REVIEW

Tertiary lymphoid organs in systemic autoimmune diseases: pathogenic or protective? [version 1; peer review: 2 approved]

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Abstract

Tertiary lymphoid organs are found at sites of chronic inflammation in autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. These organized accumulations of T and B cells resemble secondary lymphoid organs and generate autoreactive effector cells. However, whether they contribute to disease pathogenesis or have protective functions is unclear. Here, we discuss how tertiary lymphoid organs can generate potentially pathogenic cells but may also limit the extent of the response and damage in autoimmune disease.

Keywords

Tertiary Lymphoid Organs, Lymph node, Autoimmune disease, Lupus, Rheumatoid Arthritis

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Introduction

Autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis are marked by chronic inflammation in end organs that can be associated with the development of tertiary lymphoid organs (TLOs)^{1–6}. TLOs are also known as tertiary lymphoid tissues, ectopic lymphoid follicles, or ectopic lymphoid structures and are accumulations of lymphocytes and stromal cells in an organized structure that occur outside of secondary lymphoid organs (SLOs). TLOs share many features with SLOs, such as the presence of T and B cell compartmentalization into T cell zones and B cell follicles, chemokines that mediate the compartmentalization, antigen-presenting cells, lymphatic sinuses, high endothelial venules, follicular dendritic cells, and fibroblastic reticular cells (FRCs)^{7–11}. In SLE, inflammation in the kidney interstitial tissue is associated with greater risk for kidney failure¹². Up to almost half of patients have well-circumscribed aggregates of B cells, plasma cells, and T cells and a small fraction can have well-organized germinal centers with follicular dendritic cells^{1,2}. In rheumatoid arthritis, TLOs ranging from B and T cell aggregates to germinal centers are found in the inflamed synovium of about half of biopsied patients and are associated with more severe joint and systemic inflammation^{3–6,13}. TLOs are also found in other organs in other autoimmune diseases or models, such as in the salivary and lacrimal glands in Sjögren's syndrome^{14–16}, the central nervous system in multiple sclerosis^{7,17–22}, the pancreas in diabetes^{23–25}, the thymus in myasthenia gravis^{26,27}, and the intestines in inflammatory bowel disease^{28,29}. While findings in recent years have begun to delineate the mechanisms that regulate the formation of TLOs (recently reviewed in 7–11), it is unclear whether TLOs provide pathogenic or protective contributions to SLE, rheumatoid arthritis, and other autoimmune diseases. Here we will review evidence that TLOs may generate potentially pathogenic cells but that they may limit the extent of pathogenic cell activity.

Tertiary lymphoid organs can generate potentially pathogenic cells

In the setting of infections, TLOs have been generally considered to be protective, adopting SLO-like functions and acting as “outposts” of SLOs that are directly positioned at the site of inflammation. TLOs form in the lung of influenza-infected mice^{30–32} that can maintain and reactivate memory CD8+ T cells³³ and produce plasma cells and antiviral serum immunoglobulins³¹. Remarkably, although there is a delay in anti-viral immunity development, TLOs are sufficient for protection when the hosts are deficient in SLOs³³, underscoring the idea that TLOs can generate effector cells that provide effective host defense. Innate lymphoid cells (ILCs) in the lung are induced after influenza infection and have been shown to maintain lung function, epithelial integrity, and airway remodeling³⁴. Although it is unknown whether TLOs play a role in maintaining or stimulating lung ILCs after influenza infection, ILCs have been shown to be associated with TLOs and have even been associated with decreased disease progression in lung cancer^{35–37}. It is possible that influenza-induced lung TLOs also provide a suitable environment for ILCs to populate and function in a protective manner. Similar to influenza virus infection, TLOs form with pulmonary *Mycobacterium tuberculosis* (MTB) infection^{38–40}. Latent tuberculosis is associated with more frequent, well-organized TLOs while TLOs are less frequent and less well-formed in active tuberculosis⁴⁰, suggesting a protective

role for TLOs in controlling disease. The TLOs contribute to the formation of granulomas, which function to promote immunity and limit tissue damage⁴¹. Additionally, CXCL13 expression that organizes the B cell follicles serves to recruit CXCR5-expressing T helper (Th) cells into granulomas to activate macrophages that are essential to infection control^{38,40}. These studies on TLOs in infection models highlight the ability of TLOs to support immune responses that are capable of protecting the host.

Similar to immune responses generated in SLOs, immune responses targeted to self may be harmful to the host. The TLOs in SLE kidneys contain germinal centers that show clonal expansion and somatic hypermutation characteristic of germinal center responses in SLOs², demonstrating well-developed effector responses. The TLOs correlate strongly with the presence of immune complexes, suggesting that the locally generated antibodies are autoantibodies to renal antigens that can fix complement and thus cause tissue inflammation and damage². Similarly, the B cell responses associated with TLOs in the rheumatoid arthritis synovium⁴², the salivary glands in Sjögren's syndrome⁴³, and other target tissues show autoimmunity¹⁰. SLE kidneys and rheumatoid synovium are also characterized by the accumulation of Th17 cells, which can have proinflammatory roles^{44–48}. While IL-17-expressing cells could help to induce TLO formation, as has been shown in the central nervous system and in neonatal lung^{20,22,49}, the TLOs could potentially also help to support Th17 cell maintenance or acquisition of additional proinflammatory properties^{20,50,51}. Indeed, B cells are necessary for the accumulation of activated T cells, likely by presenting antigen to the T cells^{52–54}, and B cells in TLOs may be pathogenic in part by stimulating autoreactive T cells, which then can contribute to the inflammatory milieu in the affected end organs. TLOs in autoimmune diseases, then, can be a source of potentially pathogenic lymphocytes.

Tertiary lymphoid organs can potentially limit pathogenic responses

Despite the generation of autoreactive and proinflammatory cells, TLOs could also have a protective role by sequestering pathogenic lymphocytes and preventing them from leaving the specific tissue or tissue compartment to cause further damage. For example, in SLE, glomerular damage is unrelated to the extent of interstitial inflammation¹², but failure to sequester lymphocytes within the interstitial tissue could potentially result in the migration of lymphocytes to the glomeruli and worsened glomerular damage. Alternatively, in the absence of TLOs, the lymphocytes could enter the circulation to home to and potentially damage additional organs outside the kidneys. That inflammatory cells are able to find alternative niches despite the absence of TLOs is seen in MTB infection, where antigen-specific T cells still accumulate, showing an altered, perivascular location, in the absence of TLOs^{38,40}. Also, B cell selection in the pancreas is unaltered by follicular disruption of TLO in the pancreas of non-obese diabetic mice²⁵. Interestingly, TLOs within tumors but not at the tumor periphery are correlated with good outcomes in a study of pancreatic carcinoma patients⁵⁵, raising the possibility that the TLOs at the tumor periphery prevent potential anti-tumor lymphocytes from accessing the tumor parenchyma. The concept that TLOs might have a sequestration function is analogous to the sequestration of lymphocytes within SLOs with the S1P agonist fingolimod, which is used to treat multiple sclerosis⁵⁶. Fingolimod

downregulates SIP receptor 1, preventing lymphocyte egress from the SLOs and subsequent migration to end organs⁵⁷. Sequestration of potentially pathogenic cells, then, may help limit the extent of disease.

TLOs can also be protective if they provide a microenvironment that generates regulatory or reparative cells that reduce the pathogenicity of inflammatory cells. In the apoE^{-/-} model of atherosclerosis, TLOs that form on the outer aspects of the atherosclerotic vessel wall generate regulatory T cells (Tregs). These TLOs are dependent on lymphotoxin β receptor (LT β R) stimulation of presumably local vascular smooth muscle, and preventing TLO formation by deleting LT β R from smooth muscle cells resulted in more and enlarged plaques⁵⁸. These results suggested that the TLOs were protective, perhaps by the generation of the Tregs. Here, the TLO stroma may be critical for the generation of regulatory cells. Lymph node FRCs have been implicated in Treg generation by presenting self-antigen on MHCII and by guiding T cells into a tolerance-inducing environment^{59,60}. FRCs, along with endothelial cells, can additionally promote tolerance by MHCII presentation of autoantigen^{61,62} and regulate the magnitude of T cell activation by expressing inducible nitric oxide synthase^{63–65}. Tregs have also been shown to mediate tissue repair via amphiregulin in lung with influenza infection⁶⁶ and in muscle after injury⁶⁷, and thus TLO generation of Tregs can have protective effects independent of their immunosuppressive functions. Similarly, ILCs are another source of amphiregulin that is important for repair³⁴, and TLOs may potentially support their development⁶⁸. Interestingly, both SLE patients and lupus-prone mice possess decreased numbers and abnormal function of Tregs^{69–72} while exhibiting increased calcium/calmodulin-dependent protein kinase IV (CamK4)^{73,74}, which is responsible for an imbalance in Th17 cells and Tregs with a shift towards more Th17 cells. Inhibition of CamK4 corrected this imbalance in lupus-prone mice, decreasing Th17 cells and increasing Tregs in the kidney in association with reduced organ damage⁷⁵. It is tempting to speculate that the TLOs (and perhaps the SLOs) in SLE do not function correctly to foster optimal Treg generation. TLOs, then, may not only sequester potentially pathogenic cells but also provide an environment that limits the magnitude or severity of the response.

Conclusion

In conclusion, in autoimmune diseases, TLOs can generate and harbor autoreactive and proinflammatory, potentially pathogenic lymphocytes but could potentially serve to limit pathogenic responses by sequestering these cells or by reducing the magnitude of the response. Therapeutically, targeting TLOs may offer opportunities to ameliorate disease, and more understanding of the potential pathogenic and protective functions is needed. For example, can we identify TLOs that generate more pathogenic cells versus those that have more regulatory functions? Do these different functions in part reflect the evolution of TLO development and maturation? What are the vascular, stromal, and hematopoietic elements that contribute to the different microenvironments, and can we modulate them to generate a more immunoregulatory environment? Furthermore, understanding how the affected tissue outside the TLOs may be similar or distinct in supporting the generation and maintenance of autoreactive lymphocytes would enrich our understanding of the distinct nature of TLOs and also allow us to prevent the lymphocytes from potentially accumulating elsewhere upon TLO disruption. Continued improved understanding of TLO biology will help us better understand how to treat autoimmune disease.

Author contributions

All authors contributed to the writing of this manuscript.

Competing interests

The authors declare that they have no competing interests.

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