Cellular and Molecular Life Sciences (2022) 79:359
https://doi.org/10.1007/s00018-022-04388-x

REVIEW

Role of tertiary lymphoid organs in the regulation of immune responses in the periphery

Amit I. Bery[1] · Hailey M. Shepherd[2] · Wenjun Li[2] · Alexander S. Krupnick[4] · Andrew E. Gelman[2,3] · Daniel Kreisel[2,3]

Received: 14 December 2021 / Revised: 28 April 2022 / Accepted: 20 May 2022 / Published online: 11 June 2022

Abstract

Tertiary lymphoid organs (TLOs) are collections of immune cells resembling secondary lymphoid organs (SLOs) that form in peripheral, non-lymphoid tissues in response to local chronic inflammation. While their formation mimics embryologic lymphoid organogenesis, TLOs form after birth at ectopic sites in response to local inflammation resulting in their ability to mount diverse immune responses. The structure of TLOs can vary from clusters of B and T lymphocytes to highly organized structures with B and T lymphocyte compartments, germinal centers, and lymphatic vessels (LVs) and high endothelial venules (HEVs), allowing them to generate robust immune responses at sites of tissue injury. Although our understanding of the formation and function of these structures has improved greatly over the last 30 years, their role as mediators of protective or pathologic immune responses in certain chronic inflammatory diseases remains enigmatic and may differ based on the local tissue microenvironment in which they form. In this review, we highlight the role of TLOs in the regulation of immune responses in chronic infection, chronic inflammatory and autoimmune diseases, cancer, and solid organ transplantation.

Keywords Tertiary lymphoid structures · Inflammation · Autoimmune diseases · Transplantation immunology · Tumor microenvironment

Introduction

Lymphoid organs can broadly be classified into three categories. Primary lymphoid organs develop during embryogenesis and include the bone marrow and thymus which are responsible for the production of lymphoid cells [1, 2]. Secondary lymphoid organs (SLOs) regulate antigen-driven lymphocyte expansion resulting in production of memory T cells, effector B cells, and plasma cells and include lymph nodes, spleen, tonsils, Peyer's patches of the gut, and certain mucosal lymphoid tissues that develop independent of antigen [1, 2]. While lymphoid organogenesis (SLO formation) generally occurs during embryogenesis, certain mucosal lymphoid tissues, including mucosa-associated lymphoid tissue (MALT), nose-associated lymphoid tissue (NALT), and tear duct-associated lymphoid tissue (TALT), develop after birth [2–4]. TLOs, also known as tertiary lymphoid tissues, tertiary lymphoid structures, or ectopic lymphoid structures, are collections of immune cells that resemble secondary lymphoid organs organized into a follicular structure, often with germinal centers, that form in peripheral, non-lymphoid tissues in response to chronic inflammation or tissue injury [2, 5, 6]. While the signaling pathways involved in the formation and maintenance of TLOs generally mimic SLO formation, TLOs regulate immune responses in a disease- and tissue-specific manner, and thus can lead to protective or pathologic responses depending on the tissue microenvironment in which they form [2, 7, 8]. These structures have proven to be critical for the regulation of immune responses in the periphery in several chronic inflammatory conditions. In this review, we highlight the role of TLOs in the regulation of immune responses in chronic infection,

✉ Amit I. Bery
amit.bery@wustl.edu

1 Division of Pulmonary and Critical Care, Department of Medicine, Washington University School of Medicine, 660 South Euclid Avenue, Campus, Box 8052, St. Louis, MO 63110, United States

2 Department of Surgery, Washington University School of Medicine, St. Louis, MO, United States

3 Departments of Pathology & Immunology, Washington University School of Medicine, St. Louis, MO, United States

4 Department of Surgery, University of Maryland School of Medicine, Baltimore, MD, United States

chronic inflammatory and autoimmune diseases, cancer, and solid organ transplantation.

Formation of TLOs

TLOs are formed at sites of chronic inflammation or tissue injury in a process known as lymphoid neogenesis (Fig. 1) [2, 6, 9, 10]. The structure of TLOs can vary depending on inflammatory stimulus and tissue type from clusters of B and T lymphocytes to structures organized in a manner similar to SLOs with B cell follicles and germinal centers, T cell compartments, LVs, and HEVs, but generally lack a defined capsule [2, 6, 11, 12]. Unlike lymphoid organogenesis which is programmed, lymphoid neogenesis is inducible and occurs in response to local inflammation [2, 4, 6, 13]. However, while lymphoid neogenesis has largely been shown to follow similar signaling pathways as lymphoid organogenesis, the events precipitating TLO formation have not been fully elucidated and may differ by disease process and tissue of origin [2, 5, 14].

Local inflammatory responses to tissue injury trigger secretion of cytokines, such as IL-13, IL-17, and IL-22, by infiltrating immune cells and resident fibroblasts resulting in priming of local stromal cells, including fibroblasts, myofibroblasts, and endothelial cells [9, 15, 16]. The immune cells that produce this signal can differ based on the inflammatory stimulus and the tissue in which the inflammation occurs [9, 17, 18]. These signals result in local fibroblast proliferation and expression of lymphoid stromal chemokines, such as CXCL13, CCL19, and CCL21 [9]. CXCL13 is a chemokine that binds to the CXCR5 receptor on B cells and subsets of T cells and is critical for the homing of these cells and structural organization of lymphoid organs [19]. CCL19 and CCL21 are chemokines that bind the CCR7 receptor on B and T lymphocytes as well as dendritic cells (DCs) and are critical for the trafficking of these cells into lymphoid organs [20]. Expression of these chemokines by local fibroblasts results in recruitment of immune cells and further expression of chemokines (CXCL13, CCL19, CCL21) and cytokines (IL-17, IL-22). In addition, infiltrating immune cells and lymphoid tissue inducer (LTi) cells can express cytokines from the TNF superfamily such as TNF-α, lymphotoxins [LTα (also known as TNF-β), LTα1β2, LTα2β1)], and lymphotoxin-like inducible protein that competes with glycoprotein D for herpesvirus entry on T cells (LIGHT) [21, 22]. LTα1β2 and LIGHT can bind and activate the lymphotoxin β receptor (LTβR) on stromal cells. LTβR signaling mediates the differentiation of fibroblastic reticular cells (FRCs) and follicular dendritic cells (FDCs), formation of HEVs, and organization of B and T lymphocyte compartments [23]. In addition, production of TNF-α by M1 macrophages has been shown to induce aortic TLOs in a LTβR-independent fashion in a murine model of atherosclerosis. These signaling cascades result in a positive feedback loop wherein more immune cells are recruited and chemokine and cytokine production increase. As more immune cells are recruited, localization of CXCL13 and CCL21 expression can result in separate B and T cell compartments [24, 25]. LVs and HEVs form and express CCL21 which may allow naïve B and T lymphocytes to enter the TLO [11]. While lymphangiogenesis in TLOs remains poorly understood, studies have implicated LTβR signaling, differentiation of peri-venular and preexisting LV endothelial cells, and even transdifferentiation of macrophages in this process [11]. FDCs produce CXCL13 in B cell compartments and recruit follicular helper T (T_{FH}) cells to form functional germinal centers [26]. T_{FH} cells secrete IL-21, a B cell stimulatory cytokine, and express costimulatory signals including inducible T cell costimulator (ICOS) and CD40L which together result in B cell activation, proliferation, and differentiation into antibody-producing plasma cells [27–29]. Sustained signaling by $CD11c^+$ DCs appears to be critical to the maintenance and function of these structures as selective depletion of these cells in murine models of TLO formation results in dissolution of TLOs [30, 31].

One of the major unresolved issues in TLO biology is whether TLO formation always occurs due to an antigen-dependent immune response. Antigen-dependent immune responses have been implicated in the formation of TLOs in human and animal models of certain conditions, including microbial antigens in infection and vaccination [32], the nicotinic acetylcholine receptor in myasthenia gravis [33], multiple thyroid antigens in autoimmune thyroiditis [34], tumor-associated antigens in malignancy [35], and alloantigens after transplantation [36]. However, TLOs have been observed to form in conditions in which the driving antigen is not readily apparent, including chronic obstructive pulmonary disease (COPD) [37] and atherosclerosis [38]. In addition, Fleig and colleagues recently showed in a mouse model that loss of endothelial Notch signaling alone can induce perivascular TLO formation indicating that these structures can form in an antigen-independent fashion [39]. These observations have led to the development of the *inflammation-driven TLO hypothesis* (as coined by Yin and colleagues) in which TLO formation occurs due to signaling cascades induced by chronic, un-resolving inflammation in an antigen-independent manner [40].

Role in infection and chronic inflammation

TLOs can form as a protective immune response during infection with certain bacterial, fungal, and viral pathogens. Infection with *Mycobacterium tuberculosis* (MTb) results in granuloma formation followed by infiltration of immune cells and their organization into TLOs known as inducible bronchus-associated lymphoid tissue (iBALT) in both

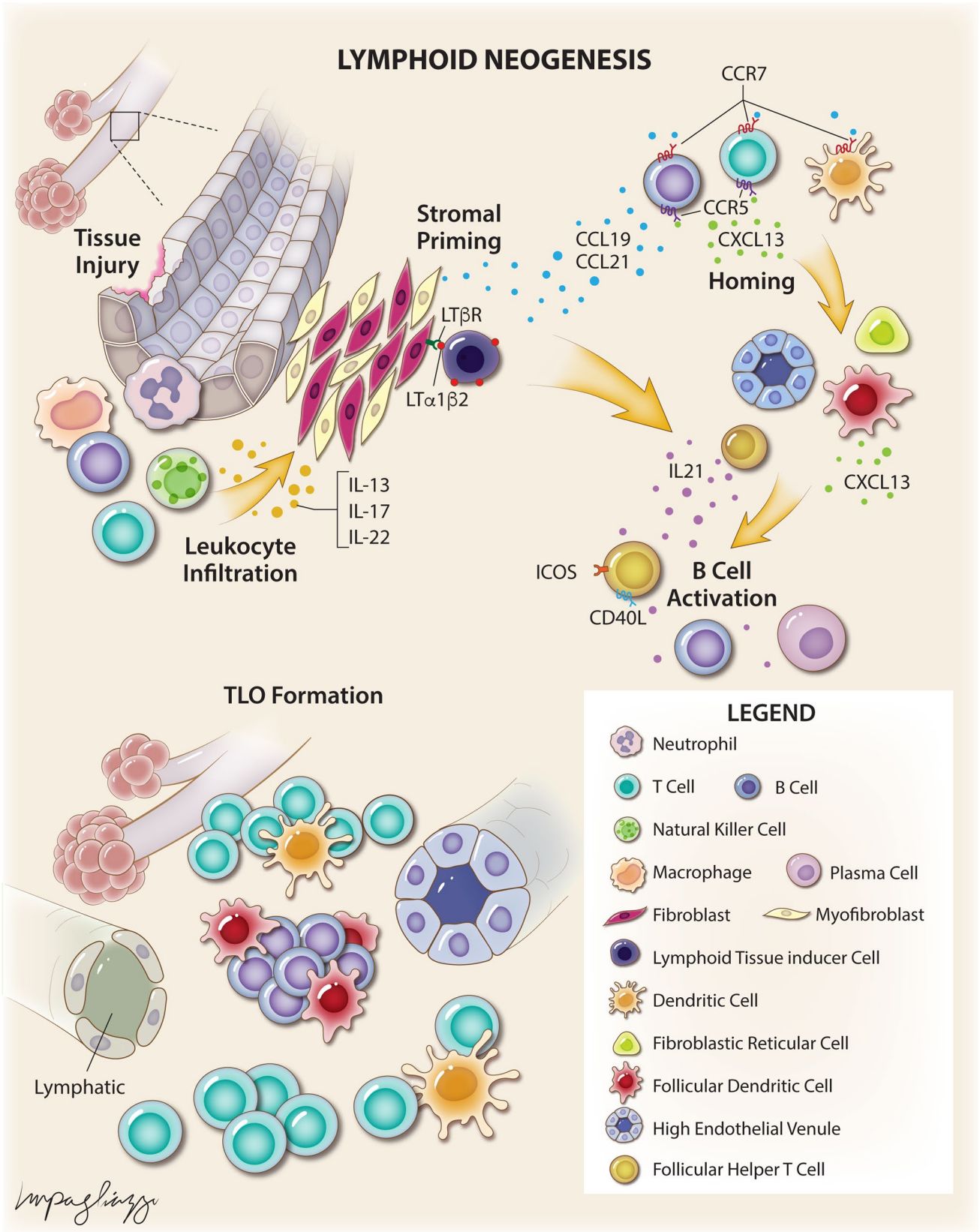

Fig. 1 Schematic illustrating mechanisms of lymphoid neogenesis

humans and animal models [41–43]. Formation of iBALT is associated with IL-17, IL-22, IL-23, CXCL13, CCL19/CCL21, and CCR5 signaling in animal models of MTb infection [42, 44–47]. iBALT may play an important role in the control of MTb infection given its presence in patients with latent TB and absence in patients with reactivated TB [48]. In addition to bacteria, iBALT has shown similar protective immune responses to fungal and viral pathogens. In a mouse model of *Pneumocystis jirovecii* infection, iBALT formation was dependent on CXCL13 and resulted in a reduced fungal burden [49]. In animal models of influenza virus infection, iBALT formation results in improved viral clearance and reduced mortality [8, 50–52]. Also, induction of BALT with virus-like particles results in improved viral clearance in influenza-naïve mice [53]. Vaccine strategies that induce BALT have been shown to elicit effective immune responses to bacterial and viral pulmonary pathogens in animal models [54–56]. These studies illustrate that TLOs can play a protective role during infection with certain bacterial, fungal, and viral pathogens.

TLOs have also been implicated in facilitating pathologic immune responses to certain infectious pathogens. iBALT has been shown to induce hypersecretion of mucus, exacerbate inflammation, and induce asthma exacerbation in mouse models of respiratory syncytial virus infection [57, 58]. iBALT has also been found in humans and animal models of cystic fibrosis and bronchiectasis where chronic infection with bacterial pathogens is common, though their role as protective or pathologic structures is poorly understood [59, 60]. Animal models of chronic *Pseudomonas aeruginosa* infection show iBALT formation is dependent on IL-17 production and results in production of anti-Pseudomonal IgM and IgA antibodies, but can also result in narrowing of small airways potentially contributing to obstructive lung diseases in which chronic *Pseudomonas aeruginosa* infection is common [61–63]. Human peptic *Helicobacter pylori* infection results in development of ectopic MALT in the gastric mucosa and is associated with gastritis and development of MALT lymphoma [64–66]. TLOs have further been associated with pathologic immune responses to infectious pathogens in the liver (*Propriobacterium acnes, Helicobacter hepaticus*, hepatitis C virus), kidney (*Leptospira interrogans* serovar *Pomona*), synovium (*Borrelia burgdorferi)*, and central nervous system (*Borrelia burgdorferi*) in humans and animal models [67–75].

TLOs can also propagate pathologic immune responses in chronic inflammatory diseases. Formation of iBALT is associated with vascular inflammation in humans and animal models of pulmonary hypertension [76, 77] and airway inflammation associated with asthma and COPD [78–83]. TLO formation results in mucosal inflammation and nasal polyp formation in human chronic rhinosinusitis [84–87]. CXCL13 and CCL21 have also been implicated in bowel mucosal TLOs and mesenteric fat inflammation in humans and animal models of inflammatory bowel disease [88–93]. Interestingly, TLOs have been shown to promote vascular inflammation in some human studies and animal models of aortic atherosclerosis but prevent atherosclerosis and plaque rupture in others [23, 94–97]. Collectively, these studies point to disease- and tissue-specific roles of TLOs in mediating protective or pathologic responses in chronic inflammatory diseases (Fig. 2, Table 1).

Role in autoimmune disease

TLOs have been observed in the target tissues of several autoimmune diseases including rheumatoid arthritis [98], Sjögren's syndrome [99], systemic lupus erythematosus [100], myasthenia gravis [33], type I diabetes mellitus [101], autoimmune thyroiditis [34, 102], and multiple sclerosis [18]. While TLOs have been observed in the majority of autoimmune diseases, their prevalence varies widely in published reports, both among diseases and even within populations having a particular autoimmune disease [98, 103–111].

Autoimmune disease-associated TLOs are theorized to develop in response to disease-specific autoantigens in the target tissues and result in local autoantibody production [112]. The events that trigger the release of autoantigens in the formation of TLOs remain elusive. Prior studies have implicated viral infections, stromal cell antigen release, and cell death pathways, with a particular focus on the production of neutrophil extracellular traps (NETs), or NETosis [112–115]. Regardless of the source of autoantigens, autoimmune disease-associated TLOs can develop functional germinal centers that express activation-induced cytidine deaminase (the enzyme implicated in immunoglobulin gene affinity maturation by somatic hypermutation and isotype class switch recombination) resulting in proliferation of B cell clones and their differentiation into plasma cells that produce autoantibodies against local autoantigens [98, 113, 116]. Furthermore, autoimmune disease-associated TLOs allow germinal center entry of autoreactive B cells whereas they are excluded from entry into germinal centers in SLOs [117, 118].

The development of TLOs in autoimmune disease can result in sustained immune activation and production of autoantibodies. Transplantation of TLO-containing tissues from patients with rheumatoid arthritis or Sjögren's syndrome into severe combined immunodeficiency (SCID) mice resulted in production of human anti-citrullinated peptide antibody or human anti-SSA (anti-Ro) and anti-SSB (anti-La) antibodies, respectively [98, 115]. In addition, transplantation of thymic tissue fragments, but not dissociated thymic cells, from patients with myasthenia gravis into SCID mice resulted in sustained production of human anti-acetylcholine receptor antibodies [119]. These studies

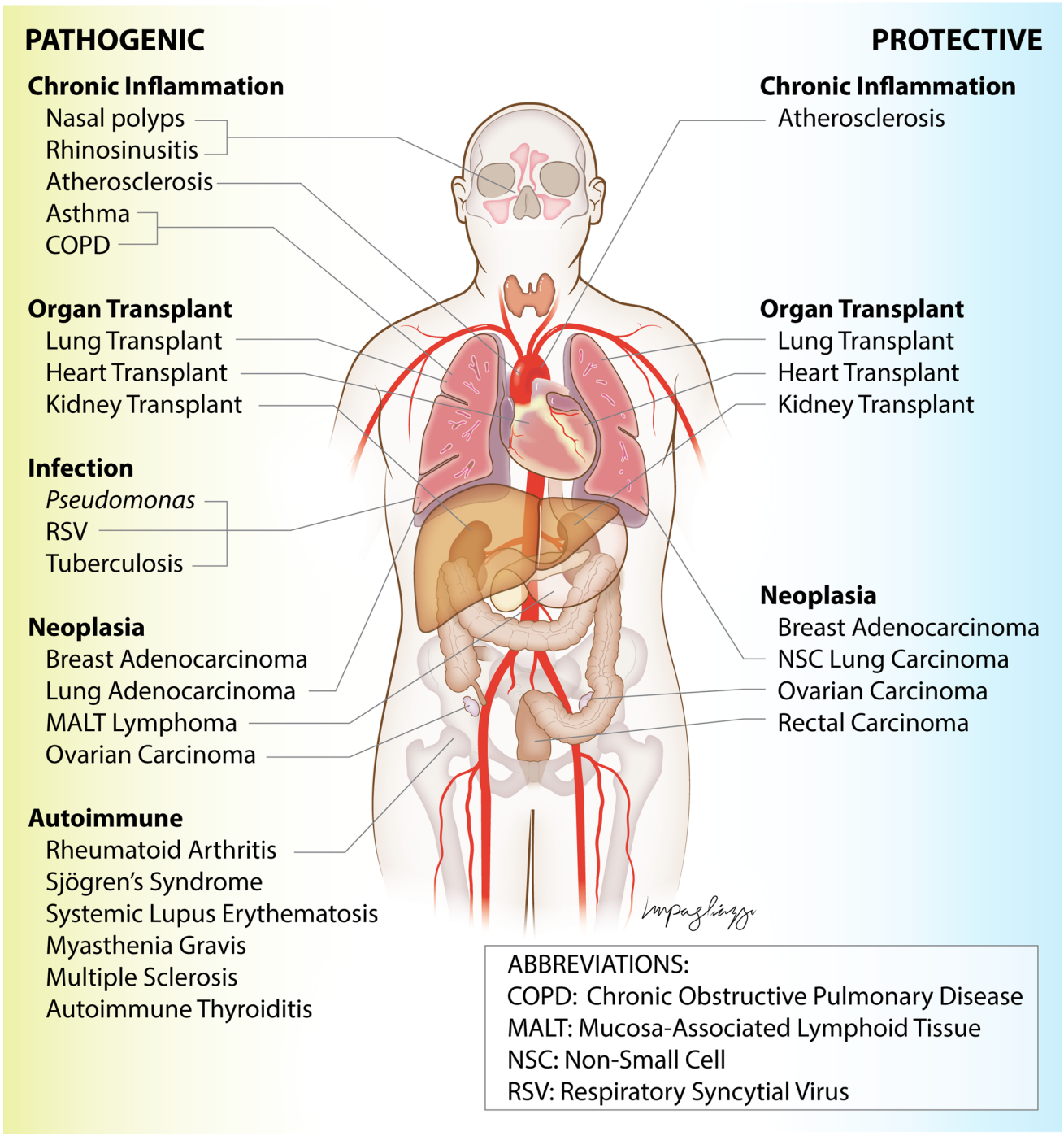

Fig. 2 Schematic showing tissue- and disease-specific roles of TLOs in regulating pathogenic or protective immune responses

illustrate the importance of the structural organization of autoimmune disease-associated TLOs to the maintenance of autoantigen-directed responses.

The presence of TLOs has been associated with variable disease severity and clinical outcomes in autoimmune diseases [5, 12]. While some reports in rheumatoid arthritis patients show no effect on disease severity [104, 120], others have shown an association between TLO formation and increased autoantibody and inflammatory cytokine production along with more erosive disease [121–124]. In patients with Sjögren's syndrome, the presence of TLOs is associated with increased autoantibody and pro-inflammatory cytokine production, clinical disease severity, and risk of development of lymphoma [125–127]. TLOs can also

Table 1 Summary of the tissue- and disease-specific roles of TLOs in regulating peripheral immune responses

Condition	Location	Species	Role	References
Autoimmune disease				
Autoimmune thyroiditis	Thyroid	Human, mouse	Pathologic	[34, 102, 111]
Diabetes mellitus, type I	Pancreas	Human, mouse	Pathologic	[21, 22, 101]
Multiple sclerosis	Meninges	Human, mouse	Pathologic	[15, 16, 18]
Myasthenia gravis	Thymus	Human	Pathologic	[33, 119]
Myositis	Muscle	Human	Pathologic	[109, 110]
Rheumatoid arthritis	Synovium, lung	Human, mouse	Pathologic	[24, 90, 91, 98, 103, 104, 112–114, 116, 120–124, 128, 131–134, 136–139]
Sjogren syndrome	Salivary gland	Human	Pathologic	[25, 29, 99, 105, 106, 115, 118, 125–127, 129, 130, 135, 140, 141]
Systemic lupus erythematosus	Kidney	Human, mouse	Pathologic	[100, 107, 108]
Chronic inflammatory disease				
Asthma	Lung	Human, mouse	Pathologic	[78, 79]
Atherosclerosis	Artery	Human, mouse	Both	[23, 38, 39, 94–97]
Bronchiectasis	Lung	Human, mouse	Unknown	[59]
Chronic obstructive pulmonary disease	Lung	Human, mouse	Pathologic	[37, 80–83]
Chronic rhinosinusitis	Nasal mucosa	Human	Pathologic	[84–87]
Cystic fibrosis	Lung	Human, mouse	Unknown	[59, 60]
Inflammatory bowel disease	Intestinal mucosa	Human	Pathologic	[88–93]
Pulmonary arterial hypertension	Lung	Human, rat	Pathologic	[76, 77]
Infection				
Borrelia burgdorferi	Synovium, central nervous system	Human, Rhesus macaque	Pathologic	[73–75]
Francisella tularensis	Lung	Mouse	Protective	[32]
Helicobacter hepaticus	Liver	Mouse	Pathologic	[68]
Helicobacter pylori	Gastric/duodenal mucosa	Human	Pathologic	[64–66]
Hepatitis C virus	Liver	Human	Pathologic	[69–71]
Influenza virus	Lung	Mouse	Protective	[30, 50–53, 56]
Leptospira interrogans serovar Pomona	Kidney	Pig	Pathologic	[72]
Modified Vaccinia virus Ankara	Lung	Mouse	Protective	[61]
Mouse-adapted SARS coronavirus	Lung	Mouse	Protective	[56]
Mycobacterium tuberculosis	Lung	Human, mouse	Protective	[41–48, 54, 55]
Pneumocystis jirovecii	Lung	Mouse	Protective	[49]
Pneumovirus of the mouse	Lung	Mouse	Protective	[56]
Propionibacterium acnes	Liver	Mouse	Pathologic	[67]
Pseudomonas aeruginosa	Lung	Mouse, rat	Unknown	[62, 63]
Respiratory syncytial virus	Lung	Mouse	Protective	[57, 58]
Malignancy				
Bladder cancer	Intratumoral	Human	Protective	[176, 177]
Breast cancer	Intratumoral, peritumoral	Human	Both	[27, 35, 144, 146, 147, 151, 159, 165, 173, 174]
Colorectal cancer	Intratumoral, peritumoral	Human	Both	[142, 158, 167, 168]
Hepatocellular carcinoma	Intratumoral, peritumoral	Human, mouse	Both	[148, 152, 153, 170]
Intrahepatic cholangiocarcinoma	Intratumoral, peritumoral	Human	Both	[163]
Lung cancer	Intratumoral	Human, mouse	Both	[145, 154, 157, 178]
Melanoma	Intratumoral, peritumoral	Human, mouse	Both	[143, 155, 156, 160, 166, 175]

Table 1 (continued)

Condition	Location	Species	Role	References
Ovarian cancer	Intratumoral	Human	Protective	[150, 161, 162]
Pancreatic cancer	Intratumoral, peritumoral	Human	Both	[164, 169]
Transplantation				
Heart transplantation	Heart	Human, mouse	Both	[36, 181–183, 185, 186, 199]
Kidney transplantation	Kidney	Human, mouse	Both	[36, 199, 202–205]
Lung transplantation	Lung	Human, mouse, rat	Both	[36, 194–198, 200, 201]

be found in the lungs (BALT) of patients with pulmonary involvement of rheumatoid arthritis and Sjögren's syndrome [128]. These TLOs are associated with increased expression of CXCL13, CCL21, ICOSL, and lymphotoxin and correlate with tissue damage and fibrosis in the lungs of patients with rheumatoid arthritis-associated interstitial lung disease [128]. The role of TLOs in clinical disease severity is less well established in other autoimmune diseases. Thus, autoimmune disease-associated TLO formation affects clinical severity in a disease- and tissue-specific manner.

The sustained immune activation associated with TLO formation may have implications for the treatment of autoimmune diseases. Studies in patients with rheumatoid arthritis or Sjögren's syndrome have shown conflicting results regarding the role of TLOs in clinical responses to disease-modifying anti-rheumatic drugs (DMARDs) including rituximab (monoclonal anti-CD20 antibody), abatacept (CTLA4-Ig fusion protein, co-stimulatory signal inhibitor), and anti-TNF therapies [129–135]. Studies in patients with rheumatoid arthritis show that treatment with rituximab is associated with elimination of circulating B cells and reduction in circulating anti-rheumatoid factor and anti-cyclic citrullinated peptide antibodies [136–138]. However, rituximab treatment has been shown to deplete but not eliminate synovial B cells, especially those found in lymphoid aggregates, and does not affect synovial autoantibody production suggesting that TLOs in rheumatoid arthritis may serve as a protective niche for autoreactive B cells [132, 136, 137, 139]. Furthermore, non-responders to rituximab treatment were more likely to have residual synovial plasma cells along with higher levels of CXCL13 and B cell repopulation [131, 136, 138]. Similarly, studies have shown that rituximab significantly reduces systemic B cell biomarkers but does not affect clonal expansion of autoantibody-producing cells in salivary glands of patients with Sjögren's syndrome, and does not affect parotid enlargement or tissue expression of B cell-activating factor (BAFF) in patients with Sjögren's syndrome-associated MALT lymphoma [140, 141]. These findings have led to a focus on therapies that target signals critical to TLO formation and maintenance including IL-17, IL-21, lymphotoxin, ICOS-ICOSL, CD40-CD40L, and BAFF [5, 12]. Thus, autoimmune disease-associated TLOs play a role in the maintenance of peripheral immune responses.

Role in cancer

The microenvironment of tumorigenesis shares similarities to that of chronic inflammation due to the constant infiltration of immune cells, providing an inflammatory milieu for tumor progression and metastasis. Active recruitment of lymphocytes to tumor-associated TLOs (TA-TLOs) has been demonstrated in humans and preclinical mouse models of colorectal cancer [142]. Additionally, TA-TLOs have been shown to drive oligo-clonal B cell responses as well as T cell priming and expansion in animal models of breast cancer and melanoma [35, 143]. However, the precise mechanisms regulating TA-TLO formation remain unknown. Many of the cytokines and lymphoid chemokines associated with TA-TLOs (e.g., CCL21, CXCL13, TNF-α) are shared with other non-neoplastic inflammatory processes. Similar to chronic infections and inflammatory diseases, the presence of TLOs in solid, non-lymphoid tumors has been associated with variable outcomes [142, 144–149]. The role of TA-TLOs in promoting pro- or anti-tumoral immune responses is disease-specific and likely depends on a variety of factors including cellular composition and location (intra-tumoral vs peri-tumoral).

TA-TLOs can be enriched in regulatory T cells (Tregs) that can inhibit anti-tumor responses and promote tumor growth. Tumor infiltration by Tregs has been associated with worse prognosis in various types of cancer [146, 150–153]. In patients with ovarian carcinoma, tumor-associated Tregs suppressed tumor-specific T cell immunity to promote the growth of human tumors in vivo [150]. Similarly, a study utilizing a genetically engineered mouse lung adenocarcinoma model showed that tumor bearing mice have a significant increase in tissue-infiltrating Tregs accumulating in TA-TLOs compared with controls [154]. These Tregs can suppress anti-tumor responses by modulating interactions between T cells and DCs [154]. Notably, depletion of Tregs enhanced DC costimulatory ligand expression and resulted in the increased proliferation of T cells, stimulating tumor destruction. Related findings have been demonstrated in

studies of patients with breast cancer, which showed that high numbers of Tregs within TA-TLOs, rather than in the tumor bed, are predictive of relapse and death [146]. In contrast to other T cells, Tregs were found to be selectively activated locally with proliferation in situ, resulting in suppression of effector T cell activation, immune escape, and tumor progression. While the complex regulatory mechanisms and function of tumor-associated Tregs remain to be elucidated, inhibition of these responses may serve as a potential therapeutic target to promote adaptive anti-tumor immune responses.

While Tregs inhibit anti-tumoral responses in TA-TLOs, other T cell subsets, along with DCs and B cells, promote anti-tumoral immune responses. Previous studies utilizing mouse models which lack lymph nodes demonstrated that effective T cell priming can occur locally at the tumor site [143, 155]. TLO induction within the tumor in a murine model of metastatic melanoma has been shown to provoke naïve T cell infiltration and differentiation, which is associated with the generation of tumor-specific T cells [156]. Additionally, the density of mature DCs in TA-TLOs is highly associated with a strong and coordinated Th1 and cytotoxic T cell response in patients with non-small cell lung cancer [157]. TA-TLOs enriched in DCs and $CD8^+$ T cells are associated with improved survival in patients with non-small cell lung cancer and rectal cancer [157, 158]. Higher density of DC and $CD4^+$ T_{FH} cell infiltration in TA-TLOs in breast cancer patients was associated with higher rates of metastasis- and disease-free survival [27, 159]. In addition, B cells in TA-TLOs have been implicated in anti-tumor responses in patients with melanoma and ovarian cancer [160, 161]. B cell follicles within TA-TLOs may serve as a site for the local generation of humoral immunity against tumor antigens. In a study of human non-small cell lung cancer, germinal centers within tumors exhibited activated somatic hypermutation and class switch recombination, which was associated with antibody reactivity against tumor antigens [145]. In addition, a high density of follicular B cells within TA-TLOs correlated with long-term survival [145]. In a study of patients with serous ovarian cancer, tumor-associated B cells produced polyclonal IgA that was able to bind receptors universally expressed on ovarian cancer cells, sensitizing tumor cells to cytolytic killing by T cells and hindering malignant progression [162]. Taken together, these findings suggest that specific immune cells in TA-TLOs can be key regulators of local adaptive immune responses at the tumor site.

TA-TLOs can be found within the tumor (intra-tumoral) or outside the tumor margin (peri-tumoral) and their specific location may be predictive of immune responses to the tumor. While the presence of intra-tumoral TLOs has been associated with anti-tumoral responses, peri-tumoral TLOs have been associated with pro-tumoral responses and worse clinical outcomes in certain solid tumors. Peri-tumoral TLOs were associated with worse overall survival compared with intra-tumoral TLOs in patients with intrahepatic cholangiocarcinoma and pancreatic ductal carcinoma [163, 164]. In breast cancer patients, peri-tumoral TLOs were associated with higher-grade tumors and reduced disease-free and overall survival [165]. Melanoma metastases were more likely to have peritumoral TLOs than primary melanoma tumors [166], and in colorectal cancer patients, peritumoral TLOs were associated with advanced disease, tumor progression, and worse prognosis [167]. However, introduction of *Helicobacter hepaticus* into the intestinal tract in a mouse model of colorectal cancer resulted in development of peritumoral TLOs and increased immune infiltration and tumor control [168]. The presence of peritumoral TLOs was also associated with a favorable prognosis in pancreatic neuroendocrine tumors [169], and with improved overall and relapse-free survival in patients with hepatocellular carcinoma [170]. While the precise mechanisms by which peritumoral TLOs promote pro-tumoral responses remain unknown, animal models have suggested that TLOs may provide a supportive niche for tumor progenitors and could provide a route for cancer dissemination through HEVs [148, 171, 172]. These findings suggest that the location of TA-TLOs may influence the type of immune responses generated and affect clinical outcomes in a disease-specific fashion.

The presence of TA-TLOs may also impact response to various forms of antineoplastic treatment. Studies in patients with breast cancer have shown that TA-TLOs predict a favorable response to chemotherapy alone and in combination with the HER2-targeting monoclonal antibody, trastuzumab [27, 173, 174]. In addition, TA-TLOs were shown to predict long-term survival in patients with non-small cell lung cancer treated with chemotherapy [145]. Furthermore, TA-TLOs have been implicated in responses to cancer immunotherapies such as immune checkpoint inhibitor therapy. The presence of TA-TLOs in biopsy specimens from patients with melanoma was associated with increased survival after treatment with immune checkpoint blockade [175], and the presence of TA-TLOs and expression of CXCL13 were associated with response to immune checkpoint inhibitor therapy in patients with muscle-invasive bladder cancer [176]. Moreover, immunotherapy may induce tumor regression by induction of TA-TLOs. As an example, a study of immunotherapy for loco-regionally advanced urothelial carcinoma found no association between the presence of TA-TLOs at baseline and treatment response; however, complete response was associated with a significant increase in TA-TLOs [177]. Additionally, a post hoc analysis of a clinical trial of neoadjuvant immune checkpoint inhibitor therapy showed that responders were significantly more likely to develop TLOs in the tumor regression bed [178]. While these studies suggest a correlation between the development of TA-TLOs and

response to immunotherapy, the mechanisms underlying this phenomenon remain elusive. In a study of melanoma treatment with immune checkpoint inhibition, patients who responded to treatment demonstrated significantly different B cell marker expression compared to non-responders in a single-cell and bulk RNA analysis [179]. Corroborating these findings using a computational method to estimate the immune composition in patients with melanoma and renal cell carcinoma who were treated with immune checkpoint blockade, clonal B cells were found to be localized within TA-TLOs, and switched memory B cells were enriched in tumors of responders. These findings have sparked interest in therapies that can induce TLO formation in immunotherapy-resistant neoplasms. As an example, LIGHT-VTP fusion protein (targets LIGHT to angiogenic tumor vessels using a vascular targeting peptide) therapy triggers TA-TLO formation and improves survival when combined with immunotherapy in a mouse model of immunotherapy-resistant tumor formation [180]. While these data suggest induction of TA-TLOs may improve responsiveness to immunotherapy in resistant tumors, mechanisms underlying these phenomena remain unclear. It is evident that TA-TLOs have a significant impact on the neoplastic microenvironment and clinical outcomes, and understanding these molecular determinants will help provide key insights into the dynamic interactions between the immune system, tumor progression, and response to treatment.

Role in solid organ transplantation

Transplantation remains the only therapeutic option for many patients who develop end-stage organ failure. The clinical practice of organ transplantation consists of surgically transferring an organ from a donor of the same species who is genetically different from the recipient. Both innate and adaptive immune responses are mounted in response to the allograft, as well as to other injurious events which may accompany the transplantation procedure (e.g., release of endogenous ligands during inflammation associated with ischemia–reperfusion injury). These immunologic processes provide an environment of chronic inflammation which may facilitate the ectopic organization of lymphoid cells within the graft tissue.

Evidence of TLO formation in transplanted solid organs was first reported in cardiac allografts in 1985 as aggregates of structured lymphoid cells located within the endocardium of allografts, which were termed “Quilty lesions” [181]. These lesions, composed of B lymphocytes, T lymphocytes, macrophages, FDCs, and HEVs were initially attributed to viral infections or cyclosporine therapy as triggers for their formation [182]. However, these associations were subsequently called into question by studies which demonstrated an absence of endocardial lesions in other patients treated with cyclosporine, as well as lesion formation in myocardial biopsies with negative viral genomic testing [183, 184]. Thus, it was suggested that Quilty lesion formation was potentially linked to rejection. Conversely, recent findings have suggested that Quilty lesions may play a protective role in cardiac allografts [185]. To this end, 42 human cardiac allograft biopsies were evaluated for the presence of Quilty lesions and histologic findings of rejection, and results showed that the presence of Tregs and TGF-β^+ cells within Quilty lesions was associated with higher rates of cardiac allograft acceptance [185]. In a study conducted by Baddoura in 2005, examination of 319 murine cardiac transplants revealed lymphoid neogenesis in 25% of allografts and the presence of these structures was generally associated with acute or chronic rejection [186]. While it remains unclear how TLO formation in cardiac allografts may impact alloimmunity and graft acceptance, understanding the local immune interactions within a transplanted heart will clarify potential avenues for developing novel therapeutic strategies to prolong graft survival.

Lung allografts have been considered one of the most highly immunogenic solid organ transplants due to their major role in host defense and prominent intrinsic lymphoid network with constant exposure to aerogenous antigens. BALT has been detected in healthy lungs of rabbits, rats, and guinea pigs, but its presence in human lungs appears to vary according to age [187, 188]. While BALT can be demonstrated in 50% of healthy infants and young children, the frequency of BALT in normal lungs of healthy human adults remains controversial with estimates ranging from 0 to 64% [189–193]. BALT was initially targeted as a possible explanation for the relatively high rate of rejection among lung allografts compared to other solid organ transplants. To further delineate to what extent rejection of lungs differs from that of other organs, Prop studied functional rejection of rat lung allografts and found that lymphocytes that resided in the BALT of donor lungs were associated with an accelerated rate of lung allograft rejection [194]. Interestingly, this was abrogated by donor irradiation prior to transplantation or by re-transplantation from a cyclosporine-treated intermediate host, suggesting that BALT that is present in donor lungs may serve as a trigger for rejection. A study of 77 trans-bronchial biopsies in human lung transplant recipients by Hasegawa’s group found that BALT was induced after transplantation and found no association of BALT with high-grade acute cellular rejection or development of bronchiolitis obliterans [195]. We have made the surprising observation that BALT is induced in tolerant lung allografts, a process that is dependent on IL-22 production by graft-infiltrating γδ T cells and type 3 innate lymphoid cells; interestingly, the iBALT is enriched in Tregs [196, 197]. Subsequent studies have shown that potentially deleterious humoral immune responses are regulated through Tregs that are present in the

BALT of tolerant lungs [198]. In addition to chronic stimulation by alloantigen, lymphatic disruption may contribute to BALT formation [13, 199]. In a study utilizing a mouse lung transplant model, Reed demonstrated that transplantation of lungs with obstructed forward flow of pulmonary lymphatics (via C-type lectin domain family 2 (CLEC2) deficiency or ablation of lymphatic endothelial cells) resulted in spontaneous formation of lymphoid aggregates within the lung grafts [200]. Interestingly, although lymphatic function was globally impaired in CLEC2-deficient mice, TLOs were observed specifically within the lungs and were absent in other tissues with a similar magnitude of lymphatic loss as that of the lung, such as the mesentery and intestine, and this effect was independent of transplantation. These findings suggest that lymphatic disruption may play a major role in the induction of TLOs in lung allografts following transplantation. Moreover, we have recently demonstrated that lymphatic egress of Tregs from TLOs within tolerant lung allografts can downregulate immune responses systemically [201]. Thus, intra-graft TLOs appear to serve both beneficial and deleterious roles in lung transplantation and may regulate immune responses within and outside of the graft.

Organized lymphoid structures in renal allografts were reported in 2004 when 35 human renal transplant biopsies and explants from acutely rejecting grafts were evaluated for lymphatic vessel distribution in relation to immune infiltrates [202]. Such grafts were found to have perilymphovascular nodular infiltrates which contained highly proliferative T and B lymphocytes and were densely associated with newly formed lymphatic vessels. The authors speculated that lymphangiogenesis could contribute to the transport of infiltrating immune cells and alloreactive responses. A study by Thaunat reported an association between the presence of TLOs in renal grafts and chronic rejection [199]. A deleterious role for TLOs in renal allografts was the prevailing view until 2011 when the induction of TLO formation was reported in tolerant mouse kidney allografts [203]. In this study, Brown demonstrated that TLOs formed in tolerant renal allografts and the presence of intra-graft TLOs was associated with superior graft function. This was further supported by a study by Miyajima utilizing a mouse kidney transplant model with identification of nodular infiltrates rich in Tregs that were present in spontaneously accepting allografts [204]. Rosales subsequently demonstrated that systemic depletion of Tregs prompted dissolution of these renal lymphoid infiltrates and abolition of tolerance, raising the possibility that Treg-rich structures within grafts may contribute to kidney allograft acceptance [205]. These findings correlate with our findings that graft-resident Tregs residing in the BALT of tolerant lung allografts downregulate local alloimmune responses. In summary, TLO formation within donor organ grafts has been associated with both rejection and tolerance. While traditional dogma suggested that intra-graft TLOs propagate deleterious immune responses, recent data have shown that TLO formation may also play an essential role in modulating graft acceptance.

Future directions

Despite major advancements in understanding the pathways that govern the formation of TLOs, major gaps remain regarding the role they play in regulating peripheral immune responses. Given the reported diversity of both their structure and composition, the establishment of criteria to standardize the staging of TLOs in various disease processes is necessary. While classification systems have been proposed in individual disease processes and model systems, standardized criteria for TLOs in human disease are lacking [10, 36, 206–208]. Establishment of such criteria is important to identify the cell types and signaling pathways required for TLO formation in each disease state and tissue. In addition, such criteria may help reveal structures or cellular components associated with protective or pathologic responses. Indeed, understanding the components making TLOs protective or pathologic in a particular disease process is critical to the identification of targets for pharmacologic intervention. Pharmacologic disruption of pathologic TLOs is an active area of investigation in autoimmune disease, as TLOs have largely been associated with the propagation of autoimmunity and worse clinical outcomes in this realm [5, 12, 208]. Pharmacologic disruption of pathologic TLOs may prove useful in other chronic inflammatory diseases, some forms of solid organ transplant rejection, and as an adjunct to chemo- and immunotherapies in certain malignancies. Furthermore, the identification of signaling pathways leading to the development of protective TLOs is paramount for the development of antineoplastic therapies for some cancers and the development of tolerance after solid organ transplantation. To this end, understanding signaling pathways inducing protective responses may allow the modification of donor organs with ex vivo organ perfusion to set the stage for tolerogenic TLOs. One major challenge in the development of pharmacologic therapies to induce or disrupt TLOs will be route of administration, as systemic therapies could result in unwanted effects in SLOs and other tissues. Thus, the utilization of strategies to localize pharmacologic agents, such as with aerosolized delivery for lungs or nanoparticle delivery targeted at specific tissues, may be necessary. Delineating the requirements for immune cell trafficking entering and exiting TLOs, for example via HEVs, interstitial tissue migration, or lymphatics, may aid with the development of targeted therapeutic approaches for specific disease processes. Finally, future studies should focus on whether the formation of TLOs in a particular disease process is dependent on antigen-driven immune responses or can occur in an antigen-independent fashion, as understanding the factors

driving TLO formation could improve strategies to develop targeted therapies to manipulate TLOs in disease.

Conclusion

TLOs have been identified as critical mediators of local disease- and tissue-specific immune responses in chronic inflammatory diseases and organ transplantation. While our understanding of the development and function of these structures has improved significantly over the last 30 years, their role in mediating protective or pathologic immune responses in certain disease processes remains elusive. Future studies should further delineate the role of TLOs in regulating immune responses in infection with certain pathogens, chronic inflammatory diseases, autoimmune diseases, cancer, and solid organ transplantation. Investigation in these areas may provide valuable insight into the mechanisms of disease progression, reveal novel therapeutic targets, and possibly identify biomarkers that predict progression of disease and response to treatment.

Acknowledgements We would like to thank Anita Impagliazzo for the medical illustrations.

Authors' contributions All authors contributed to the conception and design of the manuscript. The first draft of the manuscript was written by AB and HS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding DK is supported by National Institutes of Health grants 1P01AI116501, R01HL094601, R01HL151078, The Cystic Fibrosis Foundation, and The Foundation for Barnes-Jewish Hospital. ASK is supported by National Institutes of Health grants R01AI145108, I01BX002299 and P01AI116501. AB is supported by National Institutes of Health grant 5T32HL007317-44.

Availability of data and materials The data and material that support this review are available in the published literature and referenced in the references section.

Declarations

Conflict of interests The authors have no relevant financial or non-financial interests to disclose.

Ethics approval and consent to participate No ethical approval was required for the preparation and publication of this review.

Consent for publication The authors affirm that no consent to publish is required as all data reviewed were from published literature and no individual human research participants were involved in this review.

References

1. Pabst R (2007) Plasticity and heterogeneity of lymphoid organs. What are the criteria to call a lymphoid organ primary, secondary or tertiary? Immunol Lett 112:1–8. https://doi.org/10.1016/j.imlet.2007.06.009
2. Ruddle NH (2020) Basics of inducible lymphoid organs. Curr Top Microbiol Immunol 426:1–19. https://doi.org/10.1007/82_2020_218
3. van de Pavert SA, Mebius RE (2010) New insights into the development of lymphoid tissues. Nat Rev Immunol 10:664–674. https://doi.org/10.1038/nri2832
4. Randall TD, Mebius RE (2014) The development and function of mucosal lymphoid tissues: a balancing act with micro-organisms. Mucosal Immunol 7:455–466. https://doi.org/10.1038/mi.2014.11
5. Bombardieri M, Lewis M, Pitzalis C (2017) Ectopic lymphoid neogenesis in rheumatic autoimmune diseases. Nat Rev Rheumatol 13:141–154. https://doi.org/10.1038/nrrheum.2016.217
6. Gago da Graça C, van Baarsen LGM, Mebius RE (2021) Tertiary lymphoid structures: diversity in their development, composition, and role. J Immunol 206:273–281. https://doi.org/10.4049/jimmunol.2000873
7. Shipman WD, Dasoveanu DC, Lu TT (2017) Tertiary lymphoid organs in systemic autoimmune diseases: pathogenic or protective? F1000Res 6:196. https://doi.org/10.12688/f1000research.10595.1
8. Moyron-Quiroz JE, Rangel-Moreno J, Kusser K et al (2004) Role of inducible bronchus associated lymphoid tissue (iBALT) in respiratory immunity. Nat Med 10:927–934. https://doi.org/10.1038/nm1091
9. Nayar S, Campos J, Smith CG et al (2019) Immunofibroblasts are pivotal drivers of tertiary lymphoid structure formation and local pathology. Proc Natl Acad Sci USA 116:13490–13497. https://doi.org/10.1073/pnas.1905301116
10. Luo S, Zhu R, Yu T et al (2019) Chronic inflammation: a common promoter in tertiary lymphoid organ neogenesis. Front Immunol 10:2938. https://doi.org/10.3389/fimmu.2019.02938
11. Ruddle NH (2014) Lymphatic vessels and tertiary lymphoid organs. J Clin Invest 124:953–959. https://doi.org/10.1172/JCI71611
12. Pitzalis C, Jones GW, Bombardieri M, Jones SA (2014) Ectopic lymphoid-like structures in infection, cancer and autoimmunity. Nat Rev Immunol 14:447–462. https://doi.org/10.1038/nri3700
13. Thaunat O, Kerjaschki D, Nicoletti A (2006) Is defective lymphatic drainage a trigger for lymphoid neogenesis? Trends Immunol 27:441–445. https://doi.org/10.1016/j.it.2006.08.003
14. Drayton DL, Liao S, Mounzer RH, Ruddle NH (2006) Lymphoid organ development: from ontogeny to neogenesis. Nat Immunol 7:344–353. https://doi.org/10.1038/ni1330
15. Peters A, Pitcher LA, Sullivan JM et al (2011) Th17 cells induce ectopic lymphoid follicles in central nervous system tissue inflammation. Immunity 35:986–996. https://doi.org/10.1016/j.immuni.2011.10.015
16. Pikor NB, Astarita JL, Summers-Deluca L et al (2015) Integration of Th17- and lymphotoxin-derived signals initiates meningeal-resident stromal cell remodeling to propagate neuroinflammation. Immunity 43:1160–1173. https://doi.org/10.1016/j.immuni.2015.11.010
17. Peduto L, Dulauroy S, Lochner M et al (2009) Inflammation recapitulates the ontogeny of lymphoid stromal cells. J Immunol 182:5789–5799. https://doi.org/10.4049/jimmunol.0803974
18. Pikor NB, Prat A, Bar-Or A, Gommerman JL (2015) Meningeal tertiary lymphoid tissues and multiple sclerosis: a gathering place

for diverse types of immune cells during CNS autoimmunity. Front Immunol 6:657. https://doi.org/10.3389/fimmu.2015.00657
19. Kazanietz MG, Durando M, Cooke M (2019) CXCL13 and Its receptor CXCR5 in cancer: inflammation, immune response, and beyond. Front Endocrinol (Lausanne) 10:471. https://doi.org/10.3389/fendo.2019.00471
20. Förster R, Davalos-Misslitz AC, Rot A (2008) CCR7 and its ligands: balancing immunity and tolerance. Nat Rev Immunol 8:362–371. https://doi.org/10.1038/nri2297
21. Luther SA, Lopez T, Bai W et al (2000) BLC expression in pancreatic islets causes B cell recruitment and lymphotoxin-dependent lymphoid neogenesis. Immunity 12:471–481. https://doi.org/10.1016/s1074-7613(00)80199-5
22. Lee Y, Chin RK, Christiansen P et al (2006) Recruitment and activation of naive T cells in the islets by lymphotoxin beta receptor-dependent tertiary lymphoid structure. Immunity 25:499–509. https://doi.org/10.1016/j.immuni.2006.06.016
23. Gräbner R, Lötzer K, Döpping S et al (2009) Lymphotoxin beta receptor signaling promotes tertiary lymphoid organogenesis in the aorta adventitia of aged ApoE-/- mice. J Exp Med 206:233–248. https://doi.org/10.1084/jem.20080752
24. Manzo A, Paoletti S, Carulli M et al (2005) Systematic microanatomical analysis of CXCL13 and CCL21 in situ production and progressive lymphoid organization in rheumatoid synovitis. Eur J Immunol 35:1347–1359. https://doi.org/10.1002/eji.200425830
25. Barone F, Bombardieri M, Manzo A et al (2005) Association of CXCL13 and CCL21 expression with the progressive organization of lymphoid-like structures in Sjögren's syndrome. Arthritis Rheum 52:1773–1784. https://doi.org/10.1002/art.21062
26. Breitfeld D, Ohl L, Kremmer E et al (2000) Follicular B helper T cells express CXC chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production. J Exp Med 192:1545–1552. https://doi.org/10.1084/jem.192.11.1545
27. Gu-Trantien C, Loi S, Garaud S et al (2013) CD4$^+$ follicular helper T cell infiltration predicts breast cancer survival. J Clin Invest 123:2873–2892. https://doi.org/10.1172/JCI67428
28. Couillault C, Germain C, Dubois B, Kaplon H (2018) Identification of tertiary lymphoid structure-associated follicular helper T Cells in human tumors and tissues. Methods Mol Biol 1845:205–222. https://doi.org/10.1007/978-1-4939-8709-2_12
29. Pontarini E, Murray-Brown WJ, Croia C et al (2020) Unique expansion of IL-21+ Tfh and Tph cells under control of ICOS identifies Sjögren's syndrome with ectopic germinal centres and MALT lymphoma. Ann Rheum Dis 79:1588–1599. https://doi.org/10.1136/annrheumdis-2020-217646
30. GeurtsvanKessel CH, Willart MAM, Bergen IM et al (2009) Dendritic cells are crucial for maintenance of tertiary lymphoid structures in the lung of influenza virus-infected mice. J Exp Med 206:2339–2349. https://doi.org/10.1084/jem.20090410
31. Halle S, Dujardin HC, Bakocevic N et al (2009) Induced bronchus-associated lymphoid tissue serves as a general priming site for T cells and is maintained by dendritic cells. J Exp Med 206:2593–2601. https://doi.org/10.1084/jem.20091472
32. Chiavolini D, Rangel-Moreno J, Berg G et al (2010) Bronchus-associated lymphoid tissue (BALT) and survival in a vaccine mouse model of tularemia. PLoS ONE 5:e11156. https://doi.org/10.1371/journal.pone.0011156
33. Sims GP, Shiono H, Willcox N, Stott DI (2001) Somatic hypermutation and selection of B cells in thymic germinal centers responding to acetylcholine receptor in myasthenia gravis. J Immunol 167:1935–1944. https://doi.org/10.4049/jimmunol.167.4.1935
34. Armengol MP, Juan M, Lucas-Martín A et al (2001) Thyroid autoimmune disease: demonstration of thyroid antigen-specific B cells and recombination-activating gene expression in chemokine-containing active intrathyroidal germinal centers. Am J Pathol 159:861–873. https://doi.org/10.1016/S0002-9440(10)61762-2
35. Coronella JA, Spier C, Welch M et al (2002) Antigen-driven oligoclonal expansion of tumor-infiltrating B cells in infiltrating ductal carcinoma of the breast. J Immunol 169:1829–1836. https://doi.org/10.4049/jimmunol.169.4.1829
36. Koenig A, Thaunat O (2016) Lymphoid neogenesis and tertiary lymphoid organs in transplanted organs. Front Immunol 7:646. https://doi.org/10.3389/fimmu.2016.00646
37. Demoor T, Bracke KR, Maes T et al (2009) Role of lymphotoxin-alpha in cigarette smoke-induced inflammation and lymphoid neogenesis. Eur Respir J 34:405–416. https://doi.org/10.1183/09031936.00101408
38. Mohanta SK, Yin C, Peng L et al (2014) Artery tertiary lymphoid organs contribute to innate and adaptive immune responses in advanced mouse atherosclerosis. Circ Res 114:1772–1787. https://doi.org/10.1161/CIRCRESAHA.114.301137
39. Fleig S, Kapanadze T, Bernier-Latmani J et al (2022) Loss of vascular endothelial notch signaling promotes spontaneous formation of tertiary lymphoid structures. Nat Commun 13:2022. https://doi.org/10.1038/s41467-022-29701-x
40. Yin C, Mohanta S, Maffia P, Habenicht AJR (2017) Editorial: tertiary lymphoid organs (TLOs): powerhouses of disease immunity. Front Immunol 8:228. https://doi.org/10.3389/fimmu.2017.00228
41. Ulrichs T, Kosmiadi GA, Trusov V et al (2004) Human tuberculous granulomas induce peripheral lymphoid follicle-like structures to orchestrate local host defence in the lung. J Pathol 204:217–228. https://doi.org/10.1002/path.1628
42. Slight SR, Rangel-Moreno J, Gopal R et al (2013) CXCR5$^+$ T helper cells mediate protective immunity against tuberculosis. J Clin Invest 123:712–726. https://doi.org/10.1172/JCI65728
43. Kahnert A, Höpken UE, Stein M et al (2007) Mycobacterium tuberculosis triggers formation of lymphoid structure in murine lungs. J Infect Dis 195:46–54. https://doi.org/10.1086/508894
44. Khader SA, Rangel-Moreno J, Fountain JJ et al (2009) In a murine tuberculosis model, the absence of homeostatic chemokines delays granuloma formation and protective immunity. J Immunol 183:8004–8014. https://doi.org/10.4049/jimmunol.0901937
45. Khader SA, Guglani L, Rangel-Moreno J et al (2011) IL-23 is required for long-term control of Mycobacterium tuberculosis and B cell follicle formation in the infected lung. J Immunol 187:5402–5407. https://doi.org/10.4049/jimmunol.1101377
46. Khader SA, Bell GK, Pearl JE et al (2007) IL-23 and IL-17 in the establishment of protective pulmonary CD4+ T cell responses after vaccination and during Mycobacterium tuberculosis challenge. Nat Immunol 8:369–377. https://doi.org/10.1038/ni1449
47. Treerat P, Prince O, Cruz-Lagunas A et al (2017) Novel role for IL-22 in protection during chronic Mycobacterium tuberculosis HN878 infection. Mucosal Immunol 10:1069–1081. https://doi.org/10.1038/mi.2017.15
48. Ulrichs T, Kosmiadi GA, Jörg S et al (2005) Differential organization of the local immune response in patients with active cavitary tuberculosis or with nonprogressive tuberculoma. J Infect Dis 192:89–97. https://doi.org/10.1086/430621
49. Eddens T, Elsegeiny W, de la Garcia-Hernadez M, L, et al (2017) Pneumocystis-driven inducible bronchus-associated lymphoid tissue formation requires Th2 and Th17 immunity. Cell Rep 18:3078–3090. https://doi.org/10.1016/j.celrep.2017.03.016
50. Moyron-Quiroz JE, Rangel-Moreno J, Hartson L et al (2006) Persistence and responsiveness of immunologic memory in the absence of secondary lymphoid organs. Immunity 25:643–654. https://doi.org/10.1016/j.immuni.2006.08.022

51. Wang X, Chan CCS, Yang M et al (2011) A critical role of IL-17 in modulating the B-cell response during H5N1 influenza virus infection. Cell Mol Immunol 8:462–468. https://doi.org/10.1038/cmi.2011.38
52. Neyt K, GeurtsvanKessel CH, Deswarte K et al (2016) Early IL-1 signaling promotes iBALT induction after influenza virus infection. Front Immunol 7:312. https://doi.org/10.3389/fimmu.2016.00312
53. Richert LE, Harmsen AL, Rynda-Apple A et al (2013) Inducible bronchus-associated lymphoid tissue (iBALT) synergizes with local lymph nodes during antiviral CD4+ T cell responses. Lymphat Res Biol 11:196–202. https://doi.org/10.1089/lrb.2013.0015
54. Kaushal D, Foreman TW, Gautam US et al (2015) Mucosal vaccination with attenuated Mycobacterium tuberculosis induces strong central memory responses and protects against tuberculosis. Nat Commun 6:8533. https://doi.org/10.1038/ncomms9533
55. Ahmed M, Smith DM, Hamouda T et al (2017) A novel nanoemulsion vaccine induces mucosal Interleukin-17 responses and confers protection upon Mycobacterium tuberculosis challenge in mice. Vaccine 35:4983–4989. https://doi.org/10.1016/j.vaccine.2017.07.073
56. Wiley JA, Richert LE, Swain SD et al (2009) Inducible bronchus-associated lymphoid tissue elicited by a protein cage nanoparticle enhances protection in mice against diverse respiratory viruses. PLoS ONE 4:e7142. https://doi.org/10.1371/journal.pone.0007142
57. Kallal LE, Hartigan AJ, Hogaboam CM et al (2010) Inefficient lymph node sensitization during respiratory viral infection promotes IL-17-mediated lung pathology. J Immunol 185:4137–4147. https://doi.org/10.4049/jimmunol.1000677
58. Bystrom J, Al-Adhoubi N, Al-Bogami M et al (2013) Th17 lymphocytes in respiratory syncytial virus infection. Viruses 5:777–791. https://doi.org/10.3390/v5030777
59. Frija-Masson J, Martin C, Regard L et al (2017) Bacteria-driven peribronchial lymphoid neogenesis in bronchiectasis and cystic fibrosis. Eur Respir J 49:1601873. https://doi.org/10.1183/13993003.01873-2016
60. Hubeau C, Lorenzato M, Couetil JP et al (2001) Quantitative analysis of inflammatory cells infiltrating the cystic fibrosis airway mucosa. Clin Exp Immunol 124:69–76. https://doi.org/10.1046/j.1365-2249.2001.01456.x
61. Fleige H, Ravens S, Moschovakis GL et al (2014) IL-17-induced CXCL12 recruits B cells and induces follicle formation in BALT in the absence of differentiated FDCs. J Exp Med 211:643–651. https://doi.org/10.1084/jem.20131737
62. Iwata M, Sato A (1991) Morphological and immunohistochemical studies of the lungs and bronchus-associated lymphoid tissue in a rat model of chronic pulmonary infection with *Pseudomonas aeruginosa*. Infect Immun 59:1514–1520. https://doi.org/10.1128/iai.59.4.1514-1520.1991
63. Kitazawa H, Sato A, Iwata M (1997) A study of bronchus-associated lymphoid tissue in a rat model of chronic pulmonary infection with *Pseudomonas aeruginosa*. Kansenshogaku Zasshi 71:214–221. https://doi.org/10.11150/kansenshogakuzasshi1970.71.214
64. Genta RM, Hamner HW, Graham DY (1993) Gastric lymphoid follicles in Helicobacter pylori infection: frequency, distribution, and response to triple therapy. Hum Pathol 24:577–583. https://doi.org/10.1016/0046-8177(93)90235-9
65. Genta RM, Lew GM, Graham DY (1993) Changes in the gastric mucosa following eradication of *Helicobacter pylori*. Mod Pathol 6:281–289
66. Mazzucchelli L, Blaser A, Kappeler A et al (1999) BCA-1 is highly expressed in Helicobacter pylori-induced mucosa-associated lymphoid tissue and gastric lymphoma. J Clin Invest 104:R49-54. https://doi.org/10.1172/JCI7830
67. Yoneyama H, Matsuno K, Zhang Y et al (2001) Regulation by chemokines of circulating dendritic cell precursors, and the formation of portal tract-associated lymphoid tissue, in a granulomatous liver disease. J Exp Med 193:35–49. https://doi.org/10.1084/jem.193.1.35
68. Shomer NH, Fox JG, Juedes AE, Ruddle NH (2003) Helicobacter-induced chronic active lymphoid aggregates have characteristics of tertiary lymphoid tissue. Infect Immun 71:3572–3577. https://doi.org/10.1128/IAI.71.6.3572-3577.2003
69. Freni MA, Artuso D, Gerken G et al (1995) Focal lymphocytic aggregates in chronic hepatitis C: occurrence, immunohistochemical characterization, and relation to markers of autoimmunity. Hepatology 22:389–394
70. Sansonno D, Tucci FA, Troiani L et al (2008) Increased serum levels of the chemokine CXCL13 and up-regulation of its gene expression are distinctive features of HCV-related cryoglobulinemia and correlate with active cutaneous vasculitis. Blood 112:1620–1627. https://doi.org/10.1182/blood-2008-02-137455
71. Sansonno D, De Vita S, Iacobelli AR et al (1998) Clonal analysis of intrahepatic B cells from HCV-infected patients with and without mixed cryoglobulinemia. J Immunol 160:3594–3601
72. Pezzolato M, Maina E, Lonardi S et al (2012) Development of tertiary lymphoid structures in the kidneys of pigs with chronic leptospiral nephritis. Vet Immunol Immunopathol 145:546–550. https://doi.org/10.1016/j.vetimm.2011.12.011
73. Steere AC, Duray PH, Butcher EC (1988) Spirochetal antigens and lymphoid cell surface markers in *Lyme synovitis*. Comparison with rheumatoid synovium and tonsillar lymphoid tissue. Arthritis Rheum 31:487–495. https://doi.org/10.1002/art.1780310405
74. Ghosh S, Steere AC, Stollar BD, Huber BT (2005) In situ diversification of the antibody repertoire in chronic Lyme arthritis synovium. J Immunol 174:2860–2869. https://doi.org/10.4049/jimmunol.174.5.2860
75. Narayan K, Dail D, Li L et al (2005) The nervous system as ectopic germinal center: CXCL13 and IgG in lyme neuroborreliosis. Ann Neurol 57:813–823. https://doi.org/10.1002/ana.20486
76. Perros F, Dorfmüller P, Montani D et al (2012) Pulmonary lymphoid neogenesis in idiopathic pulmonary arterial hypertension. Am J Respir Crit Care Med 185:311–321. https://doi.org/10.1164/rccm.201105-0927OC
77. Colvin KL, Cripe PJ, Ivy DD et al (2013) Bronchus-associated lymphoid tissue in pulmonary hypertension produces pathologic autoantibodies. Am J Respir Crit Care Med 188:1126–1136. https://doi.org/10.1164/rccm.201302-0403OC
78. Chvatchko Y, Kosco-Vilbois MH, Herren S et al (1996) Germinal center formation and local immunoglobulin E (IgE) production in the lung after an airway antigenic challenge. J Exp Med 184:2353–2360. https://doi.org/10.1084/jem.184.6.2353
79. Shinoda K, Hirahara K, Iinuma T et al (2016) Thy1+IL-7+ lymphatic endothelial cells in iBALT provide a survival niche for memory T-helper cells in allergic airway inflammation. Proc Natl Acad Sci USA 113:E2842-2851. https://doi.org/10.1073/pnas.1512600113
80. Hogg JC, Chu F, Utokaparch S et al (2004) The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 350:2645–2653. https://doi.org/10.1056/NEJMoa032158
81. Litsiou E, Semitekolou M, Galani IE et al (2013) CXCL13 production in B cells via Toll-like receptor/lymphotoxin receptor signaling is involved in lymphoid neogenesis in chronic

obstructive pulmonary disease. Am J Respir Crit Care Med 187:1194–1202. https://doi.org/10.1164/rccm.201208-1543OC
82. Solleti SK, Srisuma S, Bhattacharya S et al (2016) Serpine2 deficiency results in lung lymphocyte accumulation and bronchus-associated lymphoid tissue formation. FASEB J 30:2615–2626. https://doi.org/10.1096/fj.201500159R
83. Briend E, Ferguson GJ, Mori M et al (2017) IL-18 associated with lung lymphoid aggregates drives IFNγ production in severe COPD. Respir Res 18:159. https://doi.org/10.1186/s12931-017-0641-7
84. Lau A, Lester S, Moraitis S et al (2017) Tertiary lymphoid organs in recalcitrant chronic rhinosinusitis. J Allergy Clin Immunol 139:1371-1373.e6. https://doi.org/10.1016/j.jaci.2016.08.052
85. Paramasivan S, Lester S, Lau A et al (2018) Tertiary lymphoid organs: a novel target in patients with chronic rhinosinusitis. J Allergy Clin Immunol 142:1673–1676. https://doi.org/10.1016/j.jaci.2018.07.024
86. Song J, Wang H, Zhang Y-N et al (2018) Ectopic lymphoid tissues support local immunoglobulin production in patients with chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol 141:927–937. https://doi.org/10.1016/j.jaci.2017.10.014
87. Wang Z-Z, Song J, Wang H et al (2020) B Cell-activating factor promotes b cell survival in ectopic lymphoid tissues in nasal polyps. Front Immunol 11:625630. https://doi.org/10.3389/fimmu.2020.625630
88. Surawicz CM, Belic L (1984) Rectal biopsy helps to distinguish acute self-limited colitis from idiopathic inflammatory bowel disease. Gastroenterology 86:104–113
89. Kaiserling E (2001) Newly-formed lymph nodes in the submucosa in chronic inflammatory bowel disease. Lymphology 34:22–29
90. Weninger W, Carlsen HS, Goodarzi M et al (2003) Naive T cell recruitment to nonlymphoid tissues: a role for endothelium-expressed CC chemokine ligand 21 in autoimmune disease and lymphoid neogenesis. J Immunol 170:4638–4648. https://doi.org/10.4049/jimmunol.170.9.4638
91. Carlsen HS, Baekkevold ES, Morton HC et al (2004) Monocyte-like and mature macrophages produce CXCL13 (B cell-attracting chemokine 1) in inflammatory lesions with lymphoid neogenesis. Blood 104:3021–3027. https://doi.org/10.1182/blood-2004-02-0701
92. Randolph GJ, Bala S, Rahier J-F et al (2016) Lymphoid Aggregates remodel lymphatic collecting vessels that serve mesenteric lymph nodes in Crohn disease. Am J Pathol 186:3066–3073. https://doi.org/10.1016/j.ajpath.2016.07.026
93. Guedj K, Abitbol Y, Cazals-Hatem D et al (2019) Adipocytes orchestrate the formation of tertiary lymphoid organs in the creeping fat of Crohn's disease affected mesentery. J Autoimmun 103:102281. https://doi.org/10.1016/j.jaut.2019.05.009
94. Houtkamp MA, de Boer OJ, van der Loos CM et al (2001) Adventitial infiltrates associated with advanced atherosclerotic plaques: structural organization suggests generation of local humoral immune responses. J Pathol 193:263–269. https://doi.org/10.1002/1096-9896(2000)9999:9999%3c::AID-PATH774%3e3.0.CO;2-N
95. Srikakulapu P, Hu D, Yin C et al (2016) Artery tertiary lymphoid organs control multilayered territorialized atherosclerosis B-cell responses in aged ApoE-/-Mice. Arterioscler Thromb Vasc Biol 36:1174–1185. https://doi.org/10.1161/ATVBAHA.115.306983
96. Kyaw T, Tay C, Krishnamurthi S et al (2011) B1a B lymphocytes are atheroprotective by secreting natural IgM that increases IgM deposits and reduces necrotic cores in atherosclerotic lesions. Circ Res 109:830–840. https://doi.org/10.1161/CIRCRESAHA.111.248542
97. Hu D, Mohanta SK, Yin C et al (2015) Artery tertiary lymphoid organs control aorta immunity and protect against atherosclerosis via vascular smooth muscle cell lymphotoxin β receptors. Immunity 42:1100–1115. https://doi.org/10.1016/j.immuni.2015.05.015
98. Humby F, Bombardieri M, Manzo A et al (2009) Ectopic lymphoid structures support ongoing production of class-switched autoantibodies in rheumatoid synovium. PLoS Med 6:e1. https://doi.org/10.1371/journal.pmed.0060001
99. Fonseca VR, Romão VC, Agua-Doce A et al (2018) The ratio of blood T follicular regulatory cells to T follicular helper cells marks ectopic lymphoid structure formation while activated follicular helper T Cells indicate disease activity in primary Sjögren's syndrome. Arthritis Rheumatol 70:774–784. https://doi.org/10.1002/art.40424
100. Dorraji SE, Kanapathippillai P, Hovd A-MK et al (2020) Kidney tertiary lymphoid structures in lupus nephritis develop into large interconnected networks and resemble lymph nodes in gene signature. Am J Pathol 190:2203–2225. https://doi.org/10.1016/j.ajpath.2020.07.015
101. Korpos É, Kadri N, Loismann S et al (2021) Identification and characterisation of tertiary lymphoid organs in human type 1 diabetes. Diabetologia 64:1626–1641. https://doi.org/10.1007/s00125-021-05453-z
102. Marinkovic T, Garin A, Yokota Y et al (2006) Interaction of mature CD3+CD4+ T cells with dendritic cells triggers the development of tertiary lymphoid structures in the thyroid. J Clin Invest 116:2622–2632. https://doi.org/10.1172/JCI28993
103. Takemura S, Braun A, Crowson C et al (2001) Lymphoid neogenesis in rheumatoid synovitis. J Immunol 167:1072–1080. https://doi.org/10.4049/jimmunol.167.2.1072
104. Thurlings RM, Wijbrandts CA, Mebius RE et al (2008) Synovial lymphoid neogenesis does not define a specific clinical rheumatoid arthritis phenotype. Arthritis Rheum 58:1582–1589. https://doi.org/10.1002/art.23505
105. Aziz KE, McCluskey PJ, Wakefield D (1997) Characterisation of follicular dendritic cells in labial salivary glands of patients with primary Sjögren syndrome: comparison with tonsillar lymphoid follicles. Ann Rheum Dis 56:140–143. https://doi.org/10.1136/ard.56.2.140
106. Jonsson MV, Skarstein K, Jonsson R, Brun JG (2007) Serological implications of germinal center-like structures in primary Sjögren's syndrome. J Rheumatol 34:2044–2049
107. Chang A, Henderson SG, Brandt D et al (2011) In situ B cell-mediated immune responses and tubulointerstitial inflammation in human lupus nephritis. J Immunol 186:1849–1860. https://doi.org/10.4049/jimmunol.1001983
108. Shen Y, Sun C-Y, Wu F-X et al (2012) Association of intrarenal B-cell infiltrates with clinical outcome in lupus nephritis: a study of 192 cases. Clin Dev Immunol 2012:967584. https://doi.org/10.1155/2012/967584
109. López De Padilla CM, Vallejo AN, Lacomis D et al (2009) Extranodal lymphoid microstructures in inflamed muscle and disease severity of new-onset juvenile dermatomyositis. Arthritis Rheum 60:1160–1172. https://doi.org/10.1002/art.24411
110. Salajegheh M, Pinkus JL, Amato AA et al (2010) Permissive environment for B-cell maturation in myositis muscle in the absence of B-cell follicles. Muscle Nerve 42:576–583. https://doi.org/10.1002/mus.21739
111. Mohr A, Trésallet C, Monot N et al (2020) Tissue infiltrating LTi-like group 3 innate lymphoid cells and T follicular helper cells in Graves' and Hashimoto's thyroiditis. Front Immunol 11:601. https://doi.org/10.3389/fimmu.2020.00601
112. Corsiero E, Jagemann L, Perretti M et al (2018) Characterization of a synovial B cell-derived recombinant monoclonal antibody

targeting stromal calreticulin in the rheumatoid joints. J Immunol 201:1373–1381. https://doi.org/10.4049/jimmunol.1800346
113. Corsiero E, Bombardieri M, Carlotti E et al (2016) Single cell cloning and recombinant monoclonal antibodies generation from RA synovial B cells reveal frequent targeting of citrullinated histones of NETs. Ann Rheum Dis 75:1866–1875. https://doi.org/10.1136/annrheumdis-2015-208356
114. Corsiero E, Pratesi F, Prediletto E et al (2016) NETosis as source of autoantigens in rheumatoid arthritis. Front Immunol 7:485. https://doi.org/10.3389/fimmu.2016.00485
115. Croia C, Astorri E, Murray-Brown W et al (2014) Implication of Epstein-Barr virus infection in disease-specific autoreactive B cell activation in ectopic lymphoid structures of Sjögren's syndrome. Arthritis Rheumatol 66:2545–2557. https://doi.org/10.1002/art.38726
116. Scheel T, Gursche A, Zacher J et al (2011) V-region gene analysis of locally defined synovial B and plasma cells reveals selected B cell expansion and accumulation of plasma cell clones in rheumatoid arthritis. Arthritis Rheum 63:63–72. https://doi.org/10.1002/art.27767
117. Ekland EH, Forster R, Lipp M, Cyster JG (2004) Requirements for follicular exclusion and competitive elimination of autoantigen-binding B cells. J Immunol 172:4700–4708. https://doi.org/10.4049/jimmunol.172.8.4700
118. Le Pottier L, Devauchelle V, Fautrel A et al (2009) Ectopic germinal centers are rare in Sjogren's syndrome salivary glands and do not exclude autoreactive B cells. J Immunol 182:3540–3547. https://doi.org/10.4049/jimmunol.0803588
119. Schönbeck S, Padberg F, Hohlfeld R, Wekerle H (1992) Transplantation of thymic autoimmune microenvironment to severe combined immunodeficiency mice. A new model of myasthenia gravis. J Clin Invest 90:245–250. https://doi.org/10.1172/JCI115843
120. van de Sande MGH, Thurlings RM, Boumans MJH et al (2011) Presence of lymphocyte aggregates in the synovium of patients with early arthritis in relationship to diagnosis and outcome: is it a constant feature over time? Ann Rheum Dis 70:700–703. https://doi.org/10.1136/ard.2010.139287
121. Klimiuk PA, Goronzy JJ, Björ nsson J et al (1997) Tissue cytokine patterns distinguish variants of rheumatoid synovitis. Am J Pathol 151:1311–1319
122. Bugatti S, Manzo A, Vitolo B et al (2014) High expression levels of the B cell chemoattractant CXCL13 in rheumatoid synovium are a marker of severe disease. Rheumatology (Oxford) 53:1886–1895. https://doi.org/10.1093/rheumatology/keu163
123. Xu X, Hsu H-C, Chen J et al (2009) Increased expression of activation-induced cytidine deaminase is associated with anti-CCP and rheumatoid factor in rheumatoid arthritis. Scand J Immunol 70:309–316. https://doi.org/10.1111/j.1365-3083.2009.02302.x
124. Lewis MJ, Barnes MR, Blighe K et al (2019) Molecular portraits of early rheumatoid arthritis identify clinical and treatment response phenotypes. Cell Rep 28:2455-2470.e5. https://doi.org/10.1016/j.celrep.2019.07.091
125. Theander E, Vasaitis L, Baecklund E et al (2011) Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjögren's syndrome. Ann Rheum Dis 70:1363–1368. https://doi.org/10.1136/ard.2010.144782
126. Salomonsson S, Jonsson MV, Skarstein K et al (2003) Cellular basis of ectopic germinal center formation and autoantibody production in the target organ of patients with Sjögren's syndrome. Arthritis Rheum 48:3187–3201. https://doi.org/10.1002/art.11311
127. Risselada AP, Looije MF, Kruize AA et al (2013) The role of ectopic germinal centers in the immunopathology of primary Sjögren's syndrome: a systematic review. Semin Arthritis Rheum 42:368–376. https://doi.org/10.1016/j.semarthrit.2012.07.003
128. Rangel-Moreno J, Hartson L, Navarro C et al (2006) Inducible bronchus-associated lymphoid tissue (iBALT) in patients with pulmonary complications of rheumatoid arthritis. J Clin Invest 116:3183–3194. https://doi.org/10.1172/JCI28756
129. Delli K, Haacke EA, Kroese FGM et al (2016) Towards personalised treatment in primary Sjögren's syndrome: baseline parotid histopathology predicts responsiveness to rituximab treatment. Ann Rheum Dis 75:1933–1938. https://doi.org/10.1136/annrheumdis-2015-208304
130. Pijpe J, Meijer JM, Bootsma H et al (2009) Clinical and histologic evidence of salivary gland restoration supports the efficacy of rituximab treatment in Sjögren's syndrome. Arthritis Rheum 60:3251–3256. https://doi.org/10.1002/art.24903
131. Teng YKO, Levarht EWN, Toes REM et al (2009) Residual inflammation after rituximab treatment is associated with sustained synovial plasma cell infiltration and enhanced B cell repopulation. Ann Rheum Dis 68:1011–1016. https://doi.org/10.1136/ard.2008.092791
132. Thurlings RM, Vos K, Wijbrandts CA et al (2008) Synovial tissue response to rituximab: mechanism of action and identification of biomarkers of response. Ann Rheum Dis 67:917–925. https://doi.org/10.1136/ard.2007.080960
133. Cañete JD, Celis R, Moll C et al (2009) Clinical significance of synovial lymphoid neogenesis and its reversal after anti-tumour necrosis factor alpha therapy in rheumatoid arthritis. Ann Rheum Dis 68:751–756. https://doi.org/10.1136/ard.2008.089284
134. Klaasen R, Thurlings RM, Wijbrandts CA et al (2009) The relationship between synovial lymphocyte aggregates and the clinical response to infliximab in rheumatoid arthritis: a prospective study. Arthritis Rheum 60:3217–3224. https://doi.org/10.1002/art.24913
135. Adler S, Körner M, Förger F et al (2013) Evaluation of histologic, serologic, and clinical changes in response to abatacept treatment of primary Sjögren's syndrome: a pilot study. Arthritis Care Res (Hoboken) 65:1862–1868. https://doi.org/10.1002/acr.22052
136. Kavanaugh A, Rosengren S, Lee SJ et al (2008) Assessment of rituximab's immunomodulatory synovial effects (ARISE trial). 1: clinical and synovial biomarker results. Ann Rheum Dis 67:402–408. https://doi.org/10.1136/ard.2007.074229
137. Rosengren S, Wei N, Kalunian KC et al (2008) Elevated autoantibody content in rheumatoid arthritis synovia with lymphoid aggregates and the effect of rituximab. Arthritis Res Ther 10:R105. https://doi.org/10.1186/ar2497
138. Rosengren S, Wei N, Kalunian KC et al (2011) CXCL13: a novel biomarker of B-cell return following rituximab treatment and synovitis in patients with rheumatoid arthritis. Rheumatology (Oxford) 50:603–610. https://doi.org/10.1093/rheumatology/keq337
139. Vos K, Thurlings RM, Wijbrandts CA et al (2007) Early effects of rituximab on the synovial cell infiltrate in patients with rheumatoid arthritis. Arthritis Rheum 56:772–778. https://doi.org/10.1002/art.22400
140. Hamza N, Bootsma H, Yuvaraj S et al (2012) Persistence of immunoglobulin-producing cells in parotid salivary glands of patients with primary Sjögren's syndrome after B cell depletion therapy. Ann Rheum Dis 71:1881–1887. https://doi.org/10.1136/annrheumdis-2011-201189
141. Quartuccio L, Fabris M, Moretti M et al (2008) Resistance to rituximab therapy and local BAFF overexpression in Sjögren's syndrome-related myoepithelial sialadenitis and low-grade parotid B-cell lymphoma. Open Rheumatol J 2:38–43. https://doi.org/10.2174/1874312900802010038

142. Di Caro G, Bergomas F, Grizzi F et al (2014) Occurrence of tertiary lymphoid tissue is associated with T-cell infiltration and predicts better prognosis in early-stage colorectal cancers. Clin Cancer Res 20:2147–2158. https://doi.org/10.1158/1078-0432.CCR-13-2590
143. Schrama D, Voigt H, Eggert AO et al (2008) Immunological tumor destruction in a murine melanoma model by targeted LTalpha independent of secondary lymphoid tissue. Cancer Immunol Immunother 57:85–95. https://doi.org/10.1007/s00262-007-0352-x
144. Martinet L, Garrido I, Filleron T et al (2011) Human solid tumors contain high endothelial venules: association with T- and B-lymphocyte infiltration and favorable prognosis in breast cancer. Cancer Res 71:5678–5687. https://doi.org/10.1158/0008-5472.CAN-11-0431
145. Germain C, Gnjatic S, Tamzalit F et al (2014) Presence of B cells in tertiary lymphoid structures is associated with a protective immunity in patients with lung cancer. Am J Respir Crit Care Med 189:832–844. https://doi.org/10.1164/rccm.201309-1611OC
146. Gobert M, Treilleux I, Bendriss-Vermare N et al (2009) Regulatory T cells recruited through CCL22/CCR4 are selectively activated in lymphoid infiltrates surrounding primary breast tumors and lead to an adverse clinical outcome. Cancer Res 69:2000–2009. https://doi.org/10.1158/0008-5472.CAN-08-2360
147. Figenschau SL, Fismen S, Fenton KA et al (2015) Tertiary lymphoid structures are associated with higher tumor grade in primary operable breast cancer patients. BMC Cancer 15:101. https://doi.org/10.1186/s12885-015-1116-1
148. Finkin S, Yuan D, Stein I et al (2015) Ectopic lymphoid structures function as microniches for tumor progenitor cells in hepatocellular carcinoma. Nat Immunol 16:1235–1244. https://doi.org/10.1038/ni.3290
149. Remark R, Alifano M, Cremer I et al (2013) Characteristics and clinical impacts of the immune environments in colorectal and renal cell carcinoma lung metastases: influence of tumor origin. Clin Cancer Res 19:4079–4091. https://doi.org/10.1158/1078-0432.CCR-12-3847
150. Curiel TJ, Coukos G, Zou L et al (2004) Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med 10:942–949. https://doi.org/10.1038/nm1093
151. Bates GJ, Fox SB, Han C et al (2006) Quantification of regulatory T cells enables the identification of high-risk breast cancer patients and those at risk of late relapse. J Clin Oncol 24:5373–5380. https://doi.org/10.1200/JCO.2006.05.9584
152. Gao Q, Qiu S-J, Fan J et al (2007) Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection. J Clin Oncol 25:2586–2593. https://doi.org/10.1200/JCO.2006.09.4565
153. Fu J, Xu D, Liu Z et al (2007) Increased regulatory T cells correlate with CD8 T-cell impairment and poor survival in hepatocellular carcinoma patients. Gastroenterology 132:2328–2339. https://doi.org/10.1053/j.gastro.2007.03.102
154. Joshi NS, Akama-Garren EH, Lu Y et al (2015) Regulatory T cells in tumor-associated tertiary lymphoid structures suppress anti-tumor T cell responses. Immunity 43:579–590. https://doi.org/10.1016/j.immuni.2015.08.006
155. Kirk CJ, Hartigan-O'Connor D, Mulé JJ (2001) The dynamics of the T-cell antitumor response: chemokine-secreting dendritic cells can prime tumor-reactive T cells extranodally. Cancer Res 61:8794–8802
156. Schrama D, thor Straten P, Fischer WH et al (2001) Targeting of lymphotoxin-alpha to the tumor elicits an efficient immune response associated with induction of peripheral lymphoid-like tissue. Immunity 14:111–121. https://doi.org/10.1016/s1074-7613(01)00094-2
157. Goc J, Germain C, Vo-Bourgais TKD et al (2014) Dendritic cells in tumor-associated tertiary lymphoid structures signal a Th1 cytotoxic immune contexture and license the positive prognostic value of infiltrating CD8+ T cells. Cancer Res 74:705–715. https://doi.org/10.1158/0008-5472.CAN-13-1342
158. McMullen TPW, Lai R, Dabbagh L et al (2010) Survival in rectal cancer is predicted by T cell infiltration of tumour-associated lymphoid nodules. Clin Exp Immunol 161:81–88. https://doi.org/10.1111/j.1365-2249.2010.04147.x
159. Martinet L, Filleron T, Le Guellec S et al (2013) High endothelial venule blood vessels for tumor-infiltrating lymphocytes are associated with lymphotoxin β-producing dendritic cells in human breast cancer. J Immunol 191:2001–2008. https://doi.org/10.4049/jimmunol.1300872
160. Ladányi A, Kiss J, Mohos A et al (2011) Prognostic impact of B-cell density in cutaneous melanoma. Cancer Immunol Immunother 60:1729–1738. https://doi.org/10.1007/s00262-011-1071-x
161. Nielsen JS, Sahota RA, Milne K et al (2012) CD20+ tumor-infiltrating lymphocytes have an atypical CD27- memory phenotype and together with CD8+ T cells promote favorable prognosis in ovarian cancer. Clin Cancer Res 18:3281–3292. https://doi.org/10.1158/1078-0432.CCR-12-0234
162. Biswas S, Mandal G, Payne KK et al (2021) IgA transcytosis and antigen recognition govern ovarian cancer immunity. Nature 591:464–470. https://doi.org/10.1038/s41586-020-03144-0
163. Ding G-Y, Ma J-Q, Yun J-P et al (2021) Distribution and density of tertiary lymphoid structures predict clinical outcome in intrahepatic cholangiocarcinoma. J Hepatol S0168–8278(21):02178–02184. https://doi.org/10.1016/j.jhep.2021.10.030
164. Hiraoka N, Ino Y, Yamazaki-Itoh R et al (2015) Intratumoral tertiary lymphoid organ is a favourable prognosticator in patients with pancreatic cancer. Br J Cancer 112:1782–1790. https://doi.org/10.1038/bjc.2015.145
165. Sofopoulos M, Fortis SP, Vaxevanis CK et al (2019) The prognostic significance of peritumoral tertiary lymphoid structures in breast cancer. Cancer Immunol Immunother 68:1733–1745. https://doi.org/10.1007/s00262-019-02407-8
166. Werner F, Wagner C, Simon M et al (2021) A standardized analysis of tertiary lymphoid structures in human melanoma: disease progression- and tumor site-associated changes with germinal center alteration. Front Immunol 12:675146. https://doi.org/10.3389/fimmu.2021.675146
167. Bento DC, Jones E, Junaid S et al (2015) High endothelial venules are rare in colorectal cancers but accumulate in extratumoral areas with disease progression. Oncoimmunology 4:e974374. https://doi.org/10.4161/2162402X.2014.974374
168. Overacre-Delgoffe AE, Bumgarner HJ, Cillo AR et al (2021) Microbiota-specific T follicular helper cells drive tertiary lymphoid structures and anti-tumor immunity against colorectal cancer. Immunity S1074–7613(21):00494–00495. https://doi.org/10.1016/j.immuni.2021.11.003
169. Zhang W-H, Wang W-Q, Han X et al (2020) Infiltrating pattern and prognostic value of tertiary lymphoid structures in resected non-functional pancreatic neuroendocrine tumors. J Immunother Cancer 8:e001188. https://doi.org/10.1136/jitc-2020-001188
170. Li H, Liu H, Fu H et al (2021) Peritumoral tertiary lymphoid structures correlate with protective immunity and improved prognosis in patients with hepatocellular carcinoma. Front Immunol 12:648812. https://doi.org/10.3389/fimmu.2021.648812
171. Mustapha R, Ng K, Monypenny J, Ng T (2021) Insights into unveiling a potential role of tertiary lymphoid structures in metastasis. Front Mol Biosci 8:661516. https://doi.org/10.3389/fmolb.2021.661516

172. Shen H, Wang X, Shao Z et al (2014) Alterations of high endothelial venules in primary and metastatic tumors are correlated with lymph node metastasis of oral and pharyngeal carcinoma. Cancer Biol Ther 15:342–349. https://doi.org/10.4161/cbt.27328
173. Lee HJ, Kim JY, Park IA et al (2015) Prognostic significance of tumor-infiltrating lymphocytes and the tertiary lymphoid structures in HER2-positive breast cancer treated with adjuvant trastuzumab. Am J Clin Pathol 144:278–288. https://doi.org/10.1309/AJCPIXUYDVZ0RZ3G
174. Song IH, Heo S-H, Bang WS et al (2017) predictive value of tertiary lymphoid structures assessed by high endothelial venule counts in the neoadjuvant setting of triple-negative breast cancer. Cancer Res Treat 49:399–407. https://doi.org/10.4143/crt.2016.215
175. Cabrita R, Lauss M, Sanna A et al (2020) Tertiary lymphoid structures improve immunotherapy and survival in melanoma. Nature 577:561–565. https://doi.org/10.1038/s41586-019-1914-8
176. Groeneveld CS, Fontugne J, Cabel L et al (2021) Tertiary lymphoid structures marker CXCL13 is associated with better survival for patients with advanced-stage bladder cancer treated with immunotherapy. Eur J Cancer 148:181–189. https://doi.org/10.1016/j.ejca.2021.01.036
177. van Dijk N, Gil-Jimenez A, Silina K et al (2020) Preoperative ipilimumab plus nivolumab in locoregionally advanced urothelial cancer: the NABUCCO trial. Nat Med 26:1839–1844. https://doi.org/10.1038/s41591-020-1085-z
178. Cottrell TR, Thompson ED, Forde PM et al (2018) Pathologic features of response to neoadjuvant anti-PD-1 in resected non-small-cell lung carcinoma: a proposal for quantitative immune-related pathologic response criteria (irPRC). Ann Oncol 29:1853–1860. https://doi.org/10.1093/annonc/mdy218
179. Helmink BA, Reddy SM, Gao J et al (2020) B cells and tertiary lymphoid structures promote immunotherapy response. Nature 577:549–555. https://doi.org/10.1038/s41586-019-1922-8
180. Johansson-Percival A, He B, Li Z-J et al (2017) De novo induction of intratumoral lymphoid structures and vessel normalization enhances immunotherapy in resistant tumors. Nat Immunol 18:1207–1217. https://doi.org/10.1038/ni.3836
181. Billingham ME (1985) Endomyocardial biopsy detection of acute rejection in cardiac allograft recipients. Heart Vessels Suppl 1:86–90. https://doi.org/10.1007/BF02072369
182. Forbes RD, Rowan RA, Billingham ME (1990) Endocardial infiltrates in human heart transplants: a serial biopsy analysis comparing four immunosuppression protocols. Hum Pathol 21:850–855. https://doi.org/10.1016/0046-8177(90)90055-a
183. Nakhleh RE, Copenhaver CM, Werdin K et al (1991) Lack of evidence for involvement of Epstein-Barr virus in the development of the "Quilty" lesion of transplanted hearts: an in situ hybridization study. J Heart Lung Transplant 10:504–507
184. Barone JH, Fishbein MC, Czer LS et al (1997) Absence of endocardial lymphoid infiltrates (Quilty lesions) in nonheart transplant recipients treated with cyclosporine. J Heart Lung Transplant 16:600–603
185. Moore S, Metter C, Cai Q, Torrealba J (2020) Quilty lesion FOXP3+ and TGF-Beta+ Regulatory T-Cells are associated with acceptance of heart allografts. Transplantation 104:S576–S576. https://doi.org/10.1097/01.tp.0000701688.26663.d7
186. Baddoura FK, Nasr IW, Wrobel B et al (2005) Lymphoid neogenesis in murine cardiac allografts undergoing chronic rejection. Am J Transplant 5:510–516. https://doi.org/10.1111/j.1600-6143.2004.00714.x
187. Pabst R, Gehrke I (1990) Is the bronchus-associated lymphoid tissue (BALT) an integral structure of the lung in normal mammals, including humans? Am J Respir Cell Mol Biol 3:131–135. https://doi.org/10.1165/ajrcmb/3.2.131
188. Bienenstock J, Johnston N, Perey DY (1973) Bronchial lymphoid tissue. I. Morphologic characteristics. Lab Invest 28:686–692
189. Sue-Chu M, Karjalainen EM, Altraja A et al (1998) Lymphoid aggregates in endobronchial biopsies from young elite cross-country skiers. Am J Respir Crit Care Med 158:597–601. https://doi.org/10.1164/ajrccm.158.2.9711012
190. Kawamata N, Xu B, Nishijima H et al (2009) Expression of endothelia and lymphocyte adhesion molecules in bronchus-associated lymphoid tissue (BALT) in adult human lung. Respir Res 10:97. https://doi.org/10.1186/1465-9921-10-97
191. Delventhal S, Brandis A, Ostertag H, Pabst R (1992) Low incidence of bronchus-associated lymphoid tissue (BALT) in chronically inflamed human lungs. Virchows Arch B Cell Pathol Incl Mol Pathol 62:271–274. https://doi.org/10.1007/BF02899692
192. Meuwissen HJ, Hussain M (1982) Bronchus-associated lymphoid tissue in human lung: correlation of hyperplasia with chronic pulmonary disease. Clin Immunol Immunopathol 23:548–561. https://doi.org/10.1016/0090-1229(82)90139-8
193. Richmond I, Pritchard GE, Ashcroft T et al (1993) Bronchus associated lymphoid tissue (BALT) in human lung: its distribution in smokers and non-smokers. Thorax 48:1130–1134. https://doi.org/10.1136/thx.48.11.1130
194. Prop J, Nieuwenhuis P, Wildevuur CR (1985) Lung allograft rejection in the rat. I. Accelerated rejection caused by graft lymphocytes. Transplantation 40:25–30. https://doi.org/10.1097/00007890-198507000-00006
195. Hasegawa T, Iacono A, Yousem SA (1999) The significance of bronchus-associated lymphoid tissue in human lung transplantation: is there an association with acute and chronic rejection? Transplantation 67:381–385. https://doi.org/10.1097/00007890-199902150-00007
196. Li W, Bribriesco AC, Nava RG et al (2012) Lung transplant acceptance is facilitated by early events in the graft and is associated with lymphoid neogenesis. Mucosal Immunol 5:544–554. https://doi.org/10.1038/mi.2012.30
197. Tanaka S, Gauthier JM, Fuchs A et al (2020) IL-22 is required for the induction of bronchus-associated lymphoid tissue in tolerant lung allografts. Am J Transplant 20:1251–1261. https://doi.org/10.1111/ajt.15701
198. Li W, Gauthier JM, Higashikubo R et al (2019) Bronchus-associated lymphoid tissue-resident Foxp3+ T lymphocytes prevent antibody-mediated lung rejection. J Clin Invest 129:556–568. https://doi.org/10.1172/JCI122083
199. Thaunat O, Field A-C, Dai J et al (2005) Lymphoid neogenesis in chronic rejection: evidence for a local humoral alloimmune response. Proc Natl Acad Sci U S A 102:14723–14728. https://doi.org/10.1073/pnas.0507223102
200. Reed HO, Wang L, Sonett J et al (2019) Lymphatic impairment leads to pulmonary tertiary lymphoid organ formation and alveolar damage. J Clin Invest 129:2514–2526. https://doi.org/10.1172/JCI125044
201. Li W, Gauthier JM, Tong AY et al (2020) Lymphatic drainage from bronchus-associated lymphoid tissue in tolerant lung allografts promotes peripheral tolerance. J Clin Invest 130:6718–6727. https://doi.org/10.1172/JCI136057
202. Kerjaschki D, Regele HM, Moosberger I et al (2004) Lymphatic neoangiogenesis in human kidney transplants is associated with immunologically active lymphocytic infiltrates. J Am Soc Nephrol 15:603–612. https://doi.org/10.1097/01.asn.0000113316.52371.2e
203. Brown K, Sacks SH, Wong W (2011) Tertiary lymphoid organs in renal allografts can be associated with donor-specific tolerance rather than rejection. Eur J Immunol 41:89–96. https://doi.org/10.1002/eji.201040759

204. Miyajima M, Chase CM, Alessandrini A et al (2011) Early acceptance of renal allografts in mice is dependent on foxp3(+) cells. Am J Pathol 178:1635–1645. https://doi.org/10.1016/j.ajpath.2010.12.024
205. Rosales IA, Yang C, Farkash EA et al (2021) Novel intragraft regulatory lymphoid structures in kidney allograft tolerance. Am J Transplant. https://doi.org/10.1111/ajt.16880
206. Colbeck EJ, Ager A, Gallimore A, Jones GW (2017) Tertiary lymphoid structures in cancer: drivers of antitumor immunity, immunosuppression, or bystander sentinels in disease? Front Immunol 8:1830. https://doi.org/10.3389/fimmu.2017.01830
207. Rodriguez AB, Engelhard VH (2020) Insights into tumor-associated tertiary lymphoid structures: novel targets for antitumor immunity and cancer immunotherapy. Cancer Immunol Res 8:1338–1345. https://doi.org/10.1158/2326-6066.CIR-20-0432
208. Corsiero E, Delvecchio FR, Bombardieri M, Pitzalis C (2019) B cells in the formation of tertiary lymphoid organs in autoimmunity, transplantation and tumorigenesis. Curr Opin Immunol 57:46–52. https://doi.org/10.1016/j.coi.2019.01.004