



Potential of Cells and Cytokines/Chemokines to Regulate Tertiary Lymphoid Structures in Human Diseases

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Tertiary lymphoid structures (TLS) are ectopic lymphoid tissues involved in chronic inflammation, autoimmune diseases, transplant rejection and cancer. They exhibit almost all the characteristics of secondary lymphoid organs (SLO), which are associated with adaptive immune responses; as such, they contain organized B-cell follicles with germinal centers, distinct areas containing T cells and dendritic cells, high endothelial venules, and lymphatics. In this review, we briefly describe the formation of SLO, and describe the cellular subsets and molecular cues involved in the formation and maintenance of TLS. Finally, we discuss the associations of TLS with human diseases, especially autoimmune diseases, and the potential for therapeutic targeting.

[Immune Network 2016;16(5):271-280]

Keywords: Tertiary lymphoid structures, Autoimmunity, Inflammation

DEVELOPMENT OF SECONDARY LYMPHOID ORGANS (SLO)

SLO include encapsulated organs such as the spleen and lymph nodes and un-encapsulated mucosal lymphoid organs such as Peyer's patches, tonsils, and nasal-associated lymphoid tissues. SLO develop before birth and are important locations for the initiation of adaptive immune responses since they maximize encounters between antigen, antigen-presenting cells, and lymphocytes present in blood and surrounding mucosal tissues.

SLO formation requires the interaction between CD3⁺CD4⁺CD45⁺ lymphotoxin- α 1 β 2 (LT α 1 β 2)-expressing lymphoid-tissue inducer cells and lymphotoxin- β receptor-expressing stromal organizer cells. LT α 1 β 2 activates lymphoid tissue stromal organizer cells to produce homeostatic chemokines such as CXC chemokine ligand 13 (CXCL13) and CC-chemokine ligand 21

(CCL21) and CCL19, which regulate lymphocyte homing and compartmentalization (1).

DEFINITION OF TERTIARY LYMPHOID STRUCTURES (TLS)

TLS, also named tertiary lymphoid organs or ectopic lymphoid tissues, are architecturally similar to conventional SLO. TLS include organized B-cell follicles with germinal centers (GCs), distinct T cell areas that contain some dendritic cells (DCs), high endothelial venules (HEV) that traffic immune cells from circulation into TLS, and lymphatics that transport tissue DCs into the TLS (2-4). TLS not only share spatial organization, cellular compartments, vasculature, and chemokines with SLO, but also functional characteristics including leukocytes priming, clonal expansion, somatic hyper-

Received on July 14, 2016. Revised on August 22, 2016. Accepted on August 27, 2016.

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Abbreviations: TLS, tertiary lymphoid structures; SLO, secondary lymphoid organs; DC, dendritic cell; LTi, lymphoid tissue inducer

mutation, affinity maturation, immunoglobulin class switching, B cell-receptor revision, and maintenance of peripheral tolerance (5-7). Even so, there are important differences. For example, SLO are genetically preprogrammed and pre-patterned as they arise at key locations in the body during embryogenesis under the control of a precise developmental program. SLO have distinctive features (8): that is, they trigger priming of naive T cells following interaction with DCs and resume quiescence when the “foreign” antigen is eliminated (9).

By contrast, development of TLS can be driven by environmental influences, including chronic inflammation, autoimmune diseases (10,11), transplant rejection (12), and cancer (13). TLS develop as un-encapsulated lymphoid aggregates almost everywhere in the body and do not appear at predictable sites: this is especially true when there is a continuing need for leukocyte extravasation or where antigens persist (10,14). Thus, many of the mechanisms that control the development, cellular compositions and functional maintenance of SLO and TLS are common to both.

CELLULAR COMPOSITION OF TERTIARY LYMPHOID STRUCTURES

A variety of cell types, including lymphoid tissue inducer (LTi) cells, local stromal cells, B cells, DCs, and some T cell subsets, such as T helper cells, Th17 cells, Treg cells and CD8 T cells, are critical for TLS formation (Fig. 1).

LTi cells induce TLS formation by expressing a wide range of proteins, particularly $LT\alpha 1\beta 2$ (15). LTi cells accumulate in the presence of CXCL13 and interleukin-7 (IL-7) and their receptors such as CXCR5 and IL-7R (16,17). The cells interact with antigen-specific CD4 T cells and associate with memory T cells in the GCs via OX40 and CD30 (18). However, some TLS develop independently from LTi cells or associated molecules; for example, omental milky spots in the peritoneal cavity (19) and tumor necrosis factor- α (TNF α)-dependent lymphoid tissue in the intestine (20). In addition, other cell types, like B cells (21), T cells (22), or M1-polarized proinflammatory macrophages (23), can substitute for LTi cells during TLS development, particularly when activated and expressing $LT\alpha 1\beta 2$ on the surface. For example, activated $CD3^+CD4^+$ T cells interact with DCs in a Hashimoto thyroiditis mouse model, resulting in TLS formation; this process, depends on mature $CD3^+CD4^+$ T cells but not on conventional LTi cells (24).

Stromal cells include fibroblastic reticular cells (FRCs)

that reside in the T cell zone, follicular dendritic cells (FDCs) that populate B cell follicles, marginal reticular cells adjacent to subcapsular sinus lymphatic endothelial cells, pericytes, epithelial cells, and versatile stromal cells (VSCs) (6). Stromal cells are well known for forming extracellular matrix in all lymphoid organs by providing survival signals and adhesive substrata to immune cells (25). For example, arterial TLS in the adventitial connective tissue adjoining arteries is formed through vascular smooth muscle cell lymphotoxin β (LT β) receptor signaling (26). Interactions between LTi cells and stromal cells are critical for proper TLS formation (27). In particular, increased expression of adhesion molecules such as intercellular adhesion molecule 1 (ICAM1) and chemokines such as CXCL13, CCL19 and CCL21, are critical for recruitment of hematopoietic cells (1). Thus, TLS in CNS autoimmune diseases often developed in the meninges but not in neural parenchyma; this is because stromal cells mainly reside in the meninges (28). Also, FRCs play a critical role in maintaining aberrant components in the wrong tissue at the wrong time, thereby contributing to TLS persistence in chronic inflammatory diseases (29,30).

B cells, which accumulate on the follicular DC network, are the major TLS component. Most TLS exhibit B cell class switching and the presence of activation-induced cytidine deaminase and germinal center reactions (31,32). Autoreactive B cells in TLS may escape apoptosis and negative selection due to sustained production of the B cell survival factor, BAFF. Some B cells may reach the bone marrow, where they reside as long-lived plasma cells (33). A fully structured TLS depends on LT β expression by B cells (34). After exposure to continuous stimuli in a chronic inflammatory environment, B cells upregulate lymphotoxin expression through IL-4R α signaling and promote FRC proliferation and activation via lymphotoxin-LT β R signaling (35). Moreover, B cells contribute to local immune responses to persisting autoantigens by producing proinflammatory cytokines, chemokines and growth factors, all of which are crucial for TLS formation. Also, B cells co-operate with $CD8^+$ tumor-infiltrating lymphocytes to promote anticancer immunity and act as new prognostic biomarkers for cancer survival (36,37).

A variety of T cells are involved in TLS formation or maintenance, including $CD8^+$ T cells and some $CD4^+$ T cell subsets, natural killer T cells (NKT), Th17 cells, follicular helper T (Tfh) cells, and T regulatory cells (Tregs). CCL21 recruits T cells. $CD8^+$ T cells control germinal center reactions in both SLO and TLS. Deple-

tion of synovial CD8⁺ T cells causes disintegration of GC-containing follicles, disappearance of FDCs, significantly reduced production of LT α 1 β 2 and a lack of immunoglobulin (Ig) secretion (38). CD4⁺ T helper (Th) cells in a special TLS, which is formed during chronic allergic inflammation in the lung and named inducible bronchus-associated lymphoid tissue (iBALT), show a memory phenotype (39). NKT cells restricted by the antigen-presenting molecule CD1d seem to be required for inducible formation of fat-associated lymphoid clusters, which support and coordinate the activation of innate B cells and T cells during serosal immune responses in the peritoneal cavity (40).

Th17 cells are a subset of CD4⁺ T cells subsets that are the main source of cytokines interleukin-17, IL-21, and IL-22. Th17 cells and these cytokines play

important roles in host defense against various infections and can be responsible for the pathogenesis of many autoimmune diseases (41). Interestingly, Th17 cells share many characteristics with LTi cells, including LT α 1 β expression (42). Th17 cells exert their deleterious effects by promoting formation of ectopic GCs in TLS in inflamed tissues (43), thereby facilitating chronic rejection (44). Th17 cell plasticity permits acquisition of Tfh-like effector characteristics that support TLS expansion and germinal center reactions (45). *In vitro*-generated Th17 cells transferred into mice can drive TLS formation in the subarachnoid space around vessels (22). TLS formation by Th17 cells in the CNS requires IL-17 (22), while IL-17 is needed to initiate but not to maintain iBALTs (46). Th17 cells initiate TLS formation by remodeling meningeal-resident stromal cells and affecting

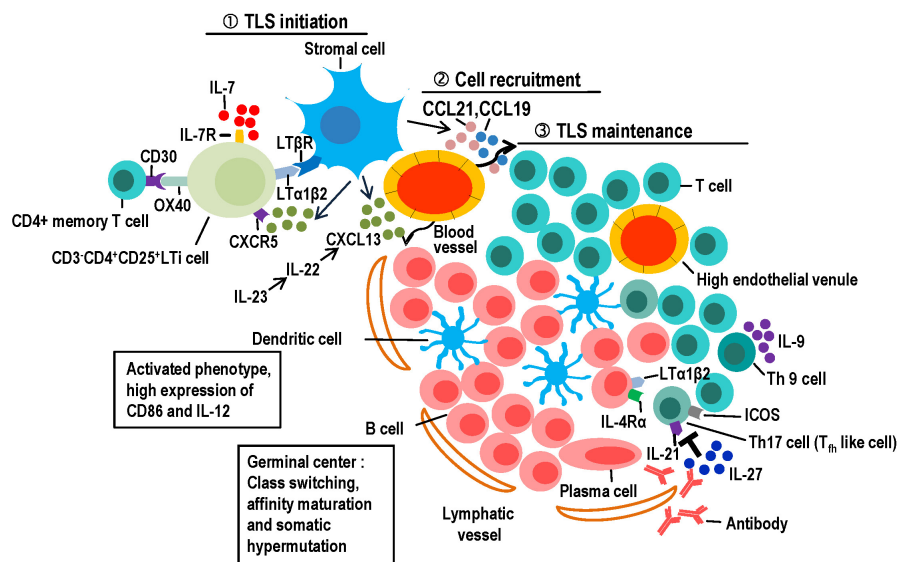


Figure 1. Potential of cells and cytokines/chemokines to regulate the induction and maintenance of Tertiary Lymphoid Structures (TLS). ① Cells of various types, especially CD3⁺CD4⁺CD25⁺ LTi cells and stromal cells, initiate TLS formation. B cells, T cells, and M1-polarized proinflammatory macrophages can substitute for LTi cells. LTi cells accumulate in the presence of CXCL13 and interleukin-7 (IL-7) and their receptors such as CXCR5 and IL-7R. LTi cells interact with antigen-specific CD4⁺ memory T cells via OX40 and CD30. ② Leukocytes from the circulation are recruited to inflammatory sites in response to certain chemokines and regulated by cytokines. Stromal cells secrete several chemokines, including CXC-chemokine ligand 13 (CXCL13), CC-chemokine ligand 21 (CCL21) and CCL19, which are responsible for the recruitment of B and T cells, respectively. IL-23 can efficiently induce IL-22, which regulates the production of CXCL13, thereby orchestrating B-cell clustering, lymphoid aggregation, and autoantibody production in the TLS. ③ Various cell types and cytokines are involved in maintaining TLS formation: a) B cells, which accumulate in the follicular DC network, are the major TLSs component. Most TLS exhibit B cell class switching, affinity maturation and somatic hypermutation. B cells upregulate lymphotoxin expression through IL-4R α signaling; b) A variety of T cells are involved in TLS maintenance, including Th17 cells and Th 9 cells. Th17 cell plasticity permits acquisition of Tfh-like effector characteristics that support germinal center reactions. Th17 cells also initiate TLS formation by remodeling stromal cells. Tfh cells are localized in the B cell follicles expressing high levels of the co-stimulatory molecules such as inducible T cell co-stimulator (ICOS) and IL-21, thereby promoting activation and differentiation of B cells for Ig class switching and Ig production. Th9 cells produce IL-9, levels of which correlate with the degree of inflammatory infiltrate and TLS organization; c) DCs in TLS often show an activated/mature phenotype, with high CD86 and IL-12 expression. DCs increase antigen presentation, form tight clusters with infiltrating CD4⁺ T cells and promote T cell proliferation; d) IL-27 can negatively regulate TLS development by blocking Th17-associated pathology.

communication between them in mice with experimental autoimmune encephalomyelitis (EAE), and propagate neuroinflammation through $LT\alpha\beta$ expression (43).

Tfh cells are localized in B cell follicles expressing high levels of the co-stimulatory molecules inducible T cell co-stimulator and IL-21, thereby promoting activation and differentiation of B cells for Ig class switching and Ig production (47). Tfh cells are linked to germinal center responses and the formation and maintenance of TLS (48). T follicular helper-like cells are indispensable for B cell expression of a classical germinal center phenotype (49). In many autoimmune diseases, Tregs are either reduced in number or functionally impaired. CCR7-deficient mice possess few Tregs in lung-draining bronchial lymph nodes suggesting that iBALT formation might be caused by non-functional Treg cells (50). Consistent with this, depletion of Tregs from mice upregulates expression of IL-17A and CXCL9 in the lungs and induces tissue neutrophilia (51).

On the other hand, lymphocytes are found in large lymph node (LN)-like, complex tumor-associated TLS in cancer patients (52); these TLS facilitate interactions between T cells and DCs. Both costimulatory ligand expression by DCs and T cell proliferation in tumor-associated TLS increase upon Treg cell depletion, leading to tumor destruction (3). TLS develop in most solid cancers and correlate with a favorable clinical outcome for cancer patients, regardless of the stage of disease (36). Thus, tumor-associated-TLS promote anti-tumor responses.

DCs in TLS often show an activated/mature phenotype, with high CD86 and IL-12 expression. Repeated injection of DCs into mice induces formation of lung iBALT (53). DC depletion leads to iBALT disintegration and fewer GC reactions, indicating that DCs are critical for TLS maintenance. DCs might increase antigen presentation, form tight clusters with infiltrating $CD4^+$ T cells, and promote T cell proliferation (24). In addition, DCs increase the production of cytokines and chemokines, including CXCL13, CCL21/CCL19 (54), B cell-activating factor (BAFF), IL-6, and IL-15 (55), as well as that of type I interferons (56). DCs also play an important role in endothelial cell differentiation (57). In human lung cancer, TLS-associated mature DCs generates a specific immune context characterized by a strong Th1 and cytotoxic orientation that confer a positive prognostic value (58).

CYTOKINES AND CHEMOKINES IN TLS

Homeostatic inflammatory cytokines and chemokines

contribute to the initiation and organization of TLS. Such molecules include $LT\alpha$, $LT\alpha1\beta2$, CXCL13, CCL21, CCL19, IL-17, IL-22, IL-23, IL-7, and IL-27, all of which play differential roles depending on the site of infection and the nature of the pathogen. $LT\alpha$ is a cytokine produced by lymphocytes and is anchored to the surface of Th1 and Th17 cells. Depleting LT -expressing Th1 and Th17 cells using a monoclonal antibody targeting surface $LT\alpha$ inhibits T cell-mediated inflammation and autoimmune disease (59). Similar to SLO formation, $LT\alpha$ can induce stromal cells in the TLS to develop into FDCs and HEVs (60). CXCL13 functions in B cell recruitment and trafficking, and is also critical for the formation and maintenance of B lymphocyte follicles in some autoimmune-associated TLS (61). CXCL13 also promotes $LT\alpha1\beta2$ secretion by B cells and T cells, which establishes a positive feedback loop that perpetuates lymphocyte recruitment (62), DC proliferation, and T cell priming (63). CCL21 helps to maintain inflammation by promoting integrin-dependent adhesion and extravasation of naive T cells (57). Without CCL21, these cells are unable to return to the circulation and accumulate in inflamed tissues, which may lead to TLS formation (64).

Almost all TLS in chronically rejected human renal allografts correlate with IL-17 expression (65). iBALT formation depends on IL-17 produced by $CD4^+$ T cells, since the latter promote secretion of high levels of CXCL13 and CCL19, which are critical for TLS formation (46). In a mouse model of EAE, Th17 cells induce TLS formation, which is in turn dependent on IL-17 and Pdp (22). Th17 cells are also associated with TLS formation in other human diseases (44). IL-22 acts downstream of the LT pathway and regulates TLS organization and maintenance in the colon during infection (66). IL-22 can also regulate production of CXCL13, which can orchestrate B-cell clustering, lymphoid aggregation, and autoantibody production in TLS (67). Blockade of either IL-22 pathway significantly impairs and reverses TLS formation, suggesting that IL-22 has an indispensable role in maintaining TLS (67). IL-22 is efficiently induced by IL-23, which is strongly associated with rheumatoid arthritis (RA) (68).

Recent evidence suggest a role for IL-7 in the development of SLO and TLS (69). IL-7 stimulates LTi cells and maintains T lymphocytes survival (70). Gene expression profiling of synovial tissue from patients with RA identified IL-7 signal transduction in tissues within TLS, which was accompanied by increased expression of IL-7 receptor ($IL-7R$)/ $IL-2R$ chains and IL-7 in cases of TLS-associated synovitis (71). Also, IL-9 expression produced

by Th9 cells in RA patients correlates with the degree of synovial inflammatory infiltrate and TLS organization (72).

However, IL-27 can negatively regulate TLS development in RA by controlling effector T cells (73). Models of inflammatory arthritis show that IL-27 blocks Th17-associated joint pathology (74).

TLS IN HUMAN DISEASES

The presence of fully functional ectopic GCs in TLS has been described in a broad variety of autoimmune diseases, including RA (75), Sjögren's syndrome (76), lupus nephritis (77), autoimmune diabetes (78), a mouse model of multiple sclerosis (43), a mouse model of spontaneous autoimmune uveitis (79), Hashimoto's thyroiditis, and Graves' disease (80). Although a wide spectrum of lymphoid arrangements coexist in the same patient, TLS includes relatively poorly organized perivascular aggregates, diffuse lymphoid infiltrates, and highly organized ectopic lymphoid follicles that display HEV development; T/B cell segregation; GC formation; and specialized reticular networks containing FDC and follicular reticular cells (4,10). In most autoimmune disorders, TLS show detrimental properties. For example, TLS are responsible for inducing or exacerbating autoimmune responses which, in human primary Sjögren's syndrome samples, correlate with increased levels of proinflammatory mediators and autoantibody production (81). Also, TLS in a mouse model of hepatocellular carcinoma serve as niches for malignant hepatocyte progenitor cells, which may lead to tumor recurrence (82); this is despite the finding that TLS protect against most tumors, including both primary tumors and metastatic tumors (13).

There is a correlation between cytokine or chemokine levels and increased complexity of TLS in autoimmune lesions, supporting a causative role for these mediators in TLS formation (75). However, some studies demonstrate that TLS are not totally consistent with arthritis activity or severity, even though they correlate with local autoantibody production (83). TLS facilitate localization of ectopic GCs and generation of new specific autoreactive B cells, thereby facilitating local antimicrobial responses, epitope spreading (84), and autoimmune exacerbation. Increased diversity of autoreactive B cells in the TLS may also be due to escape from peripheral tolerance, resulting in disturbance of autoreactive B cell selection (64).

TLS AS PROMISING TARGETS FOR THE TREATMENT OF HUMAN DISEASES

TLS help to eliminate or neutralize pathogens by generating plasma cells that produce specific antibodies. TLS may amplify autoimmune responses, tissue damage, thereby exacerbating a disease, which may then show a poor response to standard biological therapies (11). Blocking chemokines and their receptors is a promising therapeutic strategy. Treatment of an autoantibody-mediated cardiac allograft mouse model, with an inhibitory LT β R-Ig fusion protein abolished TLS formation and markedly inhibited effector antibody responses (85). A mouse anti-CXCL13 antibody demonstrated some efficacy in a mouse model of RA and in a Th17-mediated murine model of multiple sclerosis (86).

The T follicular helper-germinal center/ B-cell axis is pro-atherogenic, and genetic disruption of CD8⁺ Tregs leads to increased TLS development in the aorta and exacerbates disease. Thus, disrupting this axis or enhancing CD8⁺ Treg cell function represents a promising therapeutic approach (87). Also, Treg cell ablation within tumor-associated-TLS in a mouse model of lung cancer induces robust effector T cell responses and tumor destruction (3), suggesting that Treg cell deletion might be a promising method of in disrupting TLS development and preventing tumor progression.

Treatments aimed at depleting B cells do not alter the characteristic features of Sjögren's syndrome, which include increased clonal expansion in the salivary glands of patients; this is because established chronic TLS are already present (88). Thus, combination therapy targeting multiple steps or multiple components of TLS in human diseases deserves consideration.

CONCLUDING REMARKS

Recent years have witnessed much research into the mechanisms underlying TLS formation and their relationship with disease. To some extent, TLS could clear pathogens and therefore be beneficial to the individual. Yet many questions remain. For example, retinoic acid is demonstrated to be responsible for gut-associated lymphoid tissues formation (89). It is unknown whether retinoic acid also activates Li cells in autoimmune disease. And are LT_i cells the earliest sensors of autoantigens and tissue damage that can deliver signals to other cells and amplify the deleterious effects? Also, the exact effect of TLS in humans is still unknown. For example, to what

extent do TLS contribute to the ongoing inflammatory process and tissue damage in humans? Humanized mouse models are quite useful in human disease research. Since they can be experimentally manipulated to study human hematology and immunology in vivo, as well as cancer therapy. This model system could be a promising way to investigate the role of TLS in human diseases (90).

In addition, the differences between TLS and SLO are only partly known. It is not sure whether the immune response is different in TLS and SLO? And are there any specific cell populations in TLS that have functions different from that in SLO? Do the specific cells or cytokines contribute much to TLS formation and maintenance? And Epstein-Barr virus is thought to be a critical factor that determines TLS formation (91), as is murine cytomegalovirus in the salivary glands (92); therefore, do viruses affect TLS formation/function? In addition, is TLS development driven by different disease subtypes, or are TLS the inevitable result of persistent inflammation? And what may contribute to TLS resolution? Even though TLS are not fully understood, the functional artificial lymphoid tissue shows therapeutic promising. Since artificial lymphoid tissue induce specific immunity at ectopic sites and offer a novel breakthrough to restore the immune status and to treat uncontrollable obstinate diseases such as cancer, autoimmune diseases and severe infection (93). So it is exciting to investigate the mechanism of TLS in human diseases by combining the artificial lymphoid tissue system with humanized mouse models.

ACKNOWLEDGEMENTS

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology of Korea (2011-0014447).

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