Lymphotoxin-sensitive microenvironments in homeostasis and inflammation

Bryant Boulinne, Elisa A. Portillo, Natalia Pikor and Jennifer L. Gommerman*

Department of Immunology, University of Toronto, Toronto, ON, Canada

INTRODUCTION

Within the secondary lymphoid tissues, stromal cell networks are an integral scaffold for complex immune cell interactions necessary to mount an effective immune response to pathogens. The maintenance of the phenotype and function of some stromal cell types is critically dependent on constitutive signaling of the lymphotxin-beta receptor (LTβR). LTβR is a member of the tumor necrosis factor (TNF) superfamily of receptors and is triggered by two ligands: membrane-bound LTα1β2 heterotrimers and LIGHT, resulting in the activation of both the canonical and alternative NFκB pathways (Basta et al., 2010). During embryogenesis, the LTβR-dependent activation of NFκB within lymphoid tissue organizer (LTO) cells is achieved by interaction with LTαβ1-expressing lymphoid tissue inducer (LTI) cells, thus facilitating lymph node (LN) and Peyer’s patch (PP) development (Mebias, 2005; Ruddle and Akirav, 2009).

In the adult animal, stromal cell phenotype and function must be constitutively maintained for the lifetime of the host in order to maintain the integrity of lymphoid tissue, and much of this maintenance is accomplished by continual LTβR signaling (Gommerman and Browning, 2003). The cell types which provide LTαβ1 are generally lymphocytes, in particular B cells (Tumanov et al., 2002, 2004), but can also be LTI-like innate lymphoid cells, especially in the context of the gut (Eberl, 2005). The moment such a homeostatic program is interrupted, as achieved by a single injection of the LT pathway antagonist LTαβ1 pathway antagonist (LTαβ1) in homeostasis, the LTβR signal is achieved by interaction with LTαβ1-expressing lymphoid tissue inducer (LTI) cells, thus facilitating lymph node (LN) and Peyer’s patch (PP) development (Mebias, 2005; Ruddle and Akirav, 2009).

In the adult animal, stromal cell phenotype and function must be constitutively maintained for the lifetime of the host in order to maintain the integrity of lymphoid tissue, and much of this maintenance is accomplished by continual LTβR signaling (Gommerman and Browning, 2003). The cell types which provide LTαβ1 are generally lymphocytes, in particular B cells (Tumanov et al., 2002, 2004), but can also be LTI-like innate lymphoid cells, especially in the context of the gut (Eberl, 2005). The moment such a homeostatic program is interrupted, as achieved by a single injection of the LT pathway antagonist LTβR signal is achieved by interaction with LTαβ1-expressing lymphoid tissue inducer (LTI) cells, thus facilitating lymph node (LN) and Peyer’s patch (PP) development (Mebias, 2005; Ruddle and Akirav, 2009).

Stromal cell microenvironments within lymphoid tissues are designed to support immune cell homeostasis and to regulate ongoing immune responses to pathogens. Such stromal cell networks have been best characterized within lymphoid tissues including the spleen and peripheral lymph nodes, and systems for classifying stromal cell phenotypes and functions are emerging. In response to inflammation, stromal cell networks within lymphoid tissues change in order to accommodate and regulate lymphocyte activation. Local inflammation in non-lymphoid tissues can also induce de novo formation of lymphoid aggregates, which we term here “follicle-like structures.” Of note, the stromal cell networks that underpin such follicles are not as well characterized and may be different depending on the anatomical site. However, one common element that is integral to the maintenance of stromal cell environments, either in lymphoid tissue or in extra-lymphoid sites, is the constitutive regulation of stromal cell phenotype and/or function by the lymphotxin (LT) pathway. Here we discuss how the LT pathway influences stromal cell environments both in homeostasis and in the context of inflammation in lymphoid and non-lymphoid tissues.

LTβR-DEPENDENT REGULATION OF STROMAL CELLS IN PERIPHERAL LYMPHOID TISSUES

Lymph nodes are composed of a variety of stromal cell types whose phenotype and function are being increasingly elucidated (Malhotra et al., 2012). In general, marginal reticular cells are located in the sub-capsular sinus (SCS), under which follicular dendritic cells (FDCs) populate the follicle. Fibroblastic reticular cells (FRCs) are located in the T cell-rich paracortex area and LN medullary fibroblasts are found in the medullary cords. Vascular and lymphatic endothelial cells are an additional source of non-lymphoid cell types.

Keywords: lymphotxin, follicular dendritic cell, fibroblastic reticular cell, lymph node, chemokine, follicle-like structures.

www.frontiersin.org

July 2012 | Volume 3 | Article 243 | 5

“fimmu-03-00243” — 2012/7/28 — 19:37 — page 1 — #1
Boulaanne et al. Lymphotoxin-sensitive stromal cell environments

**FIGURE 1** Stromal cell elements in the lymph node under lymphotoxin control during homeostasis and inflammation. The LT pathway is critical for the proper maintenance and function of various stromal cell elements in the LN. During homeostasis, chemokine production by FDC in the primary follicle is required for B cell positioning (1). LTβR signaling in endothelial cells of HEV is also required for the expression of sulfotransferases that promote the proper glycosylation of PNAd (2). During inflammation, the LN becomes enlarged, stromal cells acquire new functions, and increased vascularization occurs (not depicted). In addition, clusters of B and T cells aggregate within germinal centers (GC) during T-dependent immune responses, and highly differentiated FDC within the GC environment require LTβR signaling (3). To facilitate the output of plasma cells that emerge from these GC reactions, remodeling of the medullary region has been shown to occur (4).

During inflammation, the LN becomes enlarged, stromal cells acquire new functions, and increased vascularization occurs (not depicted). In addition, clusters of B and T cells aggregate within germinal centers (GC) during T-dependent immune responses, and highly differentiated FDC within the GC environment require LTβR signaling (3). To facilitate the output of plasma cells that emerge from these GC reactions, remodeling of the medullary region has been shown to occur (4).

**FOLLICULAR DENDRITIC CELLS**

B cell follicles in lymphoid tissues are largely defined by FDC (Allen and Cyster, 2008). FDCs are an important source of the B cell chemo-attractant CXCL13 which helps to establish the polarity between B and T cell zones in lymphoid tissues. FDCs also aid in germinal center responses by secreting the B cell survival factor RAFF and by trapping immune complexes for display to activated B cells (Suzuki et al., 2010). Though the exact identity of the FDC precursor is still unclear, it is thought that FDCs derive from mesenchymal cells in situ (Munoz-Fernandez et al., 2006; Allen and Cyster, 2008). It is well established that mature primary FDCs are maintained within B cell follicles by virtue of the interaction between LTαβ on B cells and LTβR on a resident radiosensitive stromal cell precursor (Fu et al., 1998; Gonzalez et al., 1998; Endres et al., 1999). LTβR signaling stimulates FDCs to secrete CXCL13, which attracts more B cells and induces them to upregulate LTαβ, thereby initiating a positive feedback loop (Ansel et al., 2000). Constitutive signaling is required for FDC maintenance and disruption of LTαβ-LTβR signaling in vivo results in the rapid disappearance of FDCs along with a disorganization of the B cell and T cell zones (Mackay et al., 1997).
FIBROBLASTIC RETICULAR CELLS
Fibroblast-like reticular cells are found predominantly in the T cell areas of LN (Balogh et al., 2008; Turley et al., 2010). FRCs secrete fibronectin, laminin, and ER-TR7 antigen, which bind ECM collagen fibers to produce a reticular network (Katakai et al., 2004). This reticular network serves as a scaffold for cell migration and retention (Bajenoff et al., 2006), a provider of a source of IL-7 (Link et al., 2007), and as conduits that facilitate movement of chemokines and small soluble Ag (Roozendael et al., 2009), and influences T cell tolerance in the steady state (Netcher et al., 2011). Like FDCs, FRCs are thought to derive in situ from a mesenchymal precursor, and multipotent mesenchymal stem cells isolated from human tonsils and bone marrow stimulated with recombinant TNFa and LTα develop an FRC phenotype in vitro (Ame-Thomas et al., 2007). Murine FRCs cultured alone in vitro do not secrete ER-TR7 but upon co-culture with CD4+ T cells FRCs produce large amounts of reticula that are coated with ER-TR7 in an LTα and TNFα-dependent manner (Katakai et al., 2004). Similarly, LTβR-Ig treatment diminished FRC networks in pancreatic infiltrates of diabetic CXCL13-RIP mice in vivo (Link et al., 2011). However, it is unclear if the development and/or maintenance of an intact ER-TR7-producing FRC network within LN requires constitutive LTβR signaling, although the loss of T cells concomitant with a decrease in LTαβ is correlated with FRC collapse in human immunodeficiency virus (HIV) infection (Zeng et al., 2012).

HIGH ENDOTHELIAL VENULES
High endothelial venules are the portals of entry for naive lymphocytes into LN. This is because the endothelium of HEV displays adhesion molecules, notably peripheral node addressin (PNAd). High endothelial venules are the portals of entry for naive lymphocytes into LN. This is because the endothelium of HEV displays adhesion molecules, notably peripheral node addressin (PNAd). Mice that receive LTβR-Ig treatment have hypo-cellular LN due to the requirement of LTβR signaling in regulating the expression of vallotransferase enzymes that mediate post-translational modification of PNAd. Without these modifications, PNAd is aberrantly expressed in HEV and naive L-selectin+ lymphocytes transmigrate into LN tissues inefficiently (Browning et al., 2005). A similar paradigm is observed for ectopic lymphoid aggregates that develop strictly after birth called cryptopatches. In the presence of commensal bacteria, these cryptopatches mature to become isolated lymphoid follicles (ILF; Taylor and Williams, 2005). LTαβ- and LTβR-deficient animals lack both ILF and cryptopatches. It is thought that IL-7 release by the underlying stroma in the small intestinal lamina propria induces the expression of LTαβ on LTαβ-like innate lymphoid cells. This in turn results in the triggering of LTβR to form the cryptopatch which matures into an ILF (Becchi, 2005). Like IFN, ILF development also requires the CCL20/CCR6 axis (Bouskra et al., 2008). Such ILF can be an alternative location for the generation of mucosal IgA+ cells (Tsuji et al., 2008).

LTβR-DEPENDENT CHANGES IN LYMPHOID STROMAL CELLS DURING INFECTION AND INFLAMMATION
Several changes occur in the draining inflamed LN following exposure to Ag in adjacent: systems for Ag transport are mobilized, stromal cells acquire new functions, the LN becomes enlarged, neo-vascularization occurs to accommodate increased cellular input, and specialized niches that support T/B interactions are formed. In this section we describe these changes, how such changes are influenced by different types of stromal cells, and the role of the LTβR pathway in orchestrating dynamic changes in the inflamed LN.

ANTIGEN TRANSPORT
Lymph-borne Ag enters LN into the SCS. There, Ag complexes are bound by CD165/F4/80+ SCS macrophages (SCS Mϕ) that extend their processes into the SCS lumen to pick up Ag complexes (Carrasco and Batista, 2007; Hunt et al., 2007). Non-cognate B cells subsequently pick up Ag complexes from SCS Mϕ, carry them deeper into follicles, and deposit the Ag on FDCs in germinal centers (Phan et al., 2007). Interruption of this transport chain results in early dissipation of germinal centers and impaired affinity maturation. SCS Mϕ express LTβR and their presence in SCS regions requires signals from LTαβ on B cells (Phan et al., 2009). As such, the expression of LTαβ on B cells is an important form of innate defense due to its ability to signal LTβR on cells of expression of LTαβ on B cells (Tumano et al., 2004). PP-resident FDCs are somewhat different than LN FDCs in that they produce mediators that particularly encourage IgA class switch recombination (Su et al., 2010). Overarching the PP follicles is the sub-epithelial dome that hosts a rich community of DC. Interestingly, expression of the chemokine CCL20 in the follicle-associated epithelium which overlies the DC-rich sub-epithelial dome is also LTβR sensitive (Rumbo et al., 2004). The CCL20/CCR6 axis may be important for the recruitment of B cells to the PP, and since B cells can express LTαβ, this could potentially drive the subsequent organization of the PP architecture (Williams, 2006). Microfold (M) cells, which are also partially dependent on the LTβR pathway (Debard et al., 2001), are interspersed within the follicle-associated epithelium. Along with dome-resident DC, M cells play an important role in shuttling Ag from the gut lumen into the PP for sampling and generation of immune responses. In general, the stroma in PP is less well characterized than in the LN.

Also within the small intestine are lymphoid tissue structures that develop strictly after birth called cryptopatches. In the presence of commensal bacteria, these cryptopatches mature to become isolated lymphoid follicles (ILF; Taylor and Williams, 2005). LTαβ- and LTβR-deficient animals lack both ILF and cryptopatches. It is thought that IL-7 released by the underlying stroma in the small intestinal lamina propria induces the expression of LTαβ on LTαβ-like innate lymphoid cells. This in turn results in the triggering of LTβR to form the cryptopatch which matures into an ILF (Becchi, 2005). Like IFN, ILF development also requires the CCL20/CCR6 axis (Bouskra et al., 2008). Such ILF can be an alternative location for the generation of mucosal IgA+ cells (Tsuji et al., 2008).
within the SCS; the first point of Ag entry (Moseman et al., 2012). Stromal cells within the SCS have been described (Katakai et al., 2008), and it will be of interest to learn how these stromal cells interact with the Ag transport chain.

LYMPHOID TISSUE REMODELING DURING INFILTRATION AND INFECTION

Dramatic changes occur in lymphoid tissues in response to viral infections. For example, during lymphocytic choriomeningitis virus (LCMV) infection, lymphoid tissue architecture becomes disorganized but is eventually restored in a manner that depends on LTβR expression on LTβR-like innate lymphoid cells (Scandella et al., 2008). In addition to this dramatic remodeling, lymphoid stroma can be an important source of type I interferons during viral infection, and LTβR signaling in splenic stroma can drive such a Type I interferon response independent of MyD88 or TRIF-derived signals (Schneider et al., 2008).

In the LN, inflammation also greatly increases the size of the LN and this LN hypertrophy is accompanied by endothelial cell proliferation that can be promoted by the production of VEGF. FDCs within the LN are a source of VEGF and this is dependent on LTβR-LTβR signaling (Chyou et al., 2008) as well as input by the alternative LTβR ligand LIGHT (Zhu et al., 2011). Furthermore, LTβR expression on B cells can also drive HIV network extension/remodeling in response to LCMV infection independent of VEGF (Kumar et al., 2010). Thus, through various mechanisms, the LT pathway is important for accommodating the increased flow of lymphocytes into a draining reactive LN. The medullary stroma, which supports lymphocyte egress from the LN, also becomes remodeled during an immune response. This may be important for providing a niche for the incredible burst in plasma cell output that is generated following a germinal center response. In this process, collagen-poor and collagen-rich areas are created, with plasma cells settling in the collagen-rich regions, presumably to take advantage of stromal cell factors that may enhance their survival (Zhu et al., 2011).

GERMINAL CENTER FORMATION

As mentioned, mature primary FDCs are located throughout B cell follicles and rely on constitutive, low-level LTβR signaling (Fu et al., 1998; Gonzalez et al., 1998; Endres et al., 1999). During an immune response, activated Ag-specific B cells that receive co-stimulation from T cells up-regulate LTβR even further and provide stronger LTβR signals to FDCs (Fu et al., 2008). This elevated LTβR signaling prompts FDCs to mature into secondary FDCs within germinal centers. Secondary FDCs up-regulate complement receptors CD21 and CD35 as well as FcyRIIB to enhance capture of Ag complexes (Allen and Cyster, 2008). While the exact role for Ag complexes on FDCs is still debated, it is likely that they help sustain the germinal center response and enhance affinity maturation. Secondary FDCs also begin to express FDC-M1 anti-influenza B cells (Kranich et al., 2008).

INFLUENCE OF LTβR SIGNALING ON ECTOPIC LYMPHOID TISSUE

Inflammation in peripheral tissues can create an environment that is permissive to the formation of follicle-like structures (FLS). These structures have been observed in a wide variety of settings and display differing levels of organization, and in some cases have been shown to support local immune responses (Aloisi and Pujol-Borrell, 2006). In this section, we review two examples of FLS and speculate on how the LT pathway may support such structures.

INDUCIBLE BRONCHIAL LYMPHOID TISSUE

Inducible bronchus-associated lymphoid tissues (iBALT; Randall, 2010) are FLS that form in the lungs in response to respiratory inflammation due to infection (Moyron-Quiroz et al., 2004; Lugade et al., 2011), chronic inflammation (Hogg et al., 2004), or autoimmunity (Bangel-Moreno et al., 2006). The content of such structures varies from highly organized niches beneath a dome epithelium with defined T cell and B cell areas and FDC capable of supporting germinal centers, to small clusters of lymphocytes containing mostly B cells and some FDC (Moyron-Quiroz et al., 2004). Local production of CXCL15, CCL19, and CCL21 drives the recruitment of lymphocytes to iBALT follicles (Foo and Phipps, 2010). Fully formed iBALT require approximately 10 days to become organized niches in adult mice post-infection (Moyron-Quiroz et al., 2004; Halle et al., 2009) but are maintained for months (Moyron-Quiroz et al., 2006).

Unlike LN and PP which require LTαβ-LTβR signaling for their formation, studies using LTα−/− mice have shown that LTβR signaling is not required for iBALT formation or induction of CXCL13, CCL19, and CCL21 during acute inflammation (Moyron-Quiroz et al., 2004). Instead, Randall and colleagues determined that CD4+ IL-17α+ cells are necessary to initiate iBALT formation (Moyron-Quiroz et al., 2004). However, once established, CD4+ IL-17α+ cells are insufficient for optimal organization and maintenance of iBALT which instead is dependent on LTβR signaling.

FLS IN THE CENTRAL NERVOUS SYSTEM

Follicle-like structures have been documented at sites of chronic inflammation in several autoimmune diseases including: rheumatoid arthritis, Sjögren’s syndrome, systemic lupus erythematosus, and Multiple Sclerosis (MS; Aloisi and Pujol-Borrell, 2006). There is a range in the level of lymphoid-like organization of these structures: from perivascular infiltrates, to diffuse aggregates with HEV-like vessels, to organized follicles with T and B cell segregation and underlying FDC networks (Browning, 2008). The disease relevance of FLS is associated with local tissue injury and cell death. In MS, FLS preferentially accumulate in the meninges in patients at the later progressive stage of the disease (Serafini et al., 2004), and meningeal FLS are associated with increased demyelination and neuronal loss (Magliozzi et al., 2007, 2010).

A role for the LT pathway in attenuating clinical disease has previously been described in the rodent model of MS, experimental autoimmune encephalomyelitis (EAE; Gommerman et al., 2003). Pharmacological disruption of LT signaling reduces the size and number of meningeal FLS compared with control treatment (Columba-Cabezas et al., 2006). Impaired FLS formation following LT inhibition is concomitant with reduced mRNA levels of CXCL10 and CXCL11 in the brain, suggesting that LT regulates chemokine induction at peripheral sites of inflammation. However, not unlike iBALT, emerging studies in EAE also support...
the notion that distinct pathways may culminate in orchestrating FLS. For example, adoptively transferred myelin-specific Th17 cells induce EAE concomitant with FLS formation (Bajenoff et al., 2005). How signals from the L T pathway and from Th17 cells co-operate to induce and/or maintain FLS structures in the CNS is unknown.

CONCLUSION

It is clear that LTTR-generated signaling underpins the maintenance and in some cases the function of stromal cell types within lymphoid tissues. Not discussed here are examples of how LTTR signaling is also important in myeloid/DC biology (Deluca and Gommerman, 2012). Fine-tuning of dendritic cell biology by the TNF superfamily (Gommerman et al., 2009) and B cells acquire particular antigen in a receptor–ligand interaction at the boundary between the follicle and the subcapsular sinus of the lymph node (Zappa, 1996). The sequential role of mature lymphoid tissue serves as a general lympho-endothelial protein. J Neuroimmunol 179, 70–86.

Deluca, L. S., and Gommerman, J. L. (2012). Fine-tuning of dendritic cell biology by the TNF superfamily. Nat Rev Immunol. 12, 399–415.

Deluca, L. S., and Gommerman, J. L. (2008). Inducible lymphoid tissue in the adult gut: recapitulation of a fetal developmental pathway? Nat Rev Immunol. 8, 413–426.

Endres, B., Almazaner, M. B., Pitz, T., Futterer, A., Kosco-Vilbois, M. H., Nedospasov, S. A., Rajewsky, K., and Pfeifer, K. (1999). Mature follicular dendritic cell networks depend on expression of lymphoid tissue beta receptor by radioresistant stromal cells and of lymphoblasts in lymph nodes. Blood 93, 3153–3160.

Eitel, G. (2005). Inducible lymphoid tissue in the adult gut: recapitulation of a fetal developmental pathway? Nat Rev Immunol. 8, 413–426.

Endres, B., Almazaner, M. B., Pitz, T., Futterer, A., Kosco-Vilbois, M. H., Nedospasov, S. A., Rajewsky, K., and Pfeifer, K. (1999). Mature follicular dendritic cell networks depend on expression of lymphoid tissue beta receptor by radioresistant stromal cells and of lymphoblasts in lymph nodes. Blood 93, 3153–3160.

Eitel, G. (2005). Inducible lymphoid tissue in the adult gut: recapitulation of a fetal developmental pathway? Nat Rev Immunol. 8, 413–426.

Endres, B., Almazaner, M. B., Pitz, T., Futterer, A., Kosco-Vilbois, M. H., Nedospasov, S. A., Rajewsky, K., and Pfeifer, K. (1999). Mature follicular dendritic cell networks depend on expression of lymphoid tissue beta receptor by radioresistant stromal cells and of lymphoblasts in lymph nodes. Blood 93, 3153–3160.

Eitel, G. (2005). Inducible lymphoid tissue in the adult gut: recapitulation of a fetal developmental pathway? Nat Rev Immunol. 8, 413–426.

Endres, B., Almazaner, M. B., Pitz, T., Futterer, A., Kosco-Vilbois, M. H., Nedospasov, S. A., Rajewsky, K., and Pfeifer, K. (1999). Mature follicular dendritic cell networks depend on expression of lymphoid tissue beta receptor by radioresistant stromal cells and of lymphoblasts in lymph nodes. Blood 93, 3153–3160.
Lagudo, A. A., Bogot, P. N., and Thanos, Y. (2011). Viral model of chronic respiratory inflammation. *Adv Exp Med Biol* 780, 243–257.

Mackay, F., and Browning, J. L. (1998). Turning off follicular dendritic cells. *Nature* 393, 26–27.

Magliozzi, R., Howell, O., Vora, A., Serafini, B., Nicholas, R., Poppema, M., Reynolds, and Aloni, E. (2017). Measuring B-cell follicles in secondary primate multiple sclerosis. *Eur. J. Immunol.* 47, 1899–1914.

Majer, T., Scandella, E., Danuser, R., Tatakai, T., Suto, H., Sugai, M., Tatakai, T., Hara, T., Sugai, M., Gonda, Junt, T., Moseman, E. A., Iannacone, M., Mitozdecorr, M., and Nedospasov, S. (2006). Follicular dendritic cells are related to bone marrow stromal cell progenitors and to neofollicular J. Immunol. 177, 280–289.

Peterson, A., Pitchen, L. A., Sullivan, J. M., Mitozdecorr, M., Anton, S. E., Franz, W., Wucherer, M., Kerly, S., Carroll, M. C., Sebel, R. A., Betti, E., and Kuchroo, V. K. (2011). Th17 cells induce ectopic lymph follicles in central nervous system tissue inflammation. *Immunity* 35, 986–999.

Plau, T. G., Green, J. A., Gray E. E., Xu, Y., and Cyster, J. G. (2009). Immune complex relay by subcapsular sinus macrophages and non-germinal B cells drives antibody affinity maturation. *J. Immunol.* 182, 798–805.

Phan, T. G., Gregorova, I., Okada, T., and Cyster, J. G. (2007). Subcapsular encounter and complement-dependent transport of immune complexes by lymph node B cells. *J. Exp. Med.* 202, 1931–1942.

Randall, T. D. (2010). Bronchus-associated lymphoid tissue (BALT) structure and function. *Adv. Immunol.* 107, 187–241.

Rouzendaal, R., Mempel, T. R., Schoor, A., Mebius, R. E., Von Andrian, U. H., and Carroll, M. C. (2009). Conduits mediate transport of low-molecular-weight antigens to lymph node follicles. *J. Immunol.* 183, 204, 679–683.

Routbort, M., Sunni, K., Katarzyna, H., Agap, A. W., and Fagarasan, S. (2010). The sensing of environmental stimuli by follicular dendritic cells promotes immunoglobulin A generation in the gut. *Nature Immunol.* 11, 75–81.

Scheu, S., Carroll, M. C., Sobel, R. A., Betelli, E., and Kuchroo, V. K. (2011). Th17 cells induce ectopic lymph follicles in central nervous system tissue inflammation. *Immunity* 35, 986–999.

Serafini, B., Rosselli, B., Magliozzi, R., Stegall, E., and Aloni, E. (2004). Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. *Brain Pathol.* 14, 164–174.

Seppi, A., Pitcher, L. A., Sullivan, J. M., Mitozdecorr, M., Anton, S. E., Franz, W., Wucherer, M., Kerly, S., Carroll, M. C., Sebel, R. A., Betti, E., and Kuchroo, V. K. (2011). Th17 cells induce ectopic lymph follicles in central nervous system tissue inflammation. *Immunity* 35, 986–999.

Shumway, H., Ha, S., Patterson, G., Pfeffer, K., Nedospasov, S. A., Ware, C. F., and Benzel, C. A. (2008). Lymphomamediated crosstalk between B cells and splenic stroma promotes the initial type 1 interferon response to cytomegalovirus. *Cell Host Microbe* 3, 67–76.

Shu, D., Ito, T., Okada, T., and Kuchroo, V. K. (2005). Distinct role of surface lysophosphatidylcholine expressed by B cells in the organization of secondary lymphoid tissues. *J. Immunol.* 174, 259–268.

Tamanaro, A. V., Kabir, D., Lagarkova, M., Grosenikov, S., Abe, K., Shikhluk, A., Drinka, L., Stewart, C., Cherwinski, A., and Nedospasov, S. (2002). Distinct role of surface lysophosphatidylcholine expressed by B cells in the organization of secondary lymphoid tissues. *J. Immunol.* 170, 259–268.

Tamanaro, A. V., Kabir, D., Mack, J. A., Nedospasov, S. A., and Cherwinski, A. Y. (2004). Lymphoid tissue is formed by...
B cells are dispensable for maintenance of the follicle-associated epithelium but are required for development of lymphoid follicles in the Peyer’s patch. J. Immunol. 175, 86–91.

Turley, S. J., Fletcher, A. L., and Elpek, K. G. (2010). The stromal and hematopoietic antigen-presenting cells that reside in secondary lymphoid organs. Nat. Rev. Immunol. 10, 813–825.

Vu, F., Dianzani, U., Wang, C. I., Mak, T., and Gommerman, J. L. (2008). ICOS, CD40, and lymphotoxin beta receptors signal sequentially and interdependently to initiate a germinal center reaction. J. Immunol. 180, 2286–2295.

Williams, I. R. (2006). CCR6 and CCL20: partners in intestinal immunity and lymphoid organogenesis. Annu. N. Y. Acad. Sci. 1072, 52–61.

Zeng, M., Paolardini, M., Engram, J. C., Belman, G. I., Shipman, J. C., Schacker, T. W., Silvetri, G., and Haase, A. T. (2012). Critical role for CD4 T cells in maintaining lymphoid tissue structure for immune cell homeostasis and reconstitution. Blood. doi: 10.1182/blood-2012-03-418624 [Epub ahead of print].

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2012 Boulianne, Porfilio, Pikor and Gommerman. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in other forums, provided the original authors and source are credited and any copyright notices concerning any third-party graphics etc.