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*J Immunol* 2000; 165:5338-5344; doi: 10.4049/jimmunol.165.9.5338

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Human Double-Negative T Cells in Systemic Lupus Erythematosus Provide Help for IgG and Are Restricted by CD1c

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To understand the mechanism of T cell help for IgG production in systemic lupus erythematosus (SLE) we investigated the response of CD4- and CD8-negative (double-negative (DN)) T cells because 1) DN T cells are present at unusually high frequency in patients with SLE and can induce pathogenic autoantibodies; 2) the DN T cell repertoire includes cells restricted by CD1 Ag-presenting molecules; and 3) CD1c is expressed on a population of circulating B cells. We derived DN T cell lines from SLE patients and healthy individuals. In the presence of CD1c+ APCs, DN T cell lines from SLE patients produced both IL-4 and IFN-γ, whereas DN T cells from healthy donors produced IFN-γ but no IL-4. In general, cells from patients with highly active disease produced high levels of IFN-γ; cells from those with little activity produced high IL-4. Coculture of CD1c-directly reactive T cells from healthy donors with CD1c+ B cells elicited IgM Abs, but little or no IgG. In contrast, CD1c-directly reactive T cells from SLE patients induced isotype switching, with a striking increase in IgG production. Neutralizing Abs to CD1c inhibited the ability of DN T cells to induce IgG production from CD1c+ B cells, further indicating that CD1c mediated the T and B cell interaction. IgG production was also inhibited by neutralizing Abs to IL-4, correlating with the cytokine pattern of DN T cells derived from these patients. The data suggest that CD1c-restricted T cells from SLE patients can provide help to CD1c+ B cells for IgG production and could therefore promote pathogenic autoantibody responses in SLE. The Journal of Immunology, 2000, 165: 5338–5344.

Systemic lupus erythematosus (SLE) is characterized by Ab production against nonprotein self-Ags, including nucleic acids and phospholipids. Some of these autoantibodies are associated with disease severity. Autoantibody responses in SLE are T cell dependent, as evidenced by studies demonstrating a decrease in the incidence of SLE in T cell-depleted lupus-prone mice and HIV-infected individuals (1–4). Furthermore, T cells that recognize self-Ags have been shown to provide help for autoantibody production, causing IgM-producing B cells to undergo class switching into pathogenic IgG-producing B cells (5, 6). Since the model of cognate recognition holds that B cells internalize, process, and present peptide Ags to T cells to recruit help for isotype switching, the mechanism by which T cell-dependent Ab responses are generated against nonpeptide Ags is a vital question in understanding SLE pathogenesis.

Insight into the nature of T and B cell interactions in SLE has come from the study of CD4+ , CD8+ (double-negative (DN)) T cells. The frequency of DN T cells is increased in SLE (5), particularly those with active disease, suggesting that these T cells are involved in the pathogenesis of the disease. DN T cells from SLE patients have been shown to provide help for Ab production against DNA in an MHC-unrestricted manner (5, 7). We reasoned that the T helper activity of DN T cells might be mediated by CD1 because the DN T cell repertoire contains CD1-restricted T cells (8–10). CD1 presents nonpeptide Ags to T cells (9, 11–15), and CD1c is expressed on B cells (16).

To determine the mechanism by which DN T cells in SLE promote IgG production, we derived DN T cell lines from SLE patients and evaluated their function compared with that of DN T cells from healthy individuals. DN T cell lines from both SLE patients and healthy donors were restricted by CD1c, but the cytokine patterns produced by the DN T cells were distinct, in that SLE DN T cells produced IL-4 and IFN-γ, whereas DN T cells from healthy donors produced high levels of IFN-γ, but no IL-4. DN T cells from SLE donors induced isotype switching to IgG from B cells in a CD1c-restricted manner. T cell help for IgG production from CD1c+ B cells required IL-4, correlating with the cytokine pattern produced by the DN T cells from these patients. The data suggest that CD1c-restricted T cells from SLE patients can provide help to CD1c+ B cells for IgG production and therefore might promote pathogenic autoantibody responses in SLE.

Materials and Methods
Patients and clinical specimens

Lupus patients were recruited on a volunteer basis from the ambulatory population seen at the Rheumatology Clinics at the University of California-Los Angeles and Albert Einstein College of Medicine (New York, NY) Medical Centers. Twenty SLE patients were studied. All fulfilled the updated American College of Rheumatology criteria for classification as SLE (17, 18). The age of the patients ranged from 13 to 68 years, with a mean...
of 39.1 years. Eighteen patients were female; two were male. Ethnically, six were White (30%), five were African American (25%), eight were Hispanic (40%), and one was Asian (5%). The duration of disease ranged from 1 to 25 years (mean, 8.7 years). Eleven of the patients had lupus glomerulonephritis during the course of their illness; two had active nephritis at the time cells were obtained. Twelve of the 20 had Abs to DNA. The number of American College of Rheumatology criteria present at any time during illness ranged from 4 to 11 (mean, 5.4). Disease activity at the time cells were obtained was estimated using the SLE disease activity index (SLEDAI) (19). SLEDAI scores ranged from 1 to 18 (mean, 7.6). Daily prednisone doses at the time blood was obtained ranged from 0 to 40 mg/day (mean, 15.1). Six of the 20 patients were receiving cytotoxic drugs at the time of study. Characteristics of the healthy control group were: mean age, 32 years; gender, 57% female and 43% male; and ethnicity, 43% white, 43% Hispanic, and 14% Asian. None of the healthy individuals was taking medications at the time of donation. Blood samples for isolation of PBMCs were obtained by venipuncture from patients and from healthy volunteer laboratory personnel who served as control subjects. PBMCs were isolated using Ficoll-Hypaque gradient centrifugation (Ficoll-Paque, Pharmacia, Upplasa, Sweden).

Antibodies

The following Abs were used for flow cytometry and neutralizing CD1-restricted T cell responses (IgG controls; Sigma, St. Louis, MO), OKT6 (anti-CD1a; American Type Culture Collection, Manassas, VA), BCD1b3 (anti-CD1b) (20, 21), FIO/21A3 (anti-CD1c) (22), OKT3 (anti-CD3; American Type Culture Collection), OKT4 (anti-CD4; American Type Culture Collection), OKT8 (anti-CD8; American Type Culture Collection), BMA 031 (anti-TCRγδ; Caltag, South San Francisco, CA), 5A6, E9 (anti-TCRγδ; Caltag), MP4-25D2 (anti-IL-4; Pharmingen, San Diego, CA), and M3 (anti-CD40; Genzyme, Cambridge, MA).

In vitro culture of CD1-expressing monocyte-derived dendritic cells (DCs)

CD1 expression on monocytes was induced in vitro with a combination of recombinant human GM-CSF (200 U/ml; Genentech, Cambridge, MA) and recombinant human IL-4 (100 U/ml; Schering, Bloomfield, NJ) for 72 h as previously described (11, 23). Surface expression of CD1 was determined by flow cytometry using CD1-specific mAbs as shown previously (11). Cells were harvested using incubation in PBS/1% nM EDTA to detach adherent cells and were analyzed by flow cytometry or irradiated (5000 rad) and used as APCs.

Derivation of DN T cell lines and functional assays

T cell lines were derived from SLE patients as previously described for leprosy patients (12). Briefly, PBMCs were isolated by density gradient centrifugation. CD4 and CD8 T cells were depleted by two rounds of centrifugation. CD4 and CD8 T cells were depleted by two rounds of immunomagnetic selection (Dynal). B cells (5 × 10^6) were maintained by serial antigenic stimulation (heterologous CD1 b) (20, 21), F10/21A3 (anti-CD1c) (22),; OKT3 (anti-CD3; American Type Culture Collection), OKT4 (anti-CD4; American Type Culture Collection), OKT8 (anti-CD8; American Type Culture Collection), BMA 031 (anti-TCRγδ; Caltag, South San Francisco, CA), 5A6, E9 (anti-TCRγδ; Caltag), MP4-25D2 (anti-IL-4; Pharmingen, San Diego, CA), and M3 (anti-CD40; Genzyme, Cambridge, MA).

Results

DN T cells from SLE patients, but not those from healthy donors, produce IL-4 in response to CD1+ DC

DN TCRαβ T cells have been shown to increase in the blood of patients with SLE compared with that from healthy donors, and DN T cells can function as Th cells for autoantibody production (5, 7). Ag presentation for DN T cells was through an undetermined restriction element, although the T cells appeared to be MHC unrestricted. We wanted to determine whether DN T cells in SLE recognized self-Ags through CD1. We first investigated whether DN TCRαβ T cells were over-represented in our population of SLE patients. DN TCRαβ cells were present in higher proportions in the blood of SLE patients compared with healthy donors (Fig. 1, A and B). When a series of patients and healthy donors was evaluated, we found that the level of DN TCRαβ cells in SLE patients was significantly higher (3.0 ± 0.4% (n = 9) of CD3+ T cells) than that in healthy donors who matched the age, gender, and ethnic background of the SLE patients (0.6 ± 0.1 (n = 5) of CD3+ cells) or that in unmatched donors (1.0 ± 0.2% (n = 5) of the CD3+ T cells; p < 0.005, combined healthy donors; Fig. 1C), confirming earlier reports indicating elevated levels of DN T cells in SLE (5). High doses of prednisone did not exert measurable influences on the numbers of DN T cells in SLE patients. Among those studied with >2% DN cells, daily doses of prednisone ranged from 5 to 40 mg.

We wished to determine whether in addition to altered frequencies of DN T cells in SLE, functional differences existed between DN T cells in SLE and healthy individuals. Evidence for T helper activity in SLE DN T cells expressing either αβ or γδ T cells exists (5, 26, 27), although the role of CD1 in this helper activity has not been evaluated. Therefore, we derived DN T cell lines, regardless of TCR expression, from the blood of SLE patients and healthy donors by immunomagnetic depletion of CD4 and CD8 T cells. T cell lines were cultured with in vitro derived CD1+ DC and IL-2 for several weeks before determining their responses to CD1 in vitro. Thirteen T cell lines (eight expressing TCRαβ and five expressing TCRγδ) from 20 SLE patients and six T cell lines (four TCRαβ and two TCRγδ) from 11 healthy donors were derived in sufficient numbers and with a DN phenotype (Fig. 2) so that they could be tested for functional differences. To delineate whether functional differences exist between DN T cells of patients and healthy individuals, T cell lines were derived with CD1+ and CD1− APCs, and their cytokine production was measured by ELISA. Cytokine production from DN T cells of SLE patients fell into three categories, Th1 (three cell lines), Th2 (five cell lines), and Th0 (five cell lines); in contrast, DN T cells from healthy donors produced IFN-γ, but no IL-4 (Fig. 3), as we have found

![FIGURE 1. DN αβ TCR+ cells in SLE. Flow cytometric determination of T cells expressing αβ TCRs but lacking CD4 and CD8 coreceptors. PBMCs from one representative SLE patient (A) and a healthy donor (B) were labeled using fluorochrome-conjugated Abs to CD3, CD4, CD8, and αβ TCR. Lymphocytes were gated based on forward and side scatter, then for cells expressing CD3. C. Comparison of DN TCRαβ cells in SLE patients and healthy donors. The data were evaluated as described above.](http://www.jimmunol.org/doi/fig/10.1186/s13075-017-1233-9)
DN T cells from SLE patients and healthy donors recognize CD1c directly

The repertoire of DN T cells includes those that are restricted by CD1 (8–10, 28); therefore, to determine whether DN T cells from SLE patients recognized CD1 proteins, we first stimulated DN T cell lines from SLE patients with CD1+ APCs derived from the same donor and measured IL-4 production. Fig. 4 shows that DN T cell lines SLE-DN1 and SLE-DN2 produced IL-4 in response to CD1+, but not CD1−, APCs in a dose-dependent manner, suggesting that the T cells were directly reactive with CD1.

To more precisely determine the restriction element for SLE DN T cells, we used cell lines transfected with discrete isoforms of CD1 as APCs for SLE-DN1. SLE-DN1 produced IL-4 in the presence of CD1c-transfected HeLa cells, but not in the presence of untransfected or CD1a- or CD1b-transfected HeLa cells (Fig. 5A). DN T cell lines from healthy donors also showed exclusively CD1c reactivity, but produced IFN-γ (Fig. 5B) and no IL-4. The CD1c reactivity of SLE-DN1 was further confirmed by inhibiting the response with a neutralizing Ab to CD1c (data not shown). Although not all the DN T cell lines recognized CD1 proteins, we found that some DN T cells from both SLE and healthy donors can recognize CD1c directly. The data confirm the previous finding that DN T cells from SLE patients produce greater IL-4 than DN T cells from healthy donors (26) and extend them to show that some of these IL-4-producing DN T cells are CD1c restricted. Those DN T cell lines that recognized CD1c directly were selected for the studies evaluating their ability to promote IgG production described below.

CD1c-directly reactive T cells of SLE patients induce IgG Abs

We hypothesized that the distinct cytokine pattern produced by DN T cells in SLE might result in distinct helper activity on CD1c+ B cells. Therefore, we evaluated Ig production from cultures of CD1c+ B cells and DN T cells. We chose neonatal B cells as CD1c+ B cells, since 90% or more of neonatal B cells express CD1c, whereas only 15% of adult B cells express CD1c (16) (Fig. 6). B and T cells were cultured together, and cytokine and Ig production was evaluated. Although HeLa (Fig. 5) and B lymphoblastoid (data not shown) cell lines transfected with CD1c induced DN T cells to produce cytokines, neonatal B cells did not stimulate detectable levels of cytokines from DN T cells, perhaps due to a reduced level of costimulation. Previous studies have shown that neonatal B cells produce IgM but only low levels of IgG in response to agonistic signals that induce adult B cells (29) (Fig. 7A). We found that DN T cells from an SLE patient (SLE-DN3) induced relatively high levels of IgG1 (Fig. 7B) and IgG2 (Fig. 7C) compared with DN T cells from a healthy donor (NL2). We found that Ig production by neonatal B cells exhibited donor variability. Thus, to summarize the data for different T cell lines, we expressed the data as the ratio of IgG to IgM. Fig. 7D shows that three SLE DN T cell lines (one each of the Th2 (SLE DN1), Th0 (SLE DN3), and Th1 (SLE DN4) phenotypes) assist with IgG production, but DN T cells from nonlupus donors, which make IFN-γ only, do not provide help for IgG production. To account for the variability in cord blood Ig, we compared DN T cells from SLE and non-SLE donors with the same cord blood B cells and consistently observed potent T cell help from SLE DN T cells relative to DN T cells from healthy donors. These data suggest that in addition to a distinct cytokine pattern, CD1c-directly reactive T cells in SLE induce IgG Abs to a greater extent than T cells from non-SLE donors.
Mechanism of IgG induction by CD1c-directly reactive T cells from SLE

We investigated the mechanism by which DN T cells induced IgG production from CD1c<sup>+</sup> B cells using neutralizing Abs to factors known to promote IgG production. Initially, we wanted to determine whether CD1c was involved in the production of IgG from CD1c<sup>+</sup> B cells. We cultured CD1c<sup>+</sup> B cells in the presence of anti-CD1c Ab or an isotype control Ab. Anti-CD1c Ab inhibited the production of IgG1 and IgG2 from CD1c<sup>+</sup> B cells, whereas the isotype control Ab had little or no effect (Fig. 8). To further investigate the mechanism by which DN T cells induce IgG production, we used Abs to neutralize IL-4 and CD40 signaling. Both anti-IL-4 (Fig. 9, A and B) and anti-CD40 (Fig. 9, C and D) Abs inhibited the production of IgG1 and IgG2. In the case of anti-CD40 neutralization, isotype control Abs reduced IgG production to some extent, although not as strikingly as anti-CD40 Abs. We speculate that the isotype control for anti-CD40, a mouse IgG1, may bind the anti-human IgG-coating Ab to a greater extent than rat IgG1, the isotype control for IL-4. When cord blood B cells produced low levels of IgG as in the Fig. 9, C and D, the effect of this cross-inhibition may have been more noticeable than when the B cells produced higher levels of IgG as shown in Fig. 8, A–C. Together, the data suggest that IgG production from CD1c<sup>+</sup> B cells is dependent on the activation of T cells through CD1c, which, in turn, induces Ab production through IL-4 production and CD40-CD40 ligand (CD40L) interaction.

Discussion

We investigated the mechanism of T cell-dependent Ab production in SLE by studying the responses of CD4<sup>+</sup>, CD8<sup>+</sup> T cell lines from patients. Our findings indicate that DN T cell responses from both SLE and healthy donors are restricted by CD1c, but have distinct immunologic functions. First, DN T cells from SLE patients produced IL-4 and IFN-γ, in contrast to the T cells of healthy donors, which produced IFN-γ only. Second and perhaps more significant to the pathogenesis of SLE, the DN T cells of patients provided help for CD1c<sup>+</sup> B cells to produce IgG Abs, whereas IgG helper activity for CD1c<sup>+</sup> B cells was weaker or undetectable among the DN T cells from healthy donors. DN T cell help for IgG production was mediated through CD1c, IL-4, and CD40. Our data indicate that DN CD1-restricted T cells from SLE possess potent T helper activity for IgG production.

The existing paradigm to explain T cell help for Ab production holds that B cells bind and internalize Ag via surface Ig, process the Ag, then present it on an MHC molecule to the TCR. The simplest model to explain this process is for B and T cells to recognize the same Ag, but this paradigm does not provide a mechanism for nonpeptide Ag presentation to T cells. This is especially problematic in SLE, where evidence suggests that DN T cells, which are elevated in SLE, provide help for Ab production against nonprotein self-Ags (5, 7). We reasoned that CD1c could mediate cognate recognition between B cells and DN T cells in SLE, since the DN T cell repertoire includes CD1-restricted T cells (8–10), which are elevated in SLE, provide help for Ab production against microbial lipid Ag (30). Together, these findings suggest an alternative mechanism to MHC-mediated T cell help for IgG production where protein and nonprotein must exist as an Ag complex, such as histone and DNA (31).

The identification of B and T cell cognate interaction mediated by CD1c raises the question of the nature of the self-Ag presented by CD1c. CD1c is a member of the group 1 CD1 family of MHC class I-like proteins (32–34) that present lipid Ags to T cells (9, 11–15). The group 1 CD1 proteins, which are not found in mice, also include human CD1a and CD1b (33, 35); human CD1d, which is most similar to murine CD1 (36), comprises group 2. The general structural features of CD1-presented Ags are a hydrophobic region (single or diacyl fatty acid chains) coupled to a polar or charged hydrophilic end (9, 11–15, 37). The large hydrophobic pockets identified in murine CD1 (38) are thought to be capable of accommodating the fatty acid portions of these Ags. The finding that DN T cells from SLE patients are restricted by CD1c raises the...
possibility that a nonpeptide self-Ag is presented to T cells. We hypothesize that cardiolipin and other self-glycolipids are ligands for CD1c-directly reactive T cells given the prominence of anti-cardiolipin Abs in SLE, the presence of CL in plasma lipoproteins (39), their structural similarity (polar head group with lipid tail) with other CD1-restricted T cell ligands (9, 11–15, 37), and the recent report of T cell recognition of self-glycolipids (40).

In the model of cognate recognition, isotype switching from IgM to IgG requires soluble mediators as well as cell-cell contact. IL-4 in particular is a potent stimulus for inducing IgG production from B cells (41). We found that although IFN-γ was produced by DN T cells from both donor groups, IL-4 production distinguished the DN T cells in SLE from those in healthy donors. We also demonstrated that IL-4 was required for DN Th cell-induced IgG production from CD1c+ B cells, since neutralizing anti-IL-4 mAbs block the production of IgG1 and IgG2. The ability of SLE DN T cells to produce IL-4 and provide help for IgG production is consistent with data showing a critical role for IL-4 in murine models of SLE (42) and the role of IgG autoantibodies in the pathogenesis of lupus nephritis (43). It is striking that the three patients with DN T cells secreting the highest levels of IL-4 were the individuals with the lowest disease activity; each of them had a SLEDAI score of 1. In contrast, cells secreting the highest levels of IFN-γ were obtained from patients with very active disease (SLEDAI scores from 7–10). This raises the possibility that shifts between cells of Th1 and Th2 phenotypes occur in this unique CD1-restricted T cell population as disease activity changes, with Th1-like phenotypes more likely to correlate with disease activity. To date, there is no information regarding these distinct phenotypes in human group 1 CD1-restricted T cells. The decrease in IL-4 observed in DN T cell lines with patients exhibiting more severe disease may reflect a protective role in SLE for IL-4-producing T cells (44).

Lu and colleagues (45) studied cytokine production by CD4+ T cells (after short term culture) from patients with SLE stimulated by various peptides from nucleosomes. Some peptides stimulated IFN-γ production, whereas others stimulated the production of IL-10 or IL-4. Thus, as in our experiments with CD1-restricted T cells from SLE patients, variation in cytokine secretion is not unexpected.

In addition to soluble mediators, cognate recognition requires cell-cell contact for IgG production. This contact is mediated by

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**FIGURE 7.** Cord blood IgG production induced by CD1c-directly reactive T cells from SLE. DN T cell lines (5 × 10^5) from one SLE patient (SLE DN3) and one healthy donor (NL2) and cord blood B cells (5 × 10^5) were cultured for 10 days, supernatants were harvested, and total Ig was measured by ELISA for human IgM (A), IgG1 (B), and IgG2 (C). Values expressed represent the means of triplicate cultures ± SEM. Limits of detection: IgM, 0.05 ng/ml; IgG1, 0.5 ng/ml; IgG2, 1 ng/ml. D. Comparison of IgG-promoting activity of CD1c-restricted DN T cell lines from three SLE patients and two healthy donors. The data are represented as a ratio of IgG to IgM due to variability of IgG production from different cord blood donors.

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**FIGURE 8.** CD1c-mediated T cell help for IgG production. B and T cell cultures were described in Fig. 7. Neutralizing Abs to CD1c or an isotype control Ab were added to the cultures. The values shown are the means of triplicate cultures (± SEM), and the data are representative of minimum of three experiments.

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**FIGURE 9.** Mechanism of T cell help by CD1c-directly reactive T cells. B and T cell cultures were as described in Fig. 7. Neutralizing Abs to IL-4 (A and B), CD40 (C and D), or isotype control Abs were added to the cultures. Values are the means of triplicate cultures ± SEM.
CD40-CD40L interactions, as seen by a lack of IgG in CD40-deficient individuals (46–48). Our data indicated a role for CD40-CD40L interactions in DN T cell help for IgG production by CD1c⁺ B cells. CD40L expression is known to be increased in T cells from SLE patients (49, 50). Higher T cell CD40L expression might provide a more potent signal for B cells, and stronger agonistic signals through CD40 may be responsible for inducing IgG production from these CD1c⁺ neonatal B cells (P. Siegel, unpublished observation).

Studies evaluating human CD1 Ag presentation in immunological homeostasis and pathogenesis have provided substantial evidence that CD1-Ag presentation can activate T cells that secrete a Th1 pattern. We demonstrated that CD1-restricted T cells secrete Th1 cytokines and can promote cell-mediated immune responses against mycobacterial infection in humans (51). Similarly, T cells from diabetic individuals bearing invariant TCR α-chains that recognize human CD1d preferentially produced a Th1 cytokine pattern and could promote T cell destruction of islet cells and thereby exacerbate disease, whereas CD1d-restricted T cells from their healthy siblings produced a Th0 cytokine pattern (52). In the present study, we found that DN T cells derived from SLE patients that recognize CD1c produced the Th2 cytokine IL-4 and could promote B cell production of IgG. Thus, our data provide new evidence that human CD1-restricted T cell can contribute to a Th2 response and the generation of Abs. Our data are consistent with studies of murine CD1-restricted T cells, which produce IL-4 and promote humoral immunity (30, 53).

We have demonstrated that DN T cells in SLE promote IgG Ab production in a CD1c-dependent manner. Since CD1c presents lipid Ags to T cells, we speculate that CD1c⁺ B cells have evolved to recognize lipid Ags through their surface Ig and present them to DN T cells for recruitment of help for IgG production. Data from the mouse indicate that CD1a⁺ B cells spontaneously produce IgM and are deficient in IgG production relative to CD1b⁺ B cells (54) unless they receive T cell help (44). This suggests that CD1b⁺ T cells are prone to anti-self responses if inappropriate T cell help is provided. CD1b⁺ B cells are located in the marginal zones of lymphoid tissue, where B cells are more responsive to nonpeptide Ags (55–57), further suggesting that CD1b⁺ B cells are involved in Ab responses to nonpeptide Ags. Although this mechanism of Ag presentation may facilitate T and B cell interaction in host defense against microbial pathogens, our data suggest that CD1 Ag presentation may contribute to the pathogenesis of autoimmune disease. Therefore, the identification of the self-Ag that is presented by CD1c to T cells in SLE should provide a novel means of intervention in the treatment of autoimmune disease.

Acknowledgments

We thank the Dr. Robert Modlin for many helpful discussions and review of the manuscript, Dr. Michael B. Brenner for the use of a CD1c-restricted DN T cell line, the University of California-Los Angeles umbilical cord blood bank for neonatal cord blood, and Schering-Plough and Genetics Institute for their kind gifts of IL-4 and GM-CSF, respectively.

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