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)\(^1\). 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)\(^2\)-\(^3\). In SLE, inflammation in the kidney interstitial tissue is associated with greater risk for kidney failure\(^4\). 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\(^5\). 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\(^5\)-\(^8\),\(^1\). 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\(^9\)-\(^1\), the central nervous system in multiple sclerosis\(^1\),\(^1\),\(^2\),\(^3\),\(^4\), the pancreas in diabetes\(^1\),\(^5\)-\(^8\), the thymus in myasthenia gravis\(^9\),\(^1\),\(^0\),\(^1\), and the intestines in inflammatory bowel disease\(^1\)-\(^2\). While findings in recent years have begun to delineate the mechanisms that regulate the formation of TLOs (recently reviewed in \(7\)-\(1\)), 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\(^1\)-\(^2\). TLOs are also known to be involved in the formation of granulomas, which function to promote immunity and limit tissue damage\(^3\). Additionally, CXC chemokine receptor 13 (CXCR13) 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\(^3\),\(^4\). 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 SLOs\(^5\), 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 damage\(^5\). Similarly, the B cell responses associated with TLOs in the rheumatoid arthritis synovium\(^6\), the salivary glands in Sjögren’s syndrome\(^7\), and other target tissues show autoimmunity\(^8\). SLE kidneys and rheumatoid synovium are also characterized by the accumulation of Th17 cells, which can have proinflammatory roles\(^9\). While IL-17-expressing cells could help to induce TLO formation, as has been shown in the central nervous system and in neonatal lung\(^3\),\(^1\),\(^0\), the TLOs could potentially also help to support Th17 cell maintenance or acquisition of additional proinflammatory properties\(^1\),\(^3\),\(^4\). Indeed, B cells are necessary for the accumulation of activated T cells, likely by presenting antigen to the T cells\(^3\),\(^1\),\(^4\), 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 inflammation\(^1\), 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\(^1\)-\(^2\). Also, B cell selection in the pancreas is unaltered by follicular disruption of TLO in the pancreas of non-obese diabetic mice\(^3\). Interestingly, TLOs within tumors but not at the tumor periphery are correlated with good outcomes in a study of pancreatic carcinoma patients\(^4\), 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 SIP agonist fingolimod, which is used to treat multiple sclerosis\(^5\). Fingolimod
References

1. Steinmetz OM, Velden J, Kneissler U, et al.: Analysis and classification of B-cell infiltrates in lupus and ANCA-associated nephritis. Kidney Int. 2008; 74(4): 446–51. Published Abstract | Publisher Full Text | F1000 Recommendation

2. Chang A, Henderson SG, Brandt D, et al.: In situ B cell-mediated immune responses and tubulointerstitial inflammation in human lupus nephritis. J Immunol. 2011; 186(3): 1849–60. Published Abstract | Publisher Full Text | F1000 Recommendation

3. Humby F, Bombardi M, Manzo A, et al.: Ectopic lymphoid structures support ongoing production of class-switched autoantibodies in rheumatoid synovium. PLoS Med. 2009; 6(1): e1. Published Abstract | Publisher Full Text | Free Full Text

4. Wengner AM, Hipkiss UE, Petrov PK, et al.: CXCR5- and CCR7-dependent lymphoid neogenesis in a murine model of chronic antigen-induced arthritis. Arthritis Rheum. 2007; 56(10): 3271–83. Published Abstract | Publisher Full Text

5. Shi K, Hayashida K, Kaneko M, et al.: Lymphoid chemokine B cell-attracting chemokine-1 (CXCL13) is expressed in germinal center of ectopic lymphoid follicles within the synovium of chronic arthritis patients. J Immunol. 2001; 166(1): 650–5. Published Abstract | Publisher Full Text | F1000 Recommendation

6. Takemura S, Braun A, Cowson C, et al.: Lymphoid neogenesis in rheumatoid synovitis. J Immunol. 2001; 167(2): 1072–80. Published Abstract | Publisher Full Text | F1000 Recommendation

7. Pikor NB, Prat A, Bar-Or A, et al.: Meningeal Tertiary Lymphoid Tissues and Multiple Sclerosis: A Gathering Place for Diverse Types of Immune Cells

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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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.
during CNS Autoimmunity. Front Immunol. 2015; 6: 657.

8. Barone F, Gardner DH, Nayar S, et al.: Stomal Fibroblasts in Tertiary Lymphoid Structures: A Novel Target in Chronic Inflammation. Front Immunol. 2016; 7: 477.

9. Buckley CD, Barone F, Nayar S, et al.: Stomal cells in chronic inflammation and tertiary lymphoid organ formation. Annu Rev Immunol. 2015; 33: 715–45.

10. Consiero E, Nerviani A, Bombardieri M, et al.: Ectopic Lymphoid Structures: Powerhouse of Immunity. Front Immunol. 2016; 7: 420.

11. Ruddle NH: High Endothelial Venules and Lymphatic Vessels in Tertiary Lymphoid Organs: Characteristics, Functions, and Regulation. Front Immunol. 2016; 7: 491.

12. Hsieh C, Chang A, Brandt D, et al.: Predicting outcomes of lupus nephritis with tubulointerstitial inflammation and scarring. Arthritis Care Res (Hoboken). 2011; 63(8): 865–74.

13. Thurling GM, Wijbrands CA, Mebius RE, et al.: Synovial lymphoid neogenesis does not define a specific clinical rheumatoid arthritis phenotype. Arthritis Rheum. 2008; 58(8): 1582–9.

14. Fava RA, Kennedy SM, Wood SG, et al.: Lymphotoxin-beta receptor blockade reduces CXCL13 in lacrimal glands and improves corneal integrity in the NOD model of Sjögren's syndrome. Arthritis Res Ther. 2011; 13(3): R182.

15. Bombardieri M, Barone F, Lucchesi D, et al.: Inducible tertiary lymphoid structures, autoimmunity, and exocrine dysfunction in a novel model of salivary gland inflammation in C57BL/6 mice. J Immunol. 2012; 189(7): 3767–76.

16. Olderati N, St Carié EW: Recent advances in primary Sjögren's syndrome [version 1; referees: 3 approved]. F1000Res. 2016; 6: pii-F1000 Faculty Rev-1412.

17. Columba-Cabezas S, Griguoli M, Rosicarelli B, et al.: Suppression of established experimental autoimmune encephalomyelitis and formation of meningeval lymphoid follicles by lymphotoxin receptor-lig fusion protein. J Neuroimmunol. 2000; 179(1–2): 76–86.

18. Magliozzi R, Columba-Cabezas S, Serafini B, et al.: Intracerebral expression of CXCL13 and BAFF is accompanied by formation of lymphoid follicle-like structures in the meninges of mice with relapsing experimental autoimmune encephalomyelitis. J Neuroimmunol. 2004; 148(1–2): 11–23.

19. Mitsdoerffer M, Peters A: Tertiary Lymphoid Organs in Central Nervous System Autoimmunity. Front Immunol. 2016; 7: 451.

20. Peters A, Pitcher LA, Sullivan JM, et al.: Th17 cells induce ectopic lymphoid follicles in central nervous system tissue inflammation. Immunity. 2011; 35(6): 866–86.

21. Serafini B, Rosicarelli B, Magliozzi R, et al.: Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. Brain Pathol. 2004; 14(2): 164–74.

22. Fikov NB, Astaria JL, Summers-Delucia L, et al.: Integration of Th17- and Lymphoxygen-Dependent Signals Initiates Meningeal-Resident Stromal Cell Remodeling to Propagate Neuroinflammation. Immunity. 2015; 43(6): 1160–73.

23. Astori E, Bombardieri M, Gabba S, et al.: Evolution of ectopic lymphoid neogenesis and in situ autoantibody production in autoimmune encephalomyelitis in pancreatic islets. J Immunol. 2010; 185(6): 3539–68.

24. Ludwig B, Odermatt B, Landmann S, et al.: Dendritic cells induce autoimmune diabetes and maintain disease via de novo formation of local lymphoid tissue. J Exp Med. 1998; 188(8): 1493–501.

25. Henry RA, Kendal PL: CXCL13 blockade disrupts B lymphocyte organization in tertiary lymphoid structures without altering B cell receptor bias or preventing diabetes in nonobese diabetic mice. J Immunol. 2010; 185(3): 1460–5.

26. Hill ME, Shinoh H, Newcomb Davis J, et al.: The myasthenia gravis thymus: a rare source of human autoimmune-secreting plasma cells for testing potential therapeutics. J Neuroimmunol. 2008; 201–202: 50–6.

27. Zhang X, Liu S, Chang T, et al.: Intrathymic Th/Bl Cells Interaction Leads to Ectopic GCs Formation and Anti-ACHR Antibody Production: Central Role in Triggering MG Occurrence. Mol Neurobiol. 2016; 53(1): 120–31.

28. Buettner M, Lochner M: Development and Function of Secondary and Tertiary Lymphoid Organs in the Small Intestine and the Colon. Front Immunol. 2016; 7: 349.

29. Oliker BJ, Calloto C, van der Vliet J, et al.: Vagal innervation is required for the formation of tertiary lymphoid tissue in colitis. Eur J Immunol. 2016; 46(10): 2467–80.

30. Moyron-Quiroz JE, Rangel-Moreno J, Kusser K, et al.: Role of inducible bronchus associated lymphoid tissue (IBALT) in respiratory immunity. Nat Med. 2004; 10(9): 927–34.

31. GeurtsvanKessel CH, Willart MA, Bergen IM, et al.: Induced bronchus-associated lymphoid tissue serves as a general priming site for T cells and is maintained by dendritic cells. J Exp Med. 2009; 206(12): 2093–401.

32. Hallé S, Dujardin HC, Bakovic N, et al.: Lymphoid follicles by lymphotoxin beta receptor-Ig fusion protein. J Immunol. 2004; 173(2): 491.

33. Moyron-Quiroz JE, Rangel-Moreno J, Hartson L, et al.: Persistence and responsiveness of immunologic memory in the absence of secondary lymphoid organs. Immunity. 2006; 25(6): 643–54.

34. Montecelli LA, Sonnemberg GF, Abt MC, et al.: Intra-nephritic lymphoid cells promote tissue homeostasis after infection with influenza virus. Nat Immunol. 2011; 12(11): 1045–54.

35. Carrega P, Loiacono F, Di Carlo E, et al.: NCR1/LC3 concentration in human lung cancer and associate with intratumoral lymphoid structures. Nat Commun. 2015; 6: 8280.

36. Meier D, Bornmann C, Chappaz S, et al.: Ectopic lymphoid-organ development occurs through interleukin 7-mediated enhanced survival of lymphoid-tissue-inducing cells. Immunity. 2007; 26(5): 645–54.

37. Schmutz S, Bosco N, Chappaz S, et al.: Cutting edge: IL-7 regulates the peripheral pool of adult ROR gamma+ lymphoid tissue inducer cells. J Immunol. 2009; 183(4): 2127–31.

38. Khader SA, Rangel-Moreno J, Fountain JJ, et al.: In a murine tuberculosis model, the absence of homeostatic chemokines delays granuloma formation and protective immunity. J Immunol. 2009; 183(12): 8004–14.

39. Ulrichs T, Kosmiadl GA, Trusov V, et al.: Human tuberculous granulomas induce peripheral lymphoid follicle-like structures to orchestrate local host defence in the lung. J Pathol. 2004; 204(2): 217–28.

40. Slight SR, Rangel-Moreno J, Gepal R, et al.: CXCR5+ T helper cells mediate protective immunity against tuberculosis. J Clin Invest. 2013; 123(2): 715–26.

41. Bean AG, Rozar DR, Bricco H, et al.: Structural deficiencies in granuloma formation in TNF gene-targeted mice underlie the heightened susceptibility to aerosol Mycobacterium tuberculosis infection, which is not compensated by lymphoxygenin. J Immunol. 1999; 162(6): 3041–11.

42. Consiero E, Bombardieri M, Carlotti E, et al.: Single cell cloning and recombinant monoclonal antibodies generation from RA synovial B cells reveal frequent targeting of citrullinated histones of NETs. Ann Rheum Dis. 2016; 75(10): 1866–75.

43. Salomonsson S, Jonsson MV, Skarstein K, et al.: Recent advances in primary Sjögren's syndrome. Arthritis Care Res (Hoboken). 2015; 67(10): 2288–97.

44. Salomonsson S, Jonsson MV, Skarstein K, et al.: Recent advances in primary Sjögren's syndrome. Arthritis Care Res (Hoboken). 2015; 67(10): 2288–97.

45. Salomonsson S, Jonsson MV, Skarstein K, et al.: Recent advances in primary Sjögren's syndrome. Arthritis Care Res (Hoboken). 2015; 67(10): 2288–97.

46. Salomonsson S, Jonsson MV, Skarstein K, et al.: Recent advances in primary Sjögren's syndrome. Arthritis Care Res (Hoboken). 2015; 67(10): 2288–97.

47. Salomonsson S, Jonsson MV, Skarstein K, et al.: Recent advances in primary Sjögren's syndrome. Arthritis Care Res (Hoboken). 2015; 67(10): 2288–97.

48. Salomonsson S, Jonsson MV, Skarstein K, et al.: Recent advances in primary Sjögren's syndrome. Arthritis Care Res (Hoboken). 2015; 67(10): 2288–97.
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