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Initiation of Cellular Organization in Lymph Nodes Is Regulated by Non-B Cell-Derived Signals and Is Not Dependent on CXC Chemokine Ligand 13

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The molecular and cellular events that initiate the formation of T and B cell areas in developing lymph nodes are poorly understood. In this study we show that formation of the lymphoid architecture in murine neonatal lymph nodes evolves through a series of distinct stages. The initial segregation of T and B cells is regulated in a CXCL13-independent manner, characterized by the localization of B cells in a ring-like pattern in the outer cortex on day 4. However, during this CXCL13-independent phase of lymph node modeling, CXCL13 is expressed and regulated in a lymphotoxin-α2 LTα2-dependent manner. Surprisingly, neonatal B cells are unable to respond to this chemokine and also lack surface LTα2 expression. At this time, CD45+CD4+CD3- cells are the predominant LTα2-expressing cells and are also capable of responding to CXCL13. From day 4 on, architectural changes become CXCL13 dependent, and B cells become fully CXCL13 responsive, express LTα2, and cluster in anatomically distinct follicles. Because the initial induction of CXCL13 is dependent on LTα2, a role for CD45+CD4+CD3- cells in inducing chemokine expression in the developing lymph nodes is proposed and, as such, a role in initiation of the shaping of the lymphoid microenvironment. The Journal of Immunology, 2004, 173: 4889–4896.

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Materials and Methods

Animals

C57BL/6 mice were purchased from Harlan (Horst, The Netherlands) and were kept under routine laboratory conditions. LTα−/− and SCID mice were bred and kept at the in-house animal facilities of the Vrije Universiteit Medical Center. CXCL13−/− mice were described previously (21) and were bred and kept at the in-house animal facilities of Trudeau Institute.

Antibodies

For flow cytometry and immunohistology, the following Abs were used: 6B2 (anti-B220), GK-1.5 (anti-CD4), 2.4G2 (anti-CD16/CD32; all were affinity-purified from hybridoma cell culture supernatants with protein G-Sepharose (Pharmacia Biotech, Uppsala, Sweden) and labeled in our laboratory), anti-IgM F(ab)2 (Cappel, West Chester, PA), anti-IgD-PE (Dako, Carpinteria, CA), anti-IgM-FITC (PharMingen), anti-IgG-F(ab)2 (Cappel, West Chester, PA), anti-IgD-PE (Dako, Carpinteria, CA), anti-IgM-FITC (PharMingen), anti-IgG-F(ab)2 (Cappel, West Chester, PA), and labeled in our laboratory. B cells appear scattered throughout the organ, with no apparent organization.

Pores (Costar, Corning, NY). Recombinant murine CXCL13 (1 μg/ml; R&D Systems Europe) was used in the lower compartment, whereas 2.5 × 105 to 1 × 106 cells were placed in the upper compartment. Cells were allowed to migrate for 3 h at 37°C, then migrated cells were analyzed by flow cytometry.

Immunofluorescence microscopy

Six-micron cryosections were fixed in dehydrated acetone for 5 min and air-dried for an additional 10 min. Sections were incubated with primary Ab for 1 h at room temperature, followed by a 30-min incubation with a Fluor-Alexa-labeled conjugate (Molecular Probes) when needed. Sections were embedded in Fluorostab (ECN Biomedical, Aurora, OH) and analyzed on an Eclipse E800 microscope (Nikon Europe, Haarlem, The Netherlands).

For visualization of chemokines, sections were incubated overnight at 4°C with chemokine-specific Abs. The Alexa-Fluor 594 tyramide amplification system was subsequently used to enhance the signal according to the manufacturer’s protocol (Molecular Probes).

CXCL13 mRNA expression

RNA was extracted on the day of birth from whole mesenteric lymph nodes (C57BL/6) or from mesenteric lymph node rudiments (LTα−/−) using TRIzol (Invitrogen Life Technologies, Gaithersburg, MD) and reverse transcribed with oligo(dt)12-18 (Invitrogen Life Technologies) and random hexamer primers (Invitrogen Life Technologies) using standard protocols. cDNA was analyzed for the expression of CXCL13 and LTβ-R by TaqMan PCR assay using an ABI PRISM 7700 Sequence Detection System (Applied Biosystems, Foster City, CA).

In situ hybridization was performed on 6-μm cryostat sections using a digoxigenin-labeled CXCL13 probe as described previously (23).

Results

B cell follicles develop during the first week of life

To gain insight into the cellular and molecular processes underlying the initial shaping of the LN microdomains, immunohistochemical analysis of inguinal, axillary, brachial, and mesenteric LNs was performed on the day of birth and 4 and 7 days after birth. Three distinct phases could be distinguished in the segregation of T and B lymphocytes and the formation of B cell follicles. On the day of birth (day 0) the developing LNs showed no apparent organization, with B cells scattered throughout the LN, and T cells being virtually absent (stage I; Fig. 1A). Starting on approximately day 2, the first wave of αβTCR+ thymic emigrants colonized the LNs, and B cells started to localize to the outer cortex (24, 25). On day 4, the first phase of B cell migration was completed, and B cells were organized in a ring-like structure in the outer cortex of the LNs, the paracortex being occupied by numerous T lymphocytes. However, no follicles were detectable at this time (stage II; Fig. 1B). Between days 4 and 7, B cells localized in cortical clusters, and the first clearly distinguishable B cell follicles became evident on day 7 (stage III, Fig. 1, C and D). The generation of these follicles was accompanied by the emergence of FDCs, as detected by the FDC-M2 Ab (Fig. 1D) as well as positive staining for complement receptor 1 (data not shown). Because FDCs are dependent on TNF-α and LTAβ, for their development (6, 19), this suggests that insufficient levels of these signals are available before day 7.

LTαβ2-dependent expression of CXCL13 in developing LNs

Development and maintenance of splenic B cell follicles depends on local production of CXCL13, regulated largely by LTαβ signaling, as described for the thymic emigrants colonized the adult spleen (6). To determine the role of CXCL13 in the organization of developing LNs, expression of CXCL13 mRNA in newborn LNs was analyzed by RT-PCR (Fig. 2A). Mesenteric LNs (MLNs) were dissected on the day of birth, day 2, and day 8, and total RNA was extracted. By means of this method, CXCL13 mRNA was already detected within the developing LNs on the day of birth. To address whether this early expression of CXCL13 was dependent on LTαβ signaling, as described for the adult spleen, CXCL13 expression was compared between C57BL/6 MLNs isolated at birth and rudimentary MLNs (rMLNs) from LTα−/− mice (Fig. 2B). To control for possible differences in stromal cell populations between these two mouse strains,
CXCL13 levels were normalized to the expression of the LTβ-R, expressed on stromal cells. Quantitative analysis of LTβ signaling in CXCL13 message was normalized to LTβ-R using TaqMan analysis. In the absence of a LTαβ signal, an average 5-fold reduction in CXCL13 message was observed, both in total LN tissue and in sorted CD45 stromal cells. CXCL13 message was normalized to LTβ-R using TaqMan analysis. In the absence of a LTαβ signal, an average 5-fold reduction in CXCL13 message was observed, both in total LN tissue and in sorted CD45 stromal cells. These data indicate that in the developing LN stroma also CXCL13 is regulated in an LTαβ-dependent manner.

Finally, the pattern of CXCL13 expression within developing LNs was monitored by in situ hybridization. Using this method, LNs isolated on day 0, CXCL13 expression was restricted to the outer cortex, but no clear follicular expression pattern could be distinguished. From day 4 on, CXCL13 expression emerged into a follicular constellation, coincident with the initiation of B cell clusters in the outer cortex (Figs. 2E and 1B). The process of B cell clustering was completed on day 7, when B cells had organized into tightly packed follicles, CXCL13 expression could be detected within the follicles (Figs. 1, C and D, and Fig. 2F). These data show that the LTαβ-dependent follicular expression of CXCL13 is accompanied by localization of B cells in these putative follicular areas in the outer cortex.

CXCL13-independent B cell migration in neonatal lymph nodes

The fact that in adult CXCL13−/− mice, B cell follicles were disrupted indicated the necessity of CXCL13 for follicle maintenance and/or development (21). Therefore, we set out to determine during which stage of development follicle formation in CXCL13-deficient mice is halted, and MLNs dissected from neonatal CXCL13−/− mice were analyzed by immunofluorescence. In contrast to the defective LN architecture reported in MLNs of adult mice, neonatal CXCL13−/− MLNs appeared completely normal until 4 days after birth (stage II; Fig. 3A). As can easily be appreciated from Fig. 3A, the initial migration of B cells to the outer cortex seen during stage II (Fig. 1B) was completed in CXCL13−/− mice by day 4. This indicates that the first phase of B cell migration to the outer cortex was regulated in a CXCL13-independent manner. The subsequent progression to stage III, clustering of B cells in anatomically distinct follicles between days 4 and 7, did not occur in CXCL13−/− mice (Fig. 3A) and was therefore dependent on CXCL13.
phenotypic analysis was performed to assess the degree of maturity of the B cell pool in the neonatal LNs. As shown in Fig. 4A, phenotypically mature IgM⁺IgD⁺ B cells were found on the day of birth in MLNs (Fig. 4A). These data were confirmed by the fact that ~40% of CD19⁺ cells at birth expressed the κ- or λ-chain (Fig. 4B), indicative of progression beyond the pre-B cell stage. Therefore, a large part of the neonatal MLN B cells appeared phenotypically mature despite their low expression of CXCR5.

In the spleen, induction of surface LTα1β2 on B cells is the second feature attributed to CXCR5 signaling. To test whether the newborn CXCR5<sup>low</sup> B cells from MLNs had initiated expression of LTα1β2, MLNs from mice on the day of birth and those from adult mice were analyzed for the expression of LTα1β2 (Fig. 4C). Spleens from LTα<sup>−/−</sup> mice were used as negative controls. In conjunction with their hampered migratory response to CXCL13, day 0 MLN B cells were also surface LTα1β2 negative. The expression of LTα<sub>1</sub>β<sub>2</sub> became apparent from day 2 (data not shown) and reached adult levels on day 4 (Fig. 4C). This shows that although newborn B cells appear phenotypically mature, their low levels of CXCR5 lead to CXCL13 unresponsiveness as well as lack of surface LTα1β2.

**CXCL13 unresponsiveness of neonatal B cells**

The findings that B cells only start organizing in a CXCL13-dependent manner after day 4 prompted us to determine the capacity of neonatal B cells to migrate in response to CXCL13. B cells were isolated from MLNs on the day of birth, on day 4, and from adult mice and tested for their CXCL13 responsiveness in an in vitro Transwell assay (Costar, Corning, NY) (Fig. 3B). Shown are specific migrations relative to migration of B cells from adult MLNs. Surprisingly, on the day of birth, B cells were virtually CXCL13 unresponsive (Fig. 3B). The ability to respond to CXCL13 was acquired during the first days of life, reaching levels comparable to those in adults on day 4. However, at this time the B cell pool was still highly heterogeneous with regard to CXCL13-induced migration. To find an explanation for this unexpected unresponsiveness of newborn B cells, neonatal and adult MLNs were dissected, and expression levels of CXCR5, the receptor for CXCL13 (26), were compared between newborn and adult B cells. In agreement with their unresponsiveness to CXCL13 in Transwell assays, newborn MLN-derived B cells showed lower expression of CXCR5 compared with adult B cells, explaining the inability of these cells to respond to CXCL13. The acquisition of normal levels of expression and full CXCL13 responsiveness represents an additional, previously unappreciated, developmental step in B cell maturation.

**Neonatal B cells are LTα₁β₂ negative**

Because neonatal LN-derived B cells still have to acquire a distinct feature of mature B cells (CXCL13 responsiveness), an additional feature of mature B cells (CXCL13 responsiveness), an additional
of all hemopoietic cells, and upon adoptive transfer, these cells home to the B cell follicles (32, 33). These features make LTα1β2+CD45+CD4+CD3− cells likely candidates for inducing LTα1β2-dependent chemokines in the developing LN. SCID mice contain a normal population of LTα1β2+CD45+CD4+CD3− cells (32), and in Fig. 5, A and B, the predominant localization of LTα1β2+CD45+CD4+CD3− cells at the outer cortex of the SCID lymph nodes could clearly be seen due to the absence of CD4−TCR− lymphocytes. This cortical distribution was apparent around day 2 after birth in both SCID and C57BL/6 mice (32) and coincided with the migration of B cells to this area during stage II of follicle formation. Furthermore, similar to the migration of B lymphocytes, this migration of CD45+CD4+CD3− cells occurred independently of CXCL13, because a predominant cortical localization of these cells was seen in CXCL13−/− mice (Fig. 6B). However, in contrast to neonatal B cells, CD45+CD4+CD3− cells showed a very potent migratory response to CXCL13 in vitro (Fig. 6C) (34). Therefore, LTα1β2+CD45+CD4+CD3− cells display many of the features attributed to B cells in the adult spleen for induction of the LTα1β2-CXCL13 feedback loop, indicating that LTα1β2+CD45+CD4+CD3− cells may very well be responsible for the induction of homeostatic chemokines during postnatal development and initiation of the lymphoid microdomains.

Discussion
The shaping of the cellular architecture within developing LNs requires an intricate interplay among several cell types and soluble factors. Postnatal segregation of lymphocytes and arrangement into functionally and anatomically distinct microdomains is a multistep process, in which several distinct stages can be discerned (Figs. 1 and 7). During the first stage (stage I), from day of birth until day 2, LNs are still devoid of αβTCR+ T cells, and the main hemopoietic cell types present are B cells, LTα1β2+CD45+CD4+CD3− cells, and γδT cells (25). During this time, no cellular organization is apparent. The transition from stage I to stage II is marked by an influx of the first αβTCR+ T cells. In conjunction with the influx of T cells, which accumulate in the paracortex of the LN, B cells and CD45+CD4+CD3− cells start to migrate toward the outer cortex. In this study CXCL13 expression was upregulated, in an LTα1β2-dependent manner, most likely induced by LTα1β2+CD45+CD4+CD3− cells. During stage II, the pattern of CXCL13 mRNA expression indicates the creation of a microenvironment permissive for follicle formation, culminating on day 4 in the organized follicular expression of this chemokine. Stage III is initiated when B cells become responsive to CXCL13, and CXCL13-dependent migration can occur, leading to the clustering of B cells in the outer cortex and the expression of surface LTα1β2.

FIGURE 4. Newborn LNs contain phenotypically mature, but LTα1β2-negative, B cells. On the day of birth, B cells from MLNs were analyzed for the expression of surface Igs. A, Gated on CD19+ cells, ~33% of the B cells in newborn LNs express both IgM and IgD; B, roughly the same percentage of CD19+ B cells expresses the κ-L chain, indicative of maturation beyond the pre-B cell stage. C and D, Surface expression of LTα1β2 was evaluated by staining with a soluble LTα1β2-IgG fusion protein. Splenic B cells from LTα1β2− mice were used as a negative control, and B cells from either day 0 MLNs or day 4 MLNs were compared with B cells from adult C57BL/6 MLNs. At birth, no surface LTα1β2 could be detected on B cells. Expression was instigated on approximately day 2 (data not shown) and reached levels comparable to adult values on day 4. The percentage LTα1β2-expressing B cells of the total B cells is shown.
The latter enables B cells to contribute to the sustained production of CXCL13 in a similar way as described for the spleen (21). The LN architecture is completed on day 7, when FDCs become apparent, and B cells are clustered in anatomically distinct, tightly packed follicles (Fig. 7).

The observed discrepancy between CXCL13 mRNA and protein levels indicates that low levels of CXCL13 protein are likely to be present before day 10. However, because development of the lymphoid architecture in C57BL/6 mice and that in CXCL13−/− mice are completely identical until day 4, this low level of expression is obviously not essential for the early phases of T/B segregation. Furthermore, differences in the sensitivity of the CCL21 and CXCL13 Abs might exist, which could hamper determination of the exact onset of protein expression.

Recently, the importance of B cells in maintenance of the architecture in spleen and LNs of adult mice was questioned (22). Tumanov et al. (22) showed that mice with a B cell-specific LTβ deletion display normal chemokine levels, FDC, and follicular structures in the LN. Furthermore, it was shown that T cell-derived LTβ1 is sufficient to maintain the lymphoid architecture. This

![FIGURE 5. Production of homeostatic chemokines in SCID mice. LNs from SCID and C57BL/6 mice were analyzed for the expression of CXCL13 and CCL21 in combination with CD4 on days 3 and 7 after birth and in adult animals. Chemokines were stained in red, and CD4 in green. A, Three days after birth, LNs from SCID mice showed no expression of CXCL13, but showed a strong production of CCL21. This was similar to the chemokine expression patterns seen in C57BL/6 LNs using this method. B, At 10 days after birth, SCID lymph nodes showed the first CXCL13 expression in addition to the already present CCL21, again in agreement with C57BL/6 LNs. C, At 37 days after birth, CXCL13 was abundantly expressed in the cortical region of the SCID lymph nodes, colocalizing with the CD4+ cells. CCL21 expression was comparable to that at earlier time points. In C57BL/6 mice, CXCL13 was localized in the follicular areas, with CCL21 being expressed in the paracortex.](http://www.jimmunol.org/)

![FIGURE 6. Properties of CD45+CD4+CD3− cells in newborn LNs. Newborn MLNs were dissected and analyzed for surface LTα1β2 expression using a LTβ-R-IgG fusion protein. A, The only cells expressing LTα1β2 at birth are CD45+CD4+CD3− cells. B, LTα1β2+CD45+CD4+CD3− cells localize to the outer cortex in a CXCL13-independent manner, as shown in MLN from day 4 CXCL13−/− mice. T cells appear red (anti CD3ε) or yellow (anti-CD3ε together with anti-CD4), and CD45+CD4+CD3− cells appear green (anti-CD4). C, In contrast to newborn B cells, CD45+CD4+CD3− cells show a vigorous response to CXCL13 in an in vitro Transwell assay. Shown are specific migrations within one experiment. A representative example of three independent experiments is shown.](http://www.jimmunol.org/)
indicates that during adult life the lymphoid architecture is preserved by a combination of T and B cell-derived signals. However, it has to be noted that all these observations were made 8–10 days after immunization with sheep RBC. Because LTαβ levels on T cells are dependent on activation state, it is conceivable that high levels of LTαβ on activated T cells leads to the generation of a normal lymphoid architecture through reorganization of the already present CXCL13 expression into a follicular pattern.

During the first days after birth (stages I and II), the neonatal B cell pool needs to undergo additional maturation steps before being able to contribute to the LTαβ-CXCL13 feedback loop. Complete CXCL13 responsiveness is not reached until approximately day 4, when B cells show CXCL13-dependent migration and express LTαβ. The CXCL13-LTαβ positive feedback loop, which was shown to be instrumental in generating tightly packed B cell follicles and maintaining these structures in spleens of adult mice, is therefore in all probability in LNs initiated by non-B cell-derived LTαβ. The only cells in neonatal LNs that express LTαβ are CD45+CD4+CD3- cells; therefore, these cells are the most likely candidate to induce the expression of homeostatic chemokines.

Before the CXCL13-mediated migration leading to follicle formation in stage III, the initiation of T/B cell segregation as well as migration of CD45+CD4+CD3- cells during stage II are regulated independently of CXCL13. This initial segregation of T and B cells is therefore mediated by alternative chemokines. These chemokines are not dependent on T cells for their induction, because in athymic nude mice, B cell migration to the outer cortex occurs via the same kinetics as in C57BL/6 mice (data not shown). Moreover, induction is most likely LTαβ-independent, because in solitary MLNs, which occasionally develop in LTα-deficient animals, normal T/B segregation was found (35). It is conceivable that CD45+CD4+CD3- cells are also essential for inducing these unidentified chemokines. To establish the involvement of LTαβ-CD45+CD4+CD3- cells in this process, we extensively tried to eliminate these cells in vivo using depleting Abs; however, this proved infeasible, probably due to a combination of low complement levels in neonates and the high degree of apoptosis resistance of CD45+CD4+CD3- cells (our unpublished observations). Identification of the signals and chemokines that mediate this CXCL13-independent migration provides novel challenges for future research.

This study provides new insights into the complex interactions underlying the generation of distinct microenvironments in which T and B lymphocytes are allowed to efficiently sample Ags presented by APCs. This is a phenomenon seen in secondary lymphoid organs as well as in ectopic tertiary lymphoid structures commonly found in several chronic inflammatory conditions (17, 36–42). There is accumulating evidence for a high degree of homology between the generation of inflammatory lymphoid structures and the normal development of the lymphoid architecture (36, 43, 44). This indicates that understanding the factors that shape the developing LNs will probably lead to new insights into the formation of ectopic lymphoid structures and will eventually open new therapeutic avenues leading to the targeted disruption or prevention of formation of these structures during chronic inflammation.

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