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Review article

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The roles of tertiary lymphoid structures in chronic diseases

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Abstract

Tertiary lymphoid structures (TLSs) are ectopic lymphoid tissues that drive antigen-specific immune responses at sites of chronic inflammation. Unlike secondary lymphoid organs such as lymph nodes, TLSs lack capsules and have their own unique characteristics and functions. The presumed influence of TLSs on the disease course has led to widespread interest in obtaining a better understanding of their biology and function. Studies using single-cell analyses have suggested heterogeneity in TLS composition and phenotype, and consequently, functional correlates with disease progression are sometimes conflicting. The presence of TLSs correlates with a favourable disease course in cancer and infection. Conversely, in autoimmune diseases and chronic age-related inflammatory diseases including chronic kidney disease, the presence of TLSs is associated with a more severe disease course. However, the detailed mechanisms that underlie these clinical associations are not fully understood. To what extent the mechanisms of TLS development and maturation are shared across organs and diseases is also still obscure. Improved understanding of TLS development and function at the cellular and molecular levels may enable the exploitation of these structures to improve therapies for chronic diseases, including chronic kidney disease.

Sections

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Key points

- Tertiary lymphoid structures (TLSs) are organized lymphoid aggregates that develop in perivascular areas in response to disturbed tissue homeostasis.
- TLSs serve as local immune niches to promote adaptive immunity; their unencapsulated structure enables direct exposure to diverse stimuli from an inflamed environment.
- The development of TLSs in different organs involves common mechanisms that are presumably regulated by tissue-specific cues.
- The presence of TLSs correlates with a favourable disease course in many types of cancer and infection.
- In autoimmunity, chronic inflammation and ageing, the presence of TLSs correlates with pathological conditions and a more severe disease course.
- Functional characterization of TLSs in human diseases and the development of interventions to induce or reduce TLSs could lead to promising therapeutic avenues.

Introduction

The prevalence of age-related chronic diseases, including cardiovascular disease, cancer, infections and chronic kidney disease (CKD) is increasing owing to the increase in mean global life expectancy[1]. Age-related diseases are characterized by chronic inflammation, which is a key contributor to the pathogenesis of these diseases and an important therapeutic target[1]. Inflammation is a protective response that can restore tissue homeostasis following tissue injury or infection; however, sustained or unresolved inflammation has detrimental effects that can contribute to the development and progression of chronic diseases.

Tertiary lymphoid structures (TLSs) (also known as tertiary lymphoid tissues, tertiary lymphoid organs or ectopic lymphoid tissues) develop in non-lymphoid organs during chronic inflammatory conditions, including cancer, infection, autoimmunity and age-related diseases[2–5]. TLSs are organized lymphoid aggregates with a network of specialized fibroblasts that share many functional and structural characteristics with secondary lymphoid organs (SLOs), particularly lymph nodes. For example, TLSs and SLOs can drive antigen-specific immune responses[5] and are equipped with specialized blood vessels known as high endothelial venules (HEVs) that facilitate transmigration of lymphocytes from the blood into lymphoid tissues[6]. However, TLSs are less organized than SLOs and develop in response to cues that are associated with disturbed homeostasis. For example, tissue-resident cells can transdifferentiate into TLS cellular components in response to microenvironmental stimuli during tissue inflammation[7]. The advent of single-cell sequencing techniques has led to new insights into cellular diversity and molecular heterogeneity during the various stages of TLS development.

Interest in TLSs is increasing because of their presence in and presumed contribution to chronic inflammatory conditions and ageing[8–13]. The role of TLSs in these diseases is context-dependent and can be beneficial or detrimental. In cancer, for example, antitumour immune responses are generated within TLSs that are located near to tumours[14,15] and the presence of TLSs is associated with improved response to therapies in some, but not all, types of cancer[16]. Similarly, TLSs induced by infections generate anti-pathogen immune responses that are beneficial for the host[17,18]. Conversely, in autoimmunity, TLSs promote activation of autoreactive lymphocytes, resulting in autoantibody production, and the presence of TLSs is associated with a poor prognosis[19]. The development of TLSs also contributes to the progression of kidney diseases such as acute kidney injury (AKI) in elderly people[13,20]. Age-dependent TLS formation has been reported in the kidney, lung and other organs and has a role in age-related chronic inflammatory diseases[7,8,13,21–23]. These findings suggest that TLSs are important sites for modulating local immunity and are of critical importance when considering therapeutic strategies to prevent the progression of chronic diseases.

In this Review, we discuss TLS development, maintenance and function, with a focus on the roles of TLSs in autoimmune disease, cancer, infection and chronic age-related inflammatory diseases, including CKD. We also discuss the clinical implications and therapeutic potential of TLSs in various tissues and diseases.

Characteristics of TLSs and SLOs

TLSs and SLOs are mainly composed of lymphocytes with the support of specialized fibroblasts and are associated with HEVs. Molecules that are essential for SLO maintenance and function, including homeostatic chemokines and lymphotoxin, are also detected in TLSs[5]. In addition, both structures promote induction of adaptive immune responses and can contain germinal centres that are essential for cognate T cell–B cell interactions, consecutive antibody somatic hypermutation and affinity maturation[3,24]. Activation of the adaptive immune responses distinguishes TLSs from simple inflammatory cell infiltrates.

TLSs also have some unique characteristics and functions, particularly with respect to local tissue responses (Fig. 1, Table 1). The homeostatic chemokines CXCL13, CCL19 and CCL21 have crucial roles in the development and maintenance of SLOs, but CCL21 is not involved in age-dependent TLS formation in the kidney, bladder, or liver[7,22,23]. Development of TLSs is induced after birth (discussed further below) and depends on CD4 T cells or other types of immune cells[7,25,26], whereas SLO development depends on specialized embryonic lymphoid tissue inducer (LTi) cells that mediate the transition of embryonic mesenchymal lymphoid tissue organizer cells into CXCL13-producing follicular dendritic cells (FDCs) and CCL19/CCL21-producing fibroblastic reticular cells in a lymphoid tissue-dependent manner[5]. LTi cells promote lymphoid organogenesis via lymphotoxin and tumour necrosis factor (TNF)[27] and FDCs are specialized mesenchymal cells that support B cell activation[28]. After birth, other cell types such as T helper 17 (Th17) cells or B cells take over the function of LTi cells, and parenchymal and mesenchymal cells become lymphoid tissue organizer cells in adult organs during lymphoid neogenesis[25,26,29,30].

In SLOs, autoreactive B cells are eliminated via a process that depends on competition between cells with different specificities[31]. A key feature of this censoring mechanism is the selective exclusion of self-antigen-binding B cells from the normal migration route into B cell follicles, which leads to their premature death (B cells that are excluded from follicles have a half-life of less than a day)[31,32]. By contrast, autoreactive B cells can enter the follicular niche, receive survival factors and survive in TLSs[33]. In autoimmunity, disease-specific autoantibodies are produced in TLSs in target organs[34,35]. Autoantibody production in TLSs has also been reported in aged, injured kidneys[20].

SLOs are encapsulated and thereby physically separated from the inflammatory environment, whereas TLSs are directly exposed to antigens, cytokines, damage-associated molecular patterns (DAMPs) and other inflammatory factors[6,24]. This difference makes the immune response that is generated in TLSs more effective than that generated in SLOs. For example, TLSs in the lungs, termed inducible bronchus-associated lymphoid tissue (iBALT), develop in response to infection and contribute to protective immunity, even in the absence of SLOs[36]. Germinal centres in iBALT comprise plasma cells and memory B cells with greater cross-protective potential than those in the lymph nodes and spleen[18]. B cells in iBALT also proliferate more upon antigen encounter than those in lymph nodes or the spleen[18].

Heterogeneity and development of TLSs

TLSs vary in their cellular composition from loose T cell–B cell clusters to highly organized structures with distinct T cell zones and B cell areas that harbour germinal centres. TLS development is thought to be a gradual process, but detailed analysis of TLS phenotypes and the clinical relevance of TLS maturation stages is challenging. Tissue samples from patients with chronic inflammatory diseases are limited and the time of disease initiation in these samples is unknown, so establishing a correlation between TLS status and disease progression is difficult. In addition, methods for qualitative and quantitative TLS evaluation are not standardized, which might partly explain conflicting results regarding the clinical relevance of TLSs in the kidney and other organs[37–40].

Stages of maturation

To stratify the definition of TLSs, we analysed surgically resected kidney samples from patients with complicated pyelonephritis and from older patients (≥60 years) with renal cell carcinoma (RCC) as well as aged mouse kidneys with ischaemia–reperfusion injury-induced TLSs[21]. We defined TLSs as clusters of lymphocytes with signs of proliferation and showed that TLS development in human and murine kidneys occurs through distinct stages[21] (Fig. 2a). Similar TLS maturation stages have been found in patients with various types of cancer and in mouse lungs after experimental TLS induction[41,42]. These data suggest that a common developmental sequence mediates lymphoid neogenesis across different organs.

TLS can be induced in an antigen-dependent or antigen-independent manner (Box 1). They initially appear as small aggregates containing mainly T cells and B cells and then expand and mature into clusters with B cell areas supported by $CD21^+$ FDCs with or without distinct T cell areas[13,21,41]. Finally, a germinal centre reaction can be activated in the B cell areas of TLSs. We found that TLS development arrests before germinal centre development in mildly injured kidneys, whereas TLSs in severely injured kidneys are fully mature. This finding suggests that TLS maturation is associated with the severity of inflammation, kidney injury and kidney dysfunction[21].

A single-cell RNA sequencing analysis of B cells derived from human tumours identified unswitched IgD^+ B cells, switched IgG^+ B cells and a wide range of B cells that expressed genes that are associated with immature or mature germinal centres[11,12]. Analysis of B cell receptor sequences from the B cells further confirmed their clonal expansion[11]. These data support in situ B cell proliferation and maturation within TLSs in human cancer tissues.

Consistent with the observation that TLSs disappear when inflammation is resolved[17,43], TLS maturation can be reversed with immunosuppressive treatments[21], including corticosteroids[28,41]. In a retrospective study of kidney biopsy samples from clinically stable transplanted renal allografts, we found TLS s in 50% of the allografts 1 month after transplantation. Mature TLS, defined as those with FDCs,

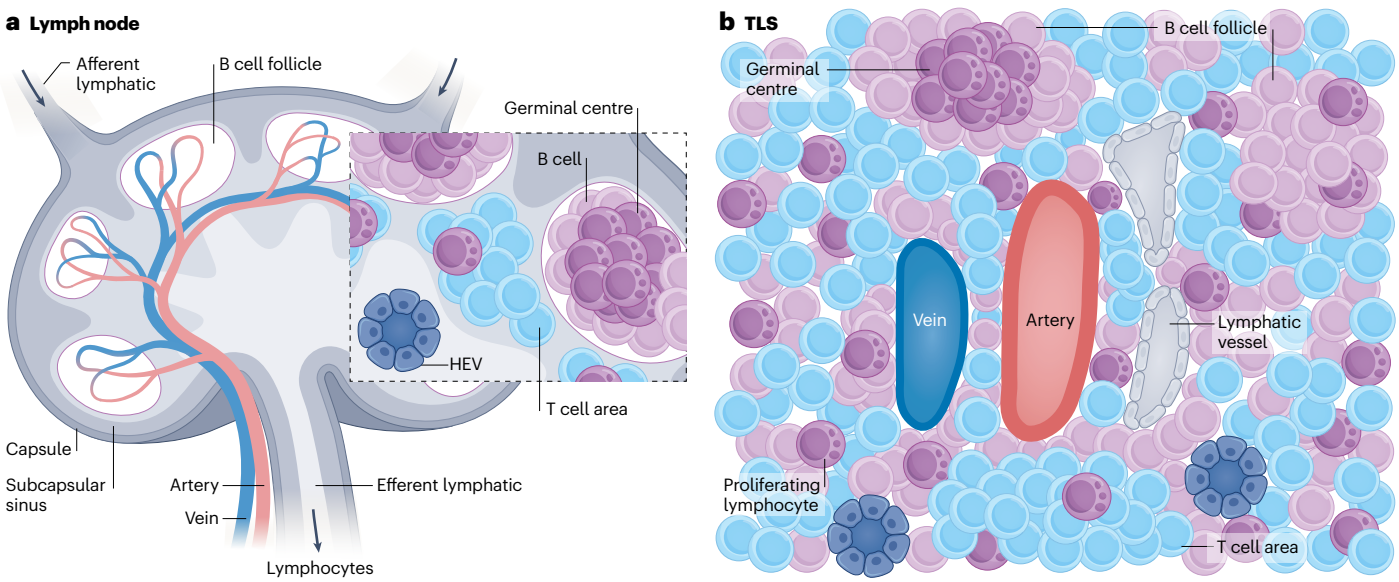

Fig. 1 | Structural differences between secondary lymphoid organs and tertiary lymphoid structures. a, In lymph nodes, immune cell subpopulations are distributed in a regular pattern and form sub-compartments. B cells form B cell follicles and occasionally develop germinal centres during antigen stimulation, whereas most T cells reside in the T cell area adjacent to B cell follicles. A fibrous capsule surrounds these distinct cellular compartments. **b**, In tertiary lymphoid structures (TLSs), T cells and B cells are mostly intermingled with each other but occasionally form distinct B cell and T cell compartments similar to those that are present in lymph nodes. TLSs lack a capsule and are exposed to local antigens, danger-associated molecular patterns, cytokines and various ions. HEV, high endothelial venule.

Table 1 | Differences between secondary lymphoid organs and tertiary lymphoid structures

Feature	Secondary lymphoid organ	Tertiary lymphoid structure	Refs.
Induction	During embryonic development	After birth	5,6,34,43
Location	Key locations under control of developmental programme	Perivascular sites in non-lymphoid organs or tissues in the setting of inflammation owing to injury, cancer, infection, autoimmunity, organ transplantation or ageing	21,24,29, 45,46,48
Development	Pre-programmed developmental programme	Tissue- and trigger-specific local inflammatory signals	5,6,34,43
Capsule	The capsule physically separates the secondary lymphoid organ from the environment	The tertiary lymphoid structure is not encapsulated so is directly exposed to factors in the tissue microenvironment including cytokines, antigens, ions and danger-associated molecular patterns	6,24,195
Structure	Compartmentalized T cell and B cell areas	Variable (ranging from mixed T cells and B cells to compartmentalized T cell and B cell areas)	5,6,21,24,195
Self-tolerance	Maintained	Disturbed (autoantibody production etc.)	19,20, 31–34,195
Function	Generation of adaptive immune responses to delivered antigens	Generation of adaptive immune responses to locally presented antigens	5,6,34,195

were present in 19% of the allografts 1 year after transplantation. The presence of mature TLSs, but not immature TLS, in 1-year biopsy samples was associated with poor graft function[44]. These results suggest that classification of TLSs into distinct maturation stages might improve their prognostic power in inflammatory kidney diseases, including kidney transplant rejection.

Involvement of perivascular cells

In most organs, TLSs develop in perivascular areas[21,29,45,46], which are rich in extracellular matrix components, small blood vessels, lymphatic vessels and neurons. Perivascular areas are conserved across organs and can act as a niche for tissue-resident immune cells[47,48]. Several types of unique cells that are involved in TLS formation and maintenance reside in the perivascular area.

Perivascular fibroblasts have a pivotal role in TLS formation[7,49,50] (Fig. 2b). These cells transdifferentiate into specialized fibroblasts that produce homeostatic chemokines and provide cues for optimal spatial immune cell organization[7,9,51–54]. The molecular cues that induce this phenotypic change are context dependent. For example, in lung fibroblasts, CXCL13 expression was induced by type I interferon (IFN) signalling[52], IL-17A, or TNF[25], whereas in salivary gland fibroblasts CXCL13 expression was induced by IL-22 (ref. 55).

The anatomical relationship between TLSs and the vasculature suggests a functional connection between blood vessels and lymphoid neogenesis. In the kidney, arteries, veins and lymphatic vessels run in parallel and TLSs are detected in perivascular, periglomerular, and subcapsular areas and in the renal pelvis, all of which contain arterial circuits[21,51,56]. Loss of Notch signalling in vascular endothelial cells, but not in lymphatic vessel endothelial cells, led to TLS formation in mouse kidneys[57]. In this model, arteries located within TLSs acquire the HEV phenotype and promote lymphocyte recruitment.

Lymphatic vessels might also have an important role in TLS induction and maintenance. These vessels spread along the arteries and veins within organs and form a dense network throughout the body[6,58]. They serve as conduits for various immune cells, including lymphocytes and dendritic cells, to traffic from peripheral non-lymphoid organs to SLOs[59]. In a model of chronic ileitis caused by TNF overabundance, TLS develop in the mesentery at the sites of lymphatic valves[60]. Lymphatic vessels, particularly lymphatic endothelial cells, produce IL-7, which is a non-redundant regulator of T cell homeostasis in SLOs and TLSs[61,62] and contributes to TLS maintenance. Genetic deletion or pharmacological neutralization of IL-7-producing lymphatic endothelial cells resulted in defective TLS formation and a decrease in the number of $CD4^+$ tissue-resident memory T (T_{RM}) cells in the mouse lung[61,63]. Thus, interaction between immune cells and non-immune cells in the perivascular area is vital for TLS development across organs including the kidney and lung.

TLSs in pathological conditions

The clinical relevance of TLSs in diseases including autoimmune conditions, cancer, infection, chronic inflammatory diseases and in ageing is context dependent. Even in the same organ, TLSs can be beneficial or detrimental depending on their composition and the aetiology and phase of the disease.

Autoimmune diseases

The formation of TLSs has been reported in almost all organ-specific human autoimmune diseases, including rheumatoid arthritis[64], lupus nephritis[65], type 1 diabetes mellitus[66], Crohn disease[67] and Sjogren syndrome[33]. The reported prevalence of TLSs in these diseases ranges from almost 100% in patients with Hashimoto thyroiditis[68] to almost 20% in patients with juvenile dermatomyositis[69]. Most, but not all, clinical studies have shown a direct correlation between the presence of TLS and disease activity[34]. The reasons for this inconsistency are unknown but may include differences in TLS definition, disease stage and treatment history as well as sampling techniques (for example, biopsy or surgical resection) and errors.

TLSs may promote breaking of self-tolerance in autoimmune disease. This hypothesis is exemplified by the finding that transplantation of tissue containing TLSs from patients with rheumatoid arthritis and myasthenia gravis into immunodeficient mice resulted in sustained production of anti-cyclic citrullinated peptide (CCP) antibodies and anti-acetylcholine receptor antibodies[19,70]. The fact that TLSs can also be detected in seronegative patients with arthritis, such as those with spondyloarthropathies[71,72], suggests that TLS can contribute to autoimmune disease pathogenesis via multiple mechanisms.

Lupus nephritis affects 30–60% of patients with SLE and is one of the most serious complications of this disease[73]. Although lupus nephritis is characterized by heterogeneous glomerulonephritis,

tubulointerstitial inflammation is common and determines the kidney prognosis[74]. Several studies have reported TLS formation in lupus nephritis[65,75]. An analysis of micro-dissected TLSs from patient kidney biopsy samples detected clonal B cells with a high degree of somatic hypermutation[65]. These findings indicate in situ germinal centre responses and the generation of autoantibodies, which could potentially contribute to kidney disease progression by binding proximal tubular cells and stimulating cytokine production[76]. The presence of follicular T cell-like CD4 T cells in kidney biopsy samples was associated with lower estimated glomerular filtration rate in patients with lupus nephritis[75], suggesting a pathogenic contribution of TLSs in this disease[77].

Interestingly, TLSs are also detected in the central nervous system in patients with SLE[78]. Similarly, in patients with rheumatoid arthritis,

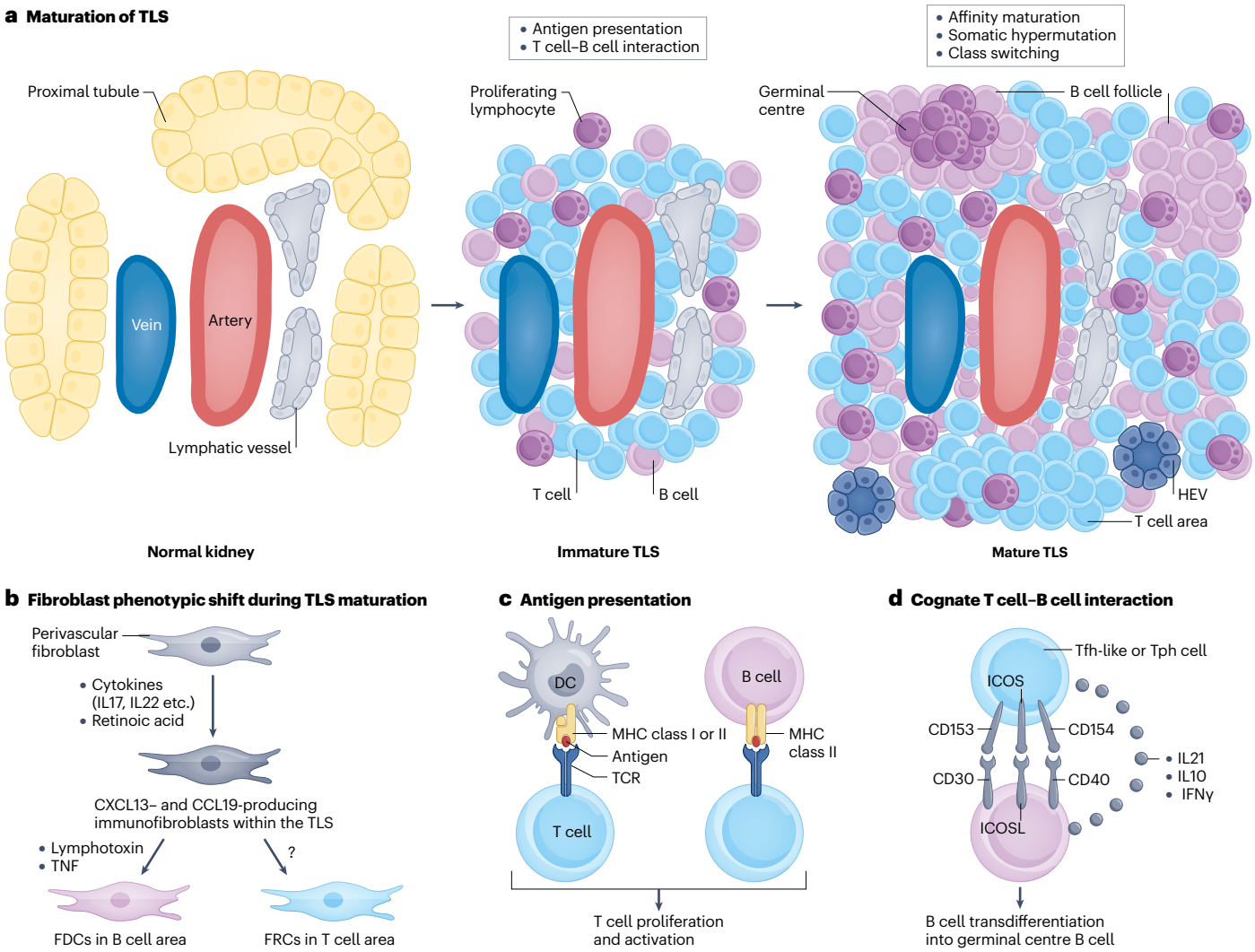

Fig. 2 | Maturation of tertiary lymphoid structures. a, In the kidney and most other organs, arteries, veins and lymphatic vessels run together. Tertiary lymphoid structures (TLSs) first appear as small aggregates containing mainly T cells and B cells at perivascular sites, and then expand and mature into clusters with distinct B cell and T cell areas. In immature TLSs, antigen presentation and intimate T cell–B cell interactions drive activation of lymphocytes and TLS maturation. Mature TLSs contain high endothelial venules (HEVs), which are specialized blood vessels that are adapted for lymphocyte trafficking. Some of the B cell areas (follicles) contain germinal centres, which are histologically defined as clusters of proliferating B cells. The germinal centres support B cell affinity maturation, class switching and somatic hypermutation. **b**, In parallel to TLS maturation, resident fibroblasts transdifferentiate into several distinct phenotypes and orchestrate TLS development. First, in response to IL-17, IL-22 and retinoic acid, perivascular fibroblasts acquire the ability to produce homeostatic chemokines such as CXC-chemokine ligand 13 (CXCL13) and CC-chemokine ligand 19 (CCL19) and recruit immune cells. These immunofibroblasts then further transdifferentiate into follicular dendritic cells (FDCs) and follicular reticular cells (FRCs), which form and support the B cell and T cell areas, respectively. Lymphotoxin (LT) and tumour necrosis factor (TNF) promote the transdifferentiation of immunofibroblasts into FDCs[50], but the signalling pathways that drive FRC differentiation are unknown. **c**, Within TLSs, dendritic cells and B cells may present local antigens to T cells, leading to T cell activation and proliferation. **d**, CD4 T cells with B cell helper functions, T follicular helper-like cells (Tfh-like cells) and T peripheral helper (Tph) cells[187], interact with B cells in TLSs via several co-stimulation molecules, including ICOS–ICOSL, CD154–CD40 and CD153–CD30, in synergy with cytokines such as IL-21 and IL-10 (ref. 13). These interactions promote B cell transdifferentiation into germinal centre B cells.

Box 1

Antigen exposure and TLS formation

Tertiary lymphoid structure (TLS) formation is thought to occur in response to chronic inflammatory cues in non-lymphoid organs in an antigen-dependent manner. In the settings of infection, cancer, transplant rejection and some autoimmune diseases, the presence of an antigen is obvious. Furthermore, evidence suggests that TLSs develop and persist owing to antigen exposure and resolve after antigen clearance. For example, in type 1 diabetes mellitus, the destruction of islet of Langerhans β-cells is caused by autoreactive T cells activated within TLSs, which resolve after the antigen stimulus is removed[196]. However, a 2022 study elegantly showed that a genetic deficiency in endothelial Notch signalling in blood vessels is sufficient to drive TLS formation in the kidney without any alterations of secondary lymphoid organs[57]. This finding is consistent with the observation that several organs in superaged (2-year-old) mice exhibit TLS without any injury[7,21], possibly as a result of the decline in endothelial Notch signalling that occurs with age[188]. Further studies are needed to identify the roles of TLSs that are induced in an antigen-independent manner, establish whether these TLSs differ from those that are induced by antigen-specific lymphocytes and identify the mechanisms by which TLSs are induced and maintained in the absence of antigens.

TLSs are detected not only in synovial tissues, but also in lung[79] and bone marrow[80]. These findings suggest the involvement of circulating cells or humoral factors in TLS development in autoimmune diseases.

Cancer

Inflammation and cancer are often accompanied by TLSs[81] but their density varies between tumour types and between individuals with the same disease (Fig. 3; Supplementary Table 1). The reasons for this heterogeneity are unclear but tumour-intrinsic molecular features may contribute. For example, higher mutational burden is associated with higher TLS density in colorectal[82–84], bladder[85] and pancreatic cancers[86]. HER2 loss and hormone receptor-positivity in breast cancer[87–89], and ALK rearrangements in non-small-cell lung cancer[90], are associated with reduced TLS density, whereas the expression of viral antigens in head and neck squamous cell carcinoma shows conflicting data concerning correlation with TLS density[91,92]. A positive correlation between TLSs and the survival of patients with bladder cancer was first reported in 1970 (ref. 93) and similar findings have been reported for many other cancer types[42]. The presence of TLSs in the tumour microenvironment correlates with increased infiltration of adaptive immune cells[42], and evidence suggests that B and T cells in TLSs are tumour specific[15,94–99]. T cell priming may take place in TLSs independently of lymph nodes, suggesting a unique local function for TLSs in the tumour microenvironment.

The maturation stage of TLSs in cancer varies from B cell aggregates to organized structures with germinal centres[42,96]. In untreated lung[40,41], colorectal[83] and bladder cancer[100], mature, germinal centre-positive TLSs are a positive prognosticator of survival, whereas immature TLSs have either no association or a weak association with survival. In hepatocellular carcinoma, mature TLSs correlate with improved survival[101–103], whereas immature TLSs serve as survival niches for tumour progenitor cells and confer a worse prognosis[104]. Similarly, in kidney cancer, TLSs are mostly immature and a higher density of these TLSs correlates with a dismal prognosis[100], a phenomenon that is replicated in RCC-derived lung metastases[105]. Thus, TLSs correlate with improved outcome in many but not all cancer types, and differences in the TLS composition or maturation may explain this discrepancy.

Based on their presumed role in B and T cell priming, a high TLS density was expected to be associated with response to immunotherapies including immune checkpoint inhibitors (ICI). Some but not all studies have reported such an association. Methodological differences, small cohort sizes and other limitations might underlie these conflicting results, underscoring the need to establish standardized TLS definitions and quantification methods for future studies.

Two studies that used transcriptomic data to quantify TLSs in tumour samples reported that these structures were associated with improved response to ICI therapy in patients with metastatic kidney cancer and melanoma[11,12]. However, a large fraction of the samples that were analysed at baseline were lymph node metastases, which may make it difficult to attribute the transcriptomic data specifically to TLSs.

A study in patients with sarcoma who received anti-PD1 therapy reported an objective response rate of 30% in those who were selected based on baseline TLS positivity compared with 2.4% in an all-comer cohort[106,107]. However, the sarcoma histological subtypes differed significantly between the TLS-positive and the all-comer cohorts[107], which could be a confounding factor[108,109]. In patients with high-risk bladder cancer, TLS density predicted response to ICI in a US phase I trial[110] but not in the phase Ib NABUCCO trial in the Netherlands[28]; all clinical variables in these trials were comparable. TLS density is highly variable even among patients with the same disease; thus, the small sample sizes of these phase I trials lack sufficient statistical power to analyse the biomarker potential of TLS and may explain the conflicting results. Retrospective analyses of patients with gastric cancer[111] and other tumour types including RCC[112] reported that the presence of mature TLSs before ICI treatment was associated with improved responses to this therapy. Together, these findings suggest that the composition of TLSs is a more reliable predictive or prognostic factor than their density. Large prospective cohort studies are needed to determine whether TLSs are associated with a positive ICI response in kidney cancer and, if so, whether the discrepancy between this positive response and the negative prognostic association of TLSs in untreated patients[100,105] can be attributed to the quality of the TLSs.

A meta-analysis showed that tumour mutation burden and CXCL13 expression by tumour-infiltrating T cells were the main positive predictors of the response to ICIs across seven different cancer types[113]. Similarly, CXCL13-expressing PD-1$^+$CD8$^+$ T cells predicted the clinical response to ICI in lung cancer[114]. The relationship between CXCL13-expressing T cells and TLSs remains to be investigated. Analyses of tumour samples from patients who have received ICI therapy or the GVAX tumour vaccine have consistently shown that those from responders have higher TLS density or higher levels of TLS-related transcripts than do those of non-responders[11,28,85,115,116]. This finding suggests that TLSs develop in the tumour microenvironment in response to an ongoing immune response.

No data are currently available from sufficiently large cohorts to determine whether TLSs are a cause or a consequence of tumour-specific immunity[3]. However, evidence suggests that TLS induction might have therapeutic potential as a stand-alone treatment or in combination with other (immune) therapies. In a mouse model of ovarian cancer, administration of recombinant CXCL13 induced TLSs and had antitumour efficacy[117]. In a peritoneal melanoma model, TLS development was increased by ICI therapy and correlated with tumour reduction[53]. Several studies have reported that treatment with ICIs in combination with intratumoural CXCL13 injection[118], administration of stimulator of interferon genes (STING) agonist[119] or TLR9 agonist[120], targeted delivery of LIGHT (also known as TNSF14), which is a ligand of the lymphotoxin β-receptor (LTβR)[121,122], or injection of lymph node-derived stromal cells[123], resulted in TLS development and improved control of experimental tumours compared with monotherapies (ICI or the second component alone). Synergistic effects were also observed when chemotherapy was combined with intratumoural CXCL13 and CCL21 injection to induce TLS development in a pancreatic cancer model[124]. In a chemotherapy-resistant colorectal cancer model, the combination of antiangiogenic agents with agonistic anti-CD40 antibody induced vascular normalization, TLS development and T cell-mediated tumour control[125]. However, in experimental glioma, agonistic anti-CD40 antibody induced immature TLSs, which correlated with an impaired response to ICI[126]. In a model of autochthonous pancreatic ductal adenocarcinoma, tumour antigen-specific DNA vaccination induced expansion of antigen-specific T cells and the development of mature TLSs but the effects on tumour growth were not reported[127]. For all of these treatments, TLS induction was just one of many immunostimulatory effects; thus, further studies are needed to investigate the specific contributions of TLSs to spontaneous or therapy-induced antitumour immunity.

HEVs could have crucial roles in TLS induction and represent a predecessor to TLSs. They develop in inflamed tissues, can promote the formation of T cell aggregates[128,129] and are major sites of lymphocyte entry into tumours[130]. In patients with metastatic melanoma, the presence of tumour-associated HEVs was associated with a greater clinical response to treatment with ICIs, including improved survival[130]. Administration of an agonistic antibody to LTβR increased the presence of HEVs in experimental sarcoma, resulting in improved effector T cell function and a reduction in tumour growth[130]. Furthermore, combined treatment with anti-VEGFR2 and anti-PDL1 antibodies stimulated tumour immunity by inducing HEVs in murine models[131]. Similarly, in a mouse metastatic breast cancer model, targeted delivery of an anti-neoplastic drug to tumours using a monoclonal antibody against surface molecules on HEVs improved tumour control[132]. Although the presence of HEVs is insufficient to drive TLS development, their role in this process warrants further investigation.

In summary, the available data suggest that mature TLSs are associated with an antitumour immune response and improved survival in multiple cancer types. However, whether TLS development is a consequence of, or a prerequisite for, effective antitumour immunity is unknown.

Infection

The roles of TLSs in the context of infection have mostly been investigated using pulmonary models. The lung is constantly exposed to pathogenic bacteria, viruses, allergens and harmful particles that are present in inhaled air[133]. In the lung, TLSs develop quickly in response to viral or bacterial infections and drive an effective immune response including antigen-specific T cells and B cells that provides protection against harmful pathogens[134,135]. Bacterial infection with *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa* or *Staphylococcus aureus* induces TLS formation in the lung[136,137]. Intratracheal mucosal vaccination against

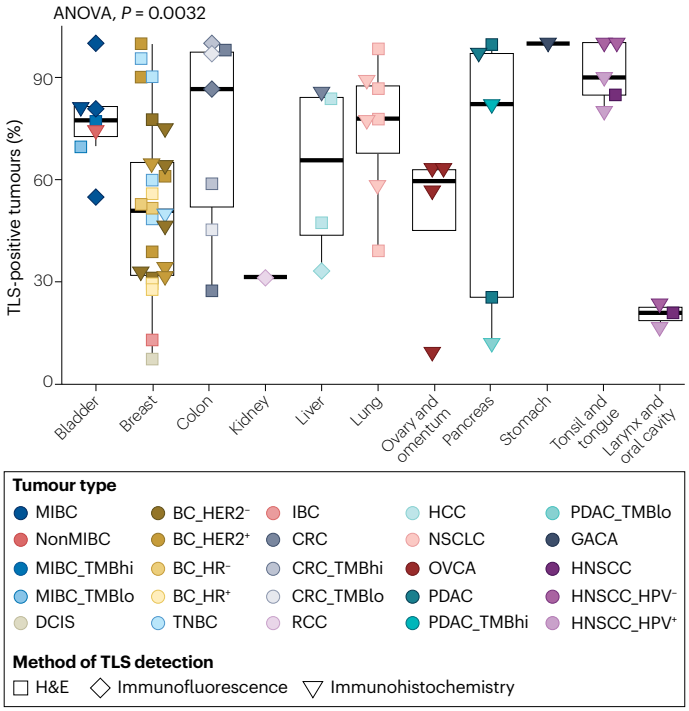

Fig. 3 | Presence of tertiary lymphoid structures in different tumour types. The proportion of tertiary lymphoid structure (TLS)-positive tumours was extracted from 57 published studies reporting histological assessment of TLSs in most common tumour types and was compared across organs by one-way ANOVA test. As TLSs mainly develop in the tumour periphery, studies that only performed TLS analysis in intratumoural areas were excluded. Treated cohorts were also excluded because neoadjuvant therapy impairs TLS development. In total, 72 cohorts were selected for analysis (see Supplementary Table 1 for details and references). Each independent cohort is represented by a separate symbol. Diverse patient characteristics were plotted as distinct cohorts where those data were provided. TLS development differs significantly between organs as well as within each organ, which may be due to differences between molecular tumour subtypes, as well as study-specific histological definitions of TLS (ranging from lymphocytic aggregates of any maturation stage to clusters with specific composition containing high endothelial venules, mature dendritic cells or organized B and T cell compartments). The proportion of TLS-positive tumours detected by H&E or immunostaining is similar, suggesting that both methods of histological assessment are reliable. BC, breast cancer; CRC, colorectal cancer; DCIS, ductal carcinoma in situ; GACA, gastric cancer; H&E, haematoxylin and eosin; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; HPV, human papilloma virus; HR, hormone receptor; IBC, invasive breast cancer (cohorts containing different molecular subtypes of breast cancer); MIBC, muscle invasive bladder cancer; NonMIBC, non-muscle invasive bladder cancer; NSCLC, non-small-cell lung cancer; OVCA, ovarian cancer; PDAC, pancreatic ductal adenocarcinoma; RCC, renal cell carcinoma; TMBhi, tumour mutational burden high (microsatellite instable CRC, or tumours with a mutational burden greater than the cohort median in MIBC and PDAC); TMBlo, tumour mutational burden low (microsatellite stable CRC or tumours with a mutation load equal to or below the cohort median in MIBC and PDAC); TNBC, triple-negative breast cancer.

M. tuberculosis also results in TLS formation and impairment of this process ameliorated vaccine-induced immunity against the bacteria, demonstrating that TLS formation is important for the induction of protective immune responses[138,139]. Mucosal vaccine-induced immunity against *M. tuberculosis* is dependent on IL-17-producing Th17 cells, which are crucial for TLS development in the lung[138].

Infection with influenza virus[52] or severe acute respiratory syndrome corona virus (SARS-CoV)[140] is also often accompanied by TLS development in the lung. In response to infection with influenza virus, mice that lacked SLOs developed TLSs, which mediated clearance of the infection and improved survival compared with mice with SLOs[17]. In mice with influenza virus infection, depletion of $CD11c^{hi}$ dendritic cells after clearance of the virus from the lung resulted in disintegration of TLSs and a reduction in antibodies to the virus[141]. These results indicate protective roles of TLSs against viral infection.

The memory T cell population is heterogeneous and includes T_{RM} cells with high expression of C-type lectin CD69 and/or the integrin CD103 (ref. 142). T_{RM} reside in non-lymphoid tissues and govern local immunity in mucosal tissue in locations such as the lung, skin and gut[142,143]. Influenza virus infection induces heterogeneous $CD4^+$ T_{RM} cells, including T resident helper (T_{RH}) cells that reside within TLSs and promote local antibody production that protects against influenza reinfection[144]. Mucosal vaccination with heat-killed *Klebsiella pneumonia* induces $CD4^+$ T_{RM} cells, which have an important role in the bacterial clearance of *K. pneumonia* infection[63]. SARS-CoV-2 infection and mRNA COVID-19 vaccination also generate T_{RM} cells[145,146] and the number of SARS-CoV-2-specific T_{RM} cells in the airway correlates with survival in patients with severe COVID-19 (ref. 147), suggesting that T_{RM} cells and TLSs are also involved in protective immunity against SARS-CoV-2. Thus, TLSs with T_{RM} cells in the lung are a key target for the development of novel mucosal vaccines against pathogens that cause severe acute respiratory diseases.

Patients with severe complicated pyelonephritis who are resistant to antibiotics and require surgical resections exhibit many TLSs in the renal cortex and pelvis[21,51], suggesting that renal TLSs also generate anti-pathogen adaptive immune responses. How the cellular and molecular components, functions and trigger of TLSs differ between kidneys and other mucosal tissues is unknown and requires further investigation.

Chronic inflammatory diseases and ageing

TLSs are induced in chronic inflammatory diseases of the lung, kidney and other organs. Ageing is also associated with chronic inflammation, which contributes to age-associated morbidity and mortality. Targeting this age-dependent non-specific inflammation, termed inflammaging, is an important strategy for preventing age-related diseases and extending the healthy lifespan[1]. Ageing is also gaining attention as a cause of TLS formation in various organs. Emerging evidence suggests that TLSs and their molecular machinery are involved in impaired tissue regeneration capacity in older people and in age-related diseases[7,8,13,148,149].

Lung. Allergens, inhaled particles, DAMPs and self-antigens can trigger TLS formation in the lung. In contrast to their protective role in lung infections, TLSs have pathogenic roles in chronic inflammatory lung diseases such as asthma and chronic obstructive pulmonary disease (COPD), which is an age-related disease induced by chronic exposure to cigarette smoke[61,150,151]. In patients with COPD, TLS number is positively associated with disease severity[152,153]. Type 3 innate lymphoid cells (ILC3s) that express neuropilin-1 have LTi activity and are involved in the initiation of TLS development via the production of IL-17A and IL-22 in patients with COPD[154]. Lymphotoxin β-receptor (LTβR) signalling promotes TLS development and LTβR ligand expression is enhanced in immune cells from these patients[151]. In mice that were chronically exposed to cigarette smoke, inhibition of LTβR signalling disrupted smoking-related TLSs in the lung and induced regeneration of lung tissue[151], indicating that TLSs contribute to shaping the pathogenesis of lung diseases during chronic inflammation.

A subpopulation of memory Th2 cells, memory pathogenic Th2 (Tpath2) cells, that produce large amounts of inflammatory cytokines, such as IL-5, IL-13 and amphiregulin, are involved in the pathogenesis of various inflammatory diseases[155,156]. Memory Tpath2 cells show the characteristics of T_{RM} cells and are maintained within lung TLSs[61,157]. Unique lymphatic endothelial cells (LECs) that express Thy1 are crucial for memory Tpath2 cell survival in TLSs in the inflamed lung, possibly by providing the key survival cytokine IL-7 (ref. 61). $Thy1^+$ LECs also produce IL-33 and the T cell-attracting chemokines CCL21 and CCL19. IL-33 induces enhanced production of IL-5, IL-13 and amphiregulin by memory Tpath2 cells. Thus, $Thy1^+$ LECs generate an inflammatory niche and regulate the quantity and quality of TLS-residing memory Tpath2 cells during chronic inflammation[155]. These data suggest that memory Tpath2 cells and $Thy1^+$ LECs, which are TLS pathogenic components in the inflamed lung, could be potent therapeutic targets for intractable inflammatory diseases.

Differences in the cellular components of lung TLSs may contribute to their opposite roles in infection and chronic inflammation. However, further studies are needed to determine the critical factors that dictate the composition of lung TLS under different inflammatory conditions.

Kidney. TLSs can be induced in CKDs, including IgA nephropathy[158–160], lupus nephritis[65], IgG4-related kidney diseases[161], interstitial nephritis[162,163], membranous nephropathy[164] and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis[165,166] as well as in kidney allografts[37,39,44,167–170]. Clinical studies have demonstrated that TLS formation is associated with poor kidney outcomes in these diseases (Supplementary Table 2).

Studies in patients with IgA nephropathy have reported that TLSs were detected in 30–40% of participants and were associated with higher levels of serum creatinine, proteinuria and blood pressure, greater severity of glomerulonephritis and future disease progression[158–160]. A study in patients with membranous nephropathy reported that TLSs were detected in 34.2% of participants and were associated with higher levels of serum creatinine, proteinuria and blood pressure, lower serum albumin concentrations and lower remission rates[164]. Notably, a higher proportion of patients with membranous nephropathy who had renal TLSs had anti-PLA2R autoantibodies than those without TLSs (72.5% versus 47.4%)[164]. However, most of these studies were observational and the cellular and molecular characteristics of TLSs as well as the mechanisms that underlie the observed associations remain unclear.

In elderly people, AKI often leads to kidney failure[149,171] but the mechanism is unclear. In mice, we found that aged (1-year-old) but not young kidneys (2-month-old) develop TLSs after injury and that TLS development was associated with impaired regenerative capacity in the aged, injured kidney[7,21]. To define the cellular and molecular basis for TLSs in the kidney, we established an inducible kidney TLS model using 1-year-old mice. Using this model, which enables various maturational stages of TLSs to be induced by changing the severity of injury, we performed a detailed analysis of the roles of stromal and

haematopoietic cells in age-dependent TLS development[7,13,21]. We found that in aged, injured kidneys, fibroblasts have crucial roles in TLS formation and maturation[54]. In young, injured kidneys, resident fibroblasts transdifferentiate into scar-producing myofibroblasts at the cost of physiological erythropoietin production, leading to fibrosis and renal anaemia, which are common pathological conditions in CKD[172–174]. In aged, injured kidneys, fibroblasts also transdifferentiate into TLS-related heterogeneous fibroblasts with distinct phenotypes[7] (Fig. 2b). In the early phase of TLS formation, fibroblasts surrounding TLSs produce retinoic acid, which promotes transdifferentiation of fibroblasts inside TLSs into neural crest marker p75NTR-expressing fibroblasts, some of which produce CXCL13 and CCL19. Subsequently, some of the fibroblasts inside TLSs lose p75NTR expression and mature into CXCL13-producing FDCs. Most of these TLS-associated fibroblasts are derived from a single lineage of resident fibroblasts[7]. These observations indicate that paracrine interactions between heterogeneous fibroblasts orchestrate TLS formation in the kidney.

Intimate cellular interactions also occur in the TLS haematopoietic compartment. We showed the accumulation of two unique age-dependent lymphocytes, senescence-associated T (SAT) cells and age-associated B cells (ABCs) in aged, injured kidneys[13]. SAT cells are unique CD4 T cells that exhibit defective proliferation and production of T cell cytokines in response to T cell receptor stimulation, but secrete abundant atypical humoral factors such as osteopontin[175,176]. ABCs are defined as Tbx21$^+$CD11b$^+$/CD11c$^+$ B cells and act as antigen-presenting cells[177,178] (Fig. 2c). In aged, injured kidneys, SAT cells and ABCs reside within TLSs in close contact with each other. SAT cells produce ABC-inducing factors, such as IL-21 and IFNγ[179] and expand together with ABCs after injury[13]. In addition to IFNγ and IL-21, unbiased receptor ligand analysis identified CD153–CD30 (Tnfsf8–Tnfrsf8) signalling between SAT cells and ABCs. In mice, genetic deficiency of CD153 or CD30 impaired functional SAT induction, resulting in a reduction in ABC numbers and attenuation of TLS formation with improved kidney function and a reduction in fibrosis and inflammation[13]. These results indicate that CD153–CD30 signalling is required for functional SAT cell induction and TLS formation and that TLS formation is maladaptive in aged, injured kidneys (Fig. 2d). SAT cells and ABCs are also induced in mouse lupus nephritis models and show similar molecular interactions to those that occur in aged, injured kidneys[180].

Cellular and molecular components of age-dependent TLS formation are similar in mice and humans, suggesting that this phenomenon is conserved across species[7,13,21]. Elderly (2-year-old) mice without kidney injury and healthy aged people without CKD spontaneously develop TLSs in the kidney[7,21,181]. Further studies are needed to identify the mechanisms that lead to this spontaneous TLS formation and the involvement of SAT cells and ABCs in this process.

Other organs. Spontaneous age-dependent TLS formation has also been observed in organs such as the liver and bladder[22,23,181]. SAT cells and ABC development are observed in age-dependent TLSs in the bladder and spleen[22,180,182] and in kidneys and visceral adipose tissues in conditions that accelerate immune ageing, such as autoimmune diseases[180,183,184] and obesity[185,186] in mouse models. Studies that investigated the effects of loss of function of SAT cells and ABCs demonstrated their pathogenic potentials in these contexts[13,180,183,184,186], which is consistent with the findings in aged, injured kidneys that are described above.

A subset of peripheral T helper cells with B cell helper functions that express PD1, CD4 and CD153 (ref. 187) and ABCs that express CD30 was identified in joint tissue from patients with rheumatoid arthritis, suggesting a role of CD153–CD30 signalling in T cell–B cell interactions in human TLSs[13]. The presence of an age-dependent human CD153$^+$PD1$^+$CD4$^+$ T cell population with B cell helper functions should be investigated in future studies.

Another potential cellular driver of age-dependent TLS formation is vascular endothelial cells. Loss of Notch signalling in endothelial cells results in TLS formation in the kidneys[57]. Notch signalling components and Notch-dependent vascular networks in bone decrease with age[188], but whether a similar age-dependent decrease in Notch signalling occurs in endothelial cells and contributes to age-dependent TLS formation remains to be investigated. Age-dependent phenotypic changes in other cell populations such as fibroblasts and pericytes could also potentially contribute to TLS formation, but this hypothesis requires further investigation. TLSs that are induced in aged organs and in autoimmune diseases might be maladaptive and are a potential novel therapeutic target[7,8,13,148].

Box 2

Unresolved questions

- What stimuli drive the initiation, maturation and maintenance of tertiary lymphoid structures (TLSs)?
- What factors determine the composition of TLSs?
- Are TLS-inducing stimuli shared between different tissues?
- Does the abundance of TLS-inducing stimuli in an organ explain its propensity for TLS development?
- What factors or mechanisms explain the heterogeneity of TLSs within an organ?
- Are TLSs a cause or a consequence of an ongoing integrated immune response?
- Can TLSs be therapeutically targeted without affecting systemic immunity?

Conclusions and future research

In the past two decades, knowledge of TLSs has substantially expanded. Molecular and phenotypic heterogeneity within TLSs is increasingly recognized in mice and humans and is associated with the disease course in autoimmune diseases, cancer, infection and chronic inflammatory diseases. Ageing has also emerged as a cause of TLS formation and the molecular details and therapeutic potential are beginning to be unravelled.

The unique contribution of TLSs to local immunity in chronic inflammatory conditions might result from their optimal adaptation to the local tissue microenvironment. However, the mechanisms by which TLSs adapt to tissue and generate tailored immune responses in situ are largely unknown and many unanswered questions remain (Box 2). For example, the initial event that leads to TLS induction and the factors that influence susceptibility to TLS development in different organs and diseases remain to be determined.

In addition to multistep interactions between immune cells and non-immune cells, factors that shape the tissue microenvironment may influence immune responses generated within TLSs. For example, several studies have shown that the ionic microenvironment directly

affects a variety of immune cells. In the tumour microenvironment, extracellular potassium released by necrotic cells suppresses T cell effector functions[189]. Furthermore, increased sodium in inflammatory tissues promotes IL-17-producing $CD4^+$ T cell development and inhibits regulatory T cell differentiation, exacerbating inflammation[190,191]. The effects of the injured tissue microenvironment on immune responses in TLSs should be further investigated.

Even in the same disease, the clinical influence of TLSs varies depending on the disease phase and the cellular composition of the TLSs. Furthermore, how TLSs influence responses to therapy and how therapy changes the function of TLSs are poorly understood. The opposing clinical correlations of TLSs in different diseases indicate that the optimal approach for targeting these structures must be defined in a context-dependent manner. It is therefore important to determine the conditions that promote the development or induce the resolution of TLSs.

Chronic inflammation is a common feature of all forms of CKD and AKI[149,192–194] and TLSs could potentially drive CKD progression by maintaining and accelerating inflammation irrespective of the aetiology. Therapeutic interventions that target TLS formation could potentially be beneficial in CKD and other chronic inflammatory and autoimmune diseases. As CKD can progress without overt symptoms, the development of non-invasive biomarkers for TLS detection will also be necessary. Furthermore, the identification of essential pathways for TLS formation will enable selective targeting to induce TLS development or resolution as required to obtain clinical benefits in different diseases. Accumulation of basic and clinical evidence, particularly in human TLSs, using standardized quantification approaches is necessary to guide the future development of novel therapeutic approaches to TLS-related chronic diseases.

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