentage of CD8α− and CD8α+ cells among DCs (gated for N418 expression).
Discussion

The results reported here show that B lymphocytes have a profound regulatory effect on the antigen-presenting function of DCs in vivo. Indeed, DCs from B cell-deprived animals have an impaired capacity to induce antigen-specific differentiation of IL-4-secreting T cells when transferred in control animals. The diminished IL-4-promoting capacity of DCs correlates with an enhanced production of IL-12. These observations suggest that B lymphocytes interact with DCs and lower the level of IL-12 released by DCs, thereby leading to priming of both Th1 and Th2 lymphocytes. Of note, it has been shown that interactions between DCs and B cells may occur regularly during B cell recirculation. The interaction is thought to be confined to small B cells, is totally T cell and antigen independent, and is not MHC restricted (20). Furthermore, cooperation between DCs and B lymphocytes has been demonstrated by Dubois et al. (21), who showed that in vitro-generated DCs promote the proliferation of naive and CD40-activated B cells and produce factors that induce differentiation of activated B cells into plasma cells. Our observations show that a bidirectional regulation occurs upon DC-B cell interaction.
Although we do not have direct evidence, several features suggest that IL-10 may be involved in this immunoregulatory process: splenocytes from μMT mice express reduced levels of IL-10 mRNA than wild-type animals; DCs from IL-10 knockout mice display properties similar to DCs from μMT mice, i.e., they have lost the capacity to induce the development of IL-4–secreting cells; treatment of DCs from μMT mice with IL-10 restored the generation of IL-4–producing cells in vivo; and numerous reports have shown that IL-10 inhibits the production of IL-12 heterodimer by DCs in vitro and in vivo (3, 10). Collectively, these observations suggest that the level of IL-12 released by DCs is regulated by B lymphocytes, presumably via the production of IL-10. Our data show that B lymphocytes may produce IL-10 constitutively. B cell–depleted spleen cells also express mRNA for IL-10 (data not shown), suggesting that other cell populations may indirectly control the level of IL-12.

Table II. IL-10–treated DCs Induce T Cells from μMT Mice to Secrete IL-4

| Recipient: Control mice | μMT mice |
|------------------------|----------|
| Injected with: U n t r e a t e d D C s | U n t r e a t e d D C s | I L - 1 0 - t r e a t e d D C s |
|------------------------|------------------|-----------------|
| Exp. 1                 |                  |                 |
| 1                      | 305.4 ± 3.1      | 80.6 ± 3.1      |
| 2                      | 187.7 ± 0.8      | N ot detectable |
| Exp. 2                 |                  |                 |
| 1                      | 593.3 ± 73.4     | 63.7 ± 35.6     |
| 2                      | 204.4 ± 8.3      | 45.3 ± 0.5      |

Secretion of IL-4 (in pg/ml) by lymph node T cells. Untreated or IL-10–treated DCs from wild-type mice were pulsed in vitro with KLH (50 μg/ml) and injected into the fore and hind footpads of control or μMT mice. 6 d later, lymph node cells were harvested and cultured with 5 μg/ml KLH and the IL-4 content was assessed by ELISA. Exp. indicates the experiment number; the indented numbers refer to individual mice. Limit for detection is 31.25 pg/ml.
Wykes et al. (23) have shown that DCs can retain unprocessed antigen and directly interact with B lymphocytes to initiate antibody synthesis. Thus, B cells recognizing the antigen expressed by DCs form short-lived clusters and could give regulatory signals to the transferred DCs. Alternatively, direct B to T cell signaling may promote IL-4 synthesis in this experimental model. It is noteworthy that T cells from μMT mice have the capacity to produce IL-4, as T cells from μMT mice produced high amounts of IL-4 in response to Schistosoma mansoni eggs (8) or O noktara virus (24). The capacity of T cells from μMT mice to secrete IL-4 is further illustrated by the observation that injection of DCs that have been treated with IL-10 to enhance their capacity to promote Th2 development (3) induces the production of significant levels of IL-4 in μMT recipient mice (Table II).

We and others have reported that subclasses of DCs directed the development of distinct helper cells in vivo (18, 19). Thus, CD8α- and CD8α+ DCs, purified from spleens, have the potential to differentially regulate the Th1/Th2 balance: CD8α- DCs induced the activation of cells secreting high levels of IL-4, IL-5, and IL-10, and low levels of IL-2 and IFN-γ, whereas CD8α+ DCs sensitize cells producing IL-2 and IFN-γ, but little IL-4, IL-5, or IL-10. We therefore compared the numbers of DCs of either subset in μMT and wild-type mice. Little difference was found between these strains, suggesting that B lymphocytes did not alter the distribution of DC subsets (Table I). Of note, the number of DCs was consistently reduced (by approximately twofold) in B cell-deprived mice as compared with wild-type animals, an observation that may result from a lack of survival or maturation signals and/or chemotaxin factors such as B cell–derived chemokines macrophage inflammatory protein (MIP)-1α and MIP-1β (25). Our results are consistent with the observations of Stockinger et al. (10) that the B cell is the crucial APC for the development of Th2 responses. Stockinger et al. also recently identified a feedback loop triggered by IL-12 that promotes Th2 differentiation (26). Thus, delivery of IL-12 by DCs during B cell activation induces the secretion of IL-6 and IL-10 by activated B cells. IL-6 and IL-10 confer the capacity to induce IL-4 expression in T cells to these B lymphocytes. These data were interpreted to indicate that DCs, through IL-12 secretion, enhance the ability of B cells to influence T cell differentiation toward Th2. Our data further extend these observations by showing that DCs themselves, after interaction with B cells, show higher IL-4-inducing activity.

Interestingly, our results may shed new light on the enigmatic observation that μMT mice showed enhanced CTL activity to tumor cells in comparison to their control littermates (27). Qin et al. reported that the presence of B cells in the priming phase resulted in disabled help for CTL-mediated tumor immunity, and interpreted these data by a competition between B cells and other APCs for antigen. Our data suggest that the absence of B cells may enhance the generation of tumor immunity by promoting a polarized Th1 response.

In conclusion, our observations suggest that at the steady state level, IL-10 released by B lymphocytes may control the level of IL-12 released by DCs, which upon encounter with an antigen would induce an unpolarized immune response. In addition, there is evidence that presentation of antigen by B lymphocytes may preferentially direct the development of Th2-type cells (28, 29). Therefore, B cells may directly (upon interaction with T cells) or indirectly (by controlling IL-12 production via DCs) favor the development of Th2-type cells that provide helper activity for antibody synthesis, thereby promoting their own effector function.

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