Short Communication

Lymphoid Tissue Homing Chemokines Are Expressed in Chronic Inflammation

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Secondary lymphoid tissue chemokine (SLC) and B lymphocyte chemoattractant (BLC) are homing chemokines that have been implicated in the trafficking of lymphocytes and dendritic cells in lymphoid organs. Lymphotoxin- α (LT α), a cytokine crucial for development of lymphoid organs, is important for expression of SLC and BLC in secondary lymphoid organs during development. Here we report that transgenic expression of LT α induces inflammation and ectopic expression of SLC and BLC in the adult animal. LT β was not necessary for induction of BLC and SLC in inflamed tissues, whereas, in contrast, tumor necrosis factor receptor-1 was found to be important for the LT α -mediated induction of these chemokines. The ectopic expression of LT α is associated with a chronic inflammation that closely resembles organized lymphoid tissue and this lymphoid neogenesis can also be seen in several chronic inflammatory diseases, including in the pancreas of the prediabetic nonobese diabetic (NOD) mouse. Expression of SLC was also observed in the pancreas of prediabetic NOD mice. This study implicates BLC and SLC in chronic inflammation and presents further evidence that LT α orchestrates lymphoid organogenesis both during development and in inflammatory processes. (*Am J Pathol* 2000, 156:1133–1138)

Lymphotoxin- α (LT α ; tumor necrosis factor- β) plays an important role in both lymphoid organ development and chronic inflammation. Mice genetically deficient in LT α have profound defects in lymphoid organ development in that they lack lymph nodes (LNs) and Peyer's patches and have a disrupted splenic organization.¹ The inflammation induced by transgenic expression of LT α under

the rat insulin promoter (RIPLT mice) in the pancreas and kidney has several characteristics of lymphoid organs with regard to cellular composition, including naive and memory T cells, B cells, dendritic cells, and follicular dendritic cells. Furthermore, there is T- and B-cell compartmentalization with formation of B lymphocyte follicles and germinal center-like structures, a specialized vascular system with high endothelial venules, and an increased expression of markers associated with LN endothelium such as mucosal addressin cell adhesion molecule (MAdCAM) and peripheral lymph node addressin.^{2,3} This cellular accumulation closely resembles the organized ectopic lymphoid tissues (tertiary lymphoid organs) seen in a number of human autoimmune diseases, including type I diabetes, rheumatoid arthritis, multiple sclerosis, and Hashimoto's thyroiditis.³ The NOD mouse spontaneously develops insulinitis, which progresses to islet destruction and diabetes.⁴ The adhesion molecules MAdCAM and peripheral lymph node addressin are also expressed in the prediabetic insulinitis of such mice.⁵ The hypothesis to be tested here is that the mechanisms by which LT α directs lymphoid organogenesis during embryogenesis and in chronic inflammation are similar, particularly with regard to chemokine induction.

LT α is a member of the immediate tumor necrosis factor (TNF) family and can be produced either as a

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secreted LT α 3 homotrimer or as a membrane-bound LT α 1 β 2 heterotrimer. The LT α 3 homotrimer interacts with the TNFR1 and TNFR2 receptors, whereas the LT α 1 β 2 heterotrimer binds to the LT β receptor (LT β R). LT α is primarily a product of activated CD4TH1, CD8, and early nonactivated B cells in the adult animal, and a recent study shows that activated naive T cells also express high levels of soluble LT α 3.⁶ LT α has a number of proinflammatory effects and induces inflammation *in vivo* in RIPLT mice at the sites of transgene expression in the pancreas and kidney.^{2,3} This occurs even in RIPLT mice genetically deficient in LT β (RIPLT.LT β $-/-$ mice),⁷ confirming earlier *in vitro* studies indicating that LT α 3 alone can induce inflammation.⁸ The LT α 3-induced inflammation is dependent on TNFR1, but not TNFR2, as shown by studies of RIPLT mice deficient in TNFR1 or TNFR2.⁷ As noted above, the LT α 3-induced inflammation in RIPLT mice exhibits characteristics of lymphoid organs.

It is likely that LT α 3 mediates some of its effects through induction of chemokines, and it has recently been shown that recombinant LT α 3 induces expression of the chemokines RANTES, IP-10, and MCP-1 in an endothelial cell line *in vitro*.⁹ The same chemokines are expressed *in vivo* in the transgene-induced inflammation in RIPLT mice,⁵ but as these chemokines do not preferentially attract naive lymphocytes they are probably not directly involved in *de novo* formation of lymphoid tissues. More likely candidates for the link between lymphoid neogenesis during development and chronic inflammation are the recently discovered chemokines BLC (also called BCA-1)^{10,11} and SLC (also called 6CKine, Exodus-2, or TCA-4).¹²⁻¹⁶ These two chemokines appear to be important for normal organization of lymphoid tissue compartments during development. BLC is constitutively expressed by stromal cells in lymphoid tissues and interacts with the CXCR5 receptor (formerly called Burkitt's lymphoma receptor 1), which is primarily expressed on mature B cells. Mice genetically deficient in CXCR5 lack inguinal LNs, possess few or abnormal Peyer's patches, and have a disorganized spleen,¹⁷ characteristics similar to those of LT α $-/-$ mice. SLC is expressed by high endothelial venules in LNs and Peyer's patches and by stromal cells in the T-cell zone of secondary lymphoid organs and it has been reported to interact with the CCR7 and possibly also the CXCR3 receptors expressed primarily on naive and mature T cells and dendritic cells.¹⁸⁻²¹ Mice homozygous for the paucity of lymph node T-cell (*p/t*) mutation lack expression of SLC and have defects in T-cell homing and dendritic cell localization in the spleen and LNs.²² A recent study by Ngo and colleagues²³ shows that mice deficient in any of several members of the LT/TNF ligand and receptor family indeed have markedly reduced expression of both BLC and SLC in secondary lymphoid organs. That report suggests that all members of the family are important for maximal production of these chemokines. The precise role of secreted LT α 3 in inducing BLC and SLC expression has not been defined, nor has the role of the lymphoid trafficking chemokines in inflammation been previously addressed.

In the present study, we have used the RIPLT transgenic mouse model to elucidate the mechanisms by which LT α induces chronic inflammation in the kidney and pancreas that is organized into lymphoid tissue. We report that LT α expressed in the kidney induces expression of both BLC and SLC in chronic inflammation in large part through TNFR1, although a role for LT β R is confirmed in the spleen. We have tested the applicability of the conclusions drawn here regarding the parallel between lymphoid neogenesis and normal development of secondary lymphoid organs by studying the NOD mouse that spontaneously exhibits inflammation. We confirm the expression of the SLC in chronic inflammation by detecting it in the pancreas of prediabetic NOD mice. Our studies are the first to implicate a role for BLC and SLC in chronic inflammation, and they present further evidence that chronic inflammation has characteristics of lymphoid neogenesis and emphasize the unifying role of LT in the processes.

Materials and Methods

Mice

The generation and subsequent genotyping of RIPLT.wt, RIPLT.LT β $-/-$, and RIPLT.TNFR1 $-/-$ mice has been previously described.^{2,7} Ten-week-old female NOD/Caj mice were kindly provided by Dr. F. Susan Wong from the NOD mouse core colony at Yale University, New Haven, CT. All animals were housed under specific pathogen-free conditions.

In Situ Hybridization

Digoxigenin (DIG)-labeled BLC and SLC antisense and sense probes were prepared by *in vitro* transcription from I.M.A.G.E. consortium expressed sequence tags 596050 and 389013, obtained from Genome Systems (St. Louis, MO), as previously described.^{10,16} Transcript yield and integrity of the probes were determined by comparison with control DIG-labeled RNA (Boehringer Mannheim, Mannheim, Germany). Mice were deeply anesthetized and intracardially perfused, first with phosphate-buffered saline and then with 4% paraformaldehyde in 0.14 mol/L Sorenson's phosphate buffer. Tissues were fixed overnight and snap-frozen in Tissue-Tek OCT compound (VWR Scientific, Bridgeport, NJ) and stored at -70°C . Sections of 5- to 10- μm thickness were cut onto poly-L-lysine-treated glass slides and *in situ* hybridization was done as previously described.²⁴ In brief, sections were fixed in 4% paraformaldehyde, pretreated with Proteinase K (Boehringer Mannheim) and acetic anhydride, prehybridized, hybridized overnight at 58°C with the DIG-labeled riboprobes, washed at high stringency, incubated with anti-DIG antibody conjugated to alkaline phosphatase (Boehringer Mannheim), and developed with nitro blue tetrazolium/5-bromo-4-chloro-3-indole-phosphate.

Northern Blot Analysis

Twenty micrograms of total RNA from spleens and kidneys of 5-week-old mice was subjected to gel electrophoresis, transferred to positively charged nylon membrane (Boehringer Mannheim), and probed using DIG-labeled BLC- and SLC-specific antisense riboprobes. The hybridization signal was detected by chemiluminescence using disodium 3-(4-methoxyspiro[1,2-dioxetane-3,2'-(5'-chloro) tricyclo [3.3.1.1^{3,7}]decan]-4-yl)phenyl phosphate (CSPD) as substrate (Boehringer Mannheim). To control for loading and RNA integrity, membranes were reprobed for β -actin mRNA using a DIG-labeled riboprobe (Boehringer Mannheim) under similar conditions. The gels were scanned and the relative intensity of the different bands were obtained using Scion Image software (Frederick, MD).

Immunohistochemistry

Mice were deeply anesthetized and sacrificed and tissues for immunohistochemistry were either immediately snap-frozen in Tissue-Tek OCT compound (VWR Scientific) or fixed in periodate-lysine-paraformaldehyde, sucrose infused, and then frozen in Tissue-Tek OCT. Sections of 5- to 8- μ m thickness were cut onto poly-L-lysine-coated slides, fixed in acetone, and rehydrated in phosphate-buffered saline, pH 7.4, with 0.01% Triton X-100. To prevent background staining and nonspecific binding of antibodies, sections were treated with 0.2 mol/L HCl and blocked with 3% bovine serum albumin/5% normal goat serum/0.01% Triton X-100 in phosphate-buffered saline. Sections were incubated overnight at 4°C with a rabbit anti-murine SLC antibody (Pepro Tech, Rocky Hill, NJ). The control was rabbit IgG control antibodies (I-1000) from Vector Laboratories (Burlingame, CA). After washing, a secondary biotinylated anti-rabbit antibody (Vector Laboratories) was applied, followed by incubation with alkaline-phosphatase-streptavidin (Vector Laboratories). Enzymatic reactivity was visualized with Vector Red (Vector Laboratories) according to the manufacturer's instructions. Tissues were counterstained in 3% methyl green.

Results and Discussion

Transgenic $LT\alpha$ Induces mRNA Expression of BLC and SLC

To determine the effect of locally produced $LT\alpha$ on mRNA expression of the homing chemokines BLC and SLC *in vivo*, Northern blotting was performed on kidneys from RIPLT.wt mice (Figure 1). For these studies we concentrated on the chronic inflammatory infiltrates seen at the site of $LT\alpha$ expression in the proximal tubules of the kidneys in RIPLT mice rather than in the pancreas. The kidneys exhibit more inflammation and lack adjacent lymphoid structures, such as the peripancreatic LNs, that could have confounded interpretations. Both BLC and

Figure 1. Northern blot analysis of BLC and SLC mRNA expression in RIPLT kidneys using DIG-labeled RNA probes. Wild-type (wt) spleen was used as a positive control tissue. Hybridization to a β -actin antisense probe was used to control for RNA loaded.

SLC mRNA transcripts were detected in the kidneys of RIPLT.wt mice, but not in kidneys from control wild-type mice. The increase in staining by densitometry of SLC mRNA in RIPLT kidney was 41 times that of wild-type kidney. BLC was increased threefold over wild-type kidney. *In situ* hybridization analysis of kidneys from RIPLT.wt mice confirmed the presence of BLC and SLC mRNA expression (Figure 2, A and B). The expression pattern was similar to that seen in the spleen and LNs of wild-type animals; BLC appeared to be produced by cells other than mononuclear cells, whereas nonmononuclear and endothelial cells expressed SLC. In a previous study, such nonmononuclear cells were identified as stromal cells by their expression of BP-3.²³ This analysis was not carried out here. Notably, inflammatory infiltrates were always found adjacent to expression of SLC and BLC, consistent with the chemotactic activity of these chemokines. Occasionally there was very low level expression of SLC in wild-type kidneys, consistent with previous reports of SLC expression in several tissues.

$LT\alpha$ has recently been shown to induce expression of the chemokines RANTES, IP-10, and MCP-1 both in an endothelial cell line *in vitro*⁹ and at the sites of transgene expression in RIPLT.wt mice *in vivo*.⁵ These chemokines are found even in RIPLT.RAG2 $-/-$ mice, which have a reduced inflammatory infiltrate, suggesting a direct action of $LT\alpha$ in their induction. It is likely that these chemokines contribute to the recruitment of leukocytes that are distinct from those recruited by BLC and SLC in the RIPLT kidneys. It is also likely that $LT\alpha$ induces expression of additional lymphoid organizing chemokines, such as Epstein-Barr virus-induced molecule 1 ligand chemo-

Figure 2. *In situ* hybridization analysis of BLC and SLC mRNA expression in RIPLT kidneys using DIG-labeled RNA probes. Chemokine expression appears as dark gray to black staining in this figure. **A, C, E, and G** show BLC expression and **B, D, F, and H** show SLC expression in kidneys from RIPLT.wt (**A** and **B**), RIPLT. $LT\beta^{-/-}$ (**C** and **D**), RIPLT. $TNFR1^{-/-}$ (**E** and **F**), and wild-type control (**G** and **H**) mice. Kidneys from RIPLT.wt mice were hybridized with sense BLC (**I**) and sense SLC (**J**) probes as negative controls. Original magnification, $\times 125$.

kine/macrophage inflammatory protein- 3β . Further studies with RIPLT mice deficient in various chemokine ligands and receptors will determine the role of the individual chemokines in $LT\alpha$ -induced inflammation. $LT\alpha$ could induce expression of BLC and SLC through direct and/or indirect mechanisms. Indirect mechanisms could, for instance, include production by infiltrating cells of other factors inducing expression of homing chemokines. *In vitro* studies with recombinant $LT\alpha$ protein and *in vivo* studies with transgenic mice lacking certain cell types will identify what role, if any, the infiltrating cells play in the expression of homing chemokines in $LT\alpha$ -induced inflammation.

$LT\alpha$ -Induced Expression of BLC and SLC Is Not Dependent on $LT\beta$ Expression

It has previously been shown that the presence of RIPLT-induced inflammation is not dependent on $LT\beta$ expression, although its cellular composition with regard to naive and memory cells is influenced by that cytokine.^{5,7} Ngo et al²³ have reported that $LT\beta$ -deficient mice have diminished expression of BLC and SLC in the spleen, and treatment of adult mice with $LT\alpha\beta$ antagonists reduces the splenic expression of these chemokines, suggesting a role for expression of membrane $LT\alpha1\beta2$ in maintaining normal levels of BLC and SLC. To determine whether $LT\alpha1\beta2$ heterotrimer is necessary for BLC and SLC expression in RIPLT-induced chronic inflammation, kidneys from RIPLT. $LT\beta^{-/-}$ mice were analyzed by Northern blotting and *in situ* hybridization. As shown in Figure 1 and Figure 2, C and D, $LT\beta$ is not needed for RIPLT-induced BLC and SLC expression in the inflammatory sites. In fact, SLC mRNA was increased 65-fold in RIPLT. $LT\beta^{-/-}$ kidneys compared to wild type, and BLC was increased threefold compared to wild-type. These levels are comparable or higher than that seen in RIPLT.wt kidney. Homotrimeric $LT\alpha3$ alone is thus capable of inducing expression of these chemokines. This is consistent with previous observations that $LT\beta$ is not required for $LT\alpha$ -induced expression of the proinflammatory chemokines RANTES, IP-10, and MCP-1 both *in vitro*,⁹ and *in vivo*.⁵ Interestingly, in contrast, we can confirm the important role of $LT\beta$ for expression of SLC and BLC in secondary lymphoid organs, as the spleens and mesenteric LN of RIPLT. $LT\beta^{-/-}$ mice did exhibit reduced expression of SLC and BLC (data not shown) as has been noted previously in $LT\beta^{-/-}$ mice.²³

The $TNFR1$ Receptor Plays an Important Role in $LT\alpha3$ -Induced Expression of BLC and SLC

Mice that expressed the RIPLT transgene in the absence of $TNFR1$ were analyzed for BLC and SLC expression in the kidneys. Expression of BLC and SLC was markedly reduced at the site of transgene expression as determined by Northern blotting (Figure 1) and *in situ* hybridization (Figure 2, E and F), in RIPLT. $TNFR1^{-/-}$ mice, in agreement with the previous finding that $TNFR1$ is important for $LT\alpha3$ -induced inflammation and lymphoid neogenesis.⁷ The signals for SLC and BLC mRNA were approximately three times less intense than those seen for RIPLT.wt kidneys. The reduction, but not complete loss, of BLC and SLC expression induced by locally produced $LT\alpha$ in the absence of $TNFR1$ is consistent with the finding that $TNFR1$ deficient mice still have some constitutive expression of these chemokines in the spleen (23; and our unpublished data), implicating a role for $LT\beta R$ during development. In inflammation, there might be a role for an additional non- $LT\beta$, non- $TNFR1$ receptor.

Figure 3. SLC mRNA is expressed in the pancreas of RIPLT and NOD mice. *In situ* hybridization analysis of SLC mRNA expression in RIPLT (A) and NOD (B) pancreas using DIG-labeled RNA probes. SLC staining of infiltrating and connective tissue cells in the RIPLT.wt and NOD mice is seen in purple, and infiltrating cells are counterstained with methyl green. Original magnification, $\times 62.5$.

SLC mRNA Is Detected in the Chronic Pancreatic Inflammation of Prediabetic NOD Mice

We were interested to determine whether the increased expression of homing chemokines seen in the somewhat artificial situation of transgene-induced inflammation was also seen in a spontaneous model of inflammation. We first analyzed expression of SLC mRNA in the pancreas of the RIPLT mouse and found that it was apparent in and around areas of inflammation, with particular prominence in the vessel walls (Figure 3A). We then analyzed expression of SLC mRNA in the insulinitis seen in the pancreas of prediabetic female NOD mice. The chronic inflammation in NOD mice has characteristics of lymphoid neogenesis and is present for several weeks without tissue destruction before the onset of diabetes.⁴ We detected SLC mRNA in the islets of Langerhans in the prediabetic female NOD mouse (Figure 3B). This was apparent in both the infiltrates and in the vessel walls and connective tissue. It appeared to be limited to the areas near those islets that contained infiltrates. SLC mRNA was rarely detected and when present it was at very low levels in the pancreas from healthy control wild-type mice. SLC protein was also detected in RIPLT and NOD pancreas (data not shown). These observations in a spontaneous inflammatory model confirm and extend the observations with the transgene-induced inflammation. These data indicate that homing chemokines are not restricted to development, but are also characteristic of lymphoid neogenesis in inflammation. The role of the LT/TNF family in NOD diabetes is unclear and complex. Nevertheless, TNF- α and TNF receptors (which can also be used by LT α) are expressed in the pancreas of NOD mice.^{25,26} Our data suggest that one role for this family of cytokines in inflammation could be through induction of homing chemokines.

In this report we have presented further evidence that the processes of lymphoid organogenesis during development and in chronic inflammation involve the same mechanisms. We have previously shown that LT α 3 alone is a potent inducer of adhesion molecules normally expressed in lymphoid tissues, such as MAdCAM-1.^{5,9}

MAdCAM-1 is expressed on high endothelial venules in the developing mesenteric and peripheral LN of perinatal animals and the mesenteric LN and Peyer's patches of adult animals.²⁷ Induction of MAdCAM-1 by LT α 3 may be an early event in the development of LNs. It is interesting that SLC has been found to stimulate $\alpha_4\beta_7$ (LPAM-1) mediated adhesion to MAdCAM-1,²⁸ and the present study thus indicates that LT α 3, in addition to regulating expression of MAdCAM-1, also stimulates MAdCAM-1 mediated homing through induction of SLC production. Another similarity between sites of inflammation and lymphoid organs that might be mediated by chemokines induced by LT α 3 is homing of antigen-presenting dendritic cells. SLC has recently been found to be an important chemoattractant for dendritic cells both *in vivo* and *in vitro*.^{22,29–32} Both interdigitating and follicular dendritic cells are present in the infiltrate of RIPLT mice,³ and it will be interesting to see if these cells have been recruited by certain chemokines by studying RIPLT mice deficient in chemokine ligands and receptors. In conclusion, our findings support the challenging hypothesis that LT α 3 is important for local recruitment of both lymphoid and antigen-presenting cells and orchestrates lymphoid neogenesis during the immune response through regulation of adhesion molecules and chemokines normally found in secondary lymphoid organs. Furthermore the observation in the NOD mouse suggests that this phenomenon has relevance for understanding the mechanisms of inflammation in autoimmune diseases. Formation of ectopic lymphoid follicles with germinal centers occurs in a number of chronic inflammatory diseases and a detailed understanding of the processes leading to this lymphoid neogenesis will provide a rationale for development of new therapeutics.

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