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The Impact of Programmed Cell Death on the Formation of Tertiary Lymphoid Structures

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Tertiary lymphoid structures are clusters of lymphoid tissue that develop post-natally at sites of chronic inflammation. They have been described in association with infection, autoimmune disorders, cancer, and allograft rejection. In their mature stage, TLS function as ectopic germinal centers, favoring the local production of autoantibodies and cytokines. TLS formation tends to parallel the severity of tissue injury and they are usually indicative of locally active immune responses. The presence of TLS in patients with solid tumors is usually associated with a better prognosis whereas their presence predicts increased maladaptive immunologic activity in patients with autoimmune disorders or allograft transplantation. Recent data highlight a correlation between active cell death and TLS formation and maturation. Our group recently identified apoptotic exosome-like vesicles, released by apoptotic cells, as novel inducers of TLS formation. Here, we review mechanisms of TLS formation and maturation with a specific focus on the emerging importance of tissue injury, programmed cell death and extracellular vesicles in TLS biogenesis.

Keywords: tertiary lymphoid structure, antibodies, inflammation, apoptosis, injury

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INTRODUCTION

Tertiary lymphoid structures (TLS) are ectopic aggregates of lymphocytes and stromal cells, which, at maturity, behave as functional sites of adaptive immune responses (1, 2). In contrast to secondary lymphoid organs (SLO) (such as spleen, lymph nodes and Peyer's patches), TLS are non-encapsulated and form postnatally. They exhibit plasticity and their presence is transient, correlating with active tissue injury and resolving after antigenic clearance and tissue repair (3). They are composed of T and B cells as well as stromal cells, such as follicular dendritic cells (FDCs) and αSMA+ fibroblasts. Macrophages can be found at the periphery of TLS (4) (**Figure 1**). TLS display different organization levels ranging from simple clusters of B and T lymphocytes to more mature structures where T and B cells are polarized and FDC expressing CD21 and p75 neurotrophin receptor are present, allowing the formation of germinal centers (GC) (1, 5–7). GC are characterized by expression of activation-induced cytidine deaminase (AID) that regulated immunoglobulin gene affinity maturation through somatic hypermutation and initiation of immunoglobulin class switch recombination. GC are sites of B cell proliferation and affinity

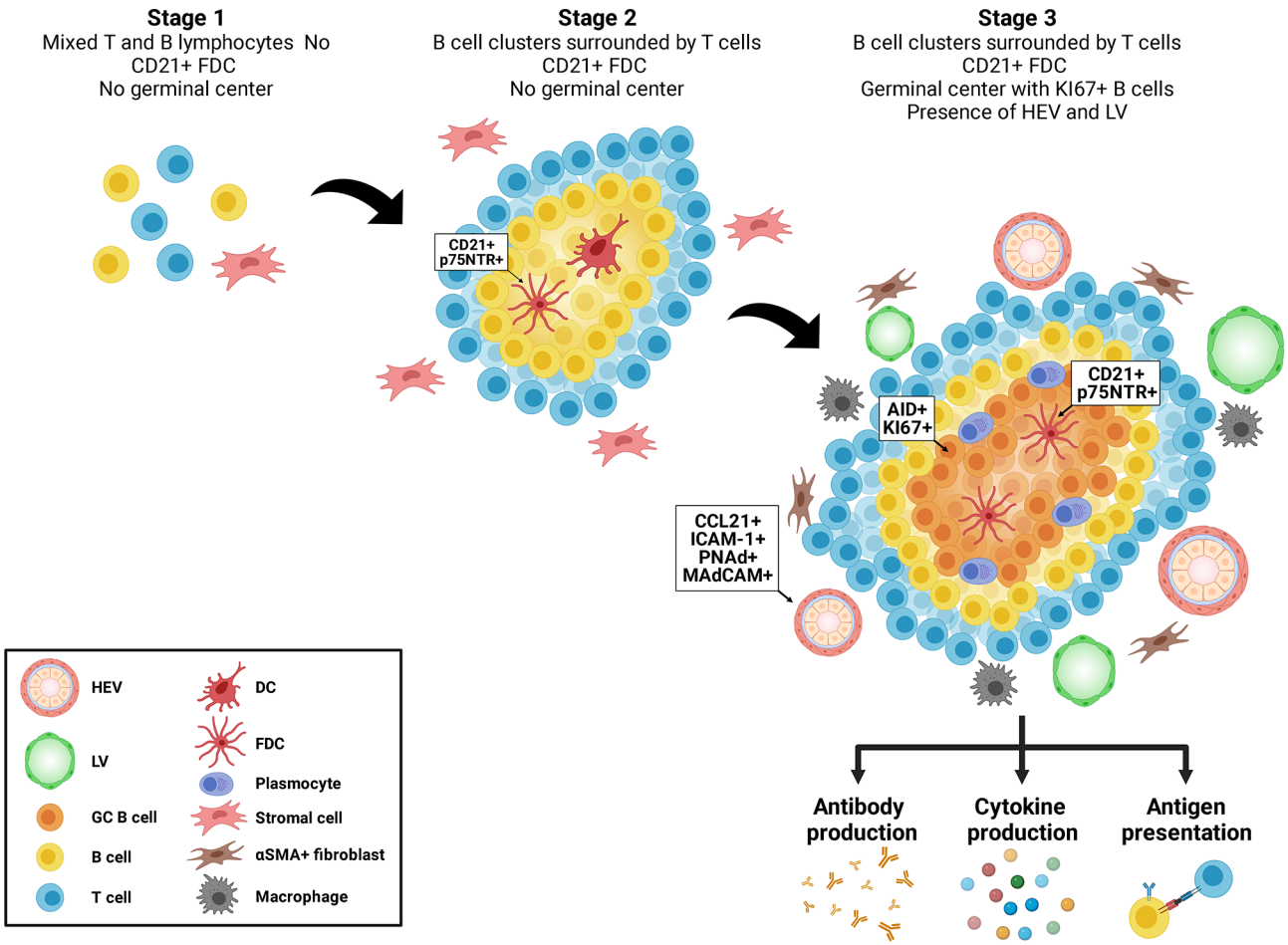

FIGURE 1 | Maturation of tertiary lymphoid structures. Tertiary lymphoid structures evolve from loose aggregates of T and B cells and stromal cells (Stage 1), to polarized clusters of T and B cells accompanied by follicular dendritic cells (FDC) (Stage 2) to mature polarized structures containing germinal centers, proliferating B cells, plasma cells, high endothelial venules (HEV) and lymphoid vessels (LV).

maturation into antibody secreting plasma cells. Lymphatic vessels and high endothelial venules (HEV), characterized by a cuboidal shape of endothelial cells and expression of CCL21, ICAM-1, PNAd and MAdCAM, are commonly found in mature stages (6) (**Figure 1**).

TLS arise in tissues whose main function is other than the generation of immune cells such as kidney, heart, pancreas, lung, colon and breast. Lymphoid neogenesis (5, 8), i.e. the process of TLS formation, can be observed in inflammatory microenvironments resulting from chronic infection, autoimmune conditions, allograft rejection and tumor growth (9, 10). Inflammatory cytokines such as TNF-α, IL-17A, IL-23 and lymphotoxins, expressed by immune cells at sites of injury induce stromal cells to produce homeostatic chemokines, such as CXCL13, CXCL12, CCL19 and CCL21. This in turn drives the recruitment of T and B cells and their organization into progressively polarized clusters (11). CXCL13 expression in TLS by CD8+ T cells and other immune cells appears pivotal to TLS maturation (12–16). Inflammation also prompts the expression of a number of chemokines and cytokines in tissue fibroblasts such as podoplanin, CCL19, IL-17, CXCL13, and adhesion molecules ICAM-1 and VCAM-1, therefore creating a microenvironment conducive to attraction and retention of lymphoid cells (17–22). Chemokines and cytokines produced by local fibroblasts and epithelial cells (19) favor the recruitment of immune cells and TLS organization. Various cytokines can also synergize and/or compensate one another, creating an environment favorable for TLS formation and maturation (2).

An important phase in TLS maturation is the formation of HEV that connect TLS with the bloodstream and enable the sustained recruitment of lymphocytes. HEVs express addressin and CCL21 allowing the entry of naïve T cells expressing the addressin ligand CD62L and CCR7, the chemokine receptor for CCL21 and CCL19. Data from tumor models also demonstrate that lymphotoxin α (LTα) and TNF receptor (TNFR) interactions, likely through infiltrating CD8+ T cells and NK cells, are also important for HEV formation (23). Others found that HEV formation can occur independently of both LTα and lymphotoxin (LT)-ß receptor (LTbR) (24). Specific requirements

for HEV formation and TLS maturation may be a consequence of the different microenvironments in which TLS are formed. The presence of FDCs within B cell follicles is another hallmark of TLS maturation. In SLO, LTbR and TNFR signaling are essential for FDC formation. In TLS, LTα1ß2 is important for FDC generation, enabling GC formation and antigen presentation (25–27). Although FDCs progenitors remain unknown, activated local stromal cells can differentiate into FDCs upon encounter with migrating immune cells in TLSs (28).

Antigenic stimulation plays an important role in the formation of TLS and, in turn, TLS are sites of antibody formation. In numerous autoimmune diseases and alloimmune conditions, pathogenic or diagnostic autoantibodies have been shown to be produced by TLS (25, 29, 30). TLS within inflamed synovium or salivary glands in patients with rheumatoid arthritis or Sjögren's syndrome, control the production of anti-citrullinated peptide antibody, anti-Ro/SSA and anti-La/SSB antibodies (3, 31, 32). In kidney and heart allografts with chronic rejection, TLS have been identified as a source of anti-HLA antibodies, the latter playing a major role in allograft rejection (33). Our group also recently identified a role for TLS in the production of autoantibodies that contribute to allograft inflammation and dysfunction (34, 35).

B cells within TLS can differentiate into antibody-producing plasma cells. They can also favor autoimmunity and alloimmunity by acting as antigen presenting cells, further perpetuating antigenic stimulation and immunogenicity (25, 29, 30). Some conflicting reports have pointed to the absence of correlation between TLS formation and autoimmunity or alloimmune disease activity. These results may stem from activation of tolerogenic pathways in certain TLS that harbor regulatory B and T cells (36, 37). While the presence of TLS is generally associated with disease severity in patients with autoimmunity and alloimmune diseases such as rheumatoid arthritis, Sjögren's syndrome, IgA nephropathy and allograft rejection (31–33, 38), TLS formation in solid tumors has been generally associated with a better prognosis. B cell aggregates in tumor TLS can participate in anti-tumor immunity by serving as antigen presenting cells and by differentiating into plasma cells producing tumor-associated antibodies. TLS B cell aggregates have generally been associated with better prognosis in lung, pancreas, colon and breast cancer (39–49).

FORMATION AND MATURATION OF TLS; FROM LYMPHOTOXINS TO IL-17

The formation and development of SLO and TLS both rely on the expression of lymphotoxins and inflammatory cytokines such as TNFα. Lymphotoxins are members of the TNF superfamily and are pivotal to the formation of SLO. Lymphoid inducer cells (LTi) arise from innate lymphoid progenitors in the fetal liver under the tight regulation of the nuclear hormone receptor retinoic acid related orphan receptor γτ (RORγτ) and the transcriptional regulator Id2 (50, 51). LTi express lymphotoxin α2ß1 on their surface and the soluble lymphotoxin α3 form. Interactions between lymphotoxins and the LTbR on stromal cells stimulate the expression of CXCL13 and CCL21, which in turn favor homing of T and B cells. Lymphotoxins-LTbR interactions are essential for the formation and maturation of SLO as HEV and FDC require persistent LTbR mediated signaling (52, 53). LTbR stimulation was originally considered also crucial for TLSs neogenesis since LTbR expression is readily upregulated in inflamed tissues and downstream signaling directly induces lymphoid neogenesis in different models (7, 17, 20, 21, 54, 55). Further studies have shown that initial recruitment of T and B cells can occur independently of LTbR signaling (18, 56) and point to IL-17 as an important regulator of TLS biogenesis.

IL-17A is the initial member of the IL-17 cytokine family that includes IL-17A, B, C, D, E and F. The IL-17 family plays important roles in host-defense against infection and behaves as a master regulator of inflammatory and autoimmune responses. It is also known to regulate the growth of several tumors, including skin, colon, pancreas, liver, lung and myeloma (57–65). A number of immune cells can produce IL-17A including LTi, Th17 T cells and γδ T cells, which has been implicated in autoimmune and inflammatory diseases such as multiple sclerosis, psoriasis, rheumatoid arthritis, crescentic glomerulonephritis, lupus nephritis and uveitis, among others (66–82).

In multiple sclerosis, IL-17-producing γδ T cells are thought to be initiators of inflammation and inductors of Th17 cells. In the experimental autoimmune encephalomyelitis (EAE) model, early accumulation of γδ T cells was observed in the central nervous system (CNS) where they release IL-17 and IL-21 to enhance the pro-inflammatory activity of αβ Th17 cells (71). Patients with multiple sclerosis also show accumulation of IL-17+ cells in chronic demyelinated areas of the CNS, and an increase in IL-17-producing γδ T cells in the cerebrospinal fluid (72, 73). Experimental models of skin inflammation identified IL-17A/F-producing γδ T cells as necessary and sufficient to trigger psoriasis-like plaque formation in IL-23- or Immiquimod-induced models (74). IL-17-secreting γδ T cells were also shown to enhance Th17 responses when skin inflammation was triggered with BCG immunization or Freund's adjuvant (75, 76). Similarly, human dermal γδ T cells are abundant in biopsies of psoriasis lesions, with an ability to produce higher levels of IL-17 compared to αβ Th17 cells upon IL-23 stimulation *in vitro* (74). In mouse models of non-autoimmune arthritis, resident and peripheral γδ T cells were reported as a major source of IL-17 (77, 78). An increase in circulating IL-17A-producing γδ T cells was also found in arthritis patients, suggesting their priming by cytokines secreted at the site of inflammation (79, 80). In Crescentic glomerulonephritis, renal IL-17A-producing γδ T cells were found to be the main contributor in the early inflammatory response by promoting kidney injury. They were predominated by IL-17A-producing Th17 at later phases (81). In the experimental autoimmune uveitis model, αβ and γδ T cells interactions was found to be important for mediation of eye inflammation. In this model, an early expansion of γδ T cells in SLO induces IL-17 production and further generation of Th17 responses by αβ cells at the inflammatory site (82).

A growing body of evidence has confirmed a role for IL-17A produced by Th17 T cells and γδ T cells in the development of TLS in the context of pulmonary infection, CNS inflammation, renal ischemia-reperfusion, obstruction and IgA nephropathy, and kidney transplantation (22, 38, 54, 83–88). In a model of LPS-

induced pulmonary infection in neonatal mice, αβ and γδ T cells were detected within Inducible Bronchus-Associated Lymphoid Tissues (iBALT). γδ T cells formed a large proportion of infiltrating cells and both contributed to IL-17 production. Adoptive transfer of these purified T cell subsets, separately or together, to LPS-treated *Tcrbd*$^{-/-}$ neonatal mice, showed preferential contribution of γδ T cells in promoting iBALT development and of αβ T cells in forming larger areas of iBALT (83). Using another model of pulmonary infection induced by *Pseudomonas aeruginosa*, γδ T cells were found to be the main source of IL-17 within iBALT, inducing CXCL-12 production by IL-17R+ stromal cells, B cell recruitment and follicles formation independent of FDC. When induced in *IL-17a/f* $^{-/-}$ or γδ T cells-deficient mice upon infection, lymphoid structures were less organized and, in the absence of γδ T cells, showed a reduction in number and size (84). In the EAE model, TLS formation in the CNS was also shown to require IL-17 production. Among various Th cell subsets adoptively transferred to mice, IL-17-secreting podoplanin-positive Th17 cells generated large organized and well structured ectopic lymphoid follicles in the CNS (22). Renal TLOs induced by ischemia-reperfusion injury in aged mice were reported to be enriched in Th17 cell differentiation, with increased expression of IL-17A and IL-23R (38). Moreover, human renal rejected graft samples show a correlation between shorter graft survival and high interstitial infiltration of Th17 cells, producing IL-17 and IL-21 and promoting lymphoid neogenesis (85).

We have recently shown that γδ T17 cells play a critical role in IL-17 overexpression and lymphoid neogenesis in a model of vascular rejection (34). The importance of IL-17 in the activation of autoimmune responses in the context of transplantation appears to stem from its capacity to initiate recruitment of immune cells to sites of injury and promote maturation of antigen-presenting cells (89–94). As Th17 cells are the classic producers of IL-17, they have been suggested to play a pivotal role in autoimmune pathways triggered following transplantation. Intriguingly, our findings demonstrate the importance of γδ T cells, rather than Th17 cells, in coordinating the IL-17 response triggered by vascular injury of vascular allografts (34). These observations are in line with previous studies showing that human IL-17-producing γδ T cells are generated in the periphery and recruited to inflamed tissues (95, 96). This process takes place more rapidly compared to the activation of conventional T lymphocytes as γδ T cells can be activated in the absence of a cognate TCR ligand (97).

Collectively, depending on the nature of the insult and the tissue implicated, peripheral or resident IL-17-producing γδ T cells may be involved at early phases to organize immunological events in response to inflammatory signals, and promote further conventional T cell responses at the site of inflammation.

TISSUE INJURY, CELL DEATH, AND EXTRACELLULAR VESICLES REGULATE TLS BIOGENESIS

The production of danger associated molecular patterns (DAMPs) at sites of injury is considered pivotal to TLS biogenesis. Various animal models and disease states in humans highlight a clear correlation between the degree of tissue injury, TLS number and maturation stages (4, 38, 98). In models of renal ischemia-reperfusion injury and ureteral obstruction in mice, the severity of renal damage is associated with TLS biogenesis. Aged mice, which show enhanced tissue injury after ischemia-reperfusion, were recently found to exhibit an increased propensity to TLS formation, translating into accentuated renal dysfunction (4, 98). Yet the precise DAMPs and mediators that are prompting TLS formation through activation of Th17 T cells and/or γδ T cells are only beginning to be characterized.

Our group and others showed that apoptosis, a type of programmed cell death classically considered non-inflammatory, can prompt the release of a number of mediators of importance in regulating immune cells towards either anti- but also pro-inflammatory and immunogenic responses (99–101). Activation of caspase-3 in dying cells leads to the release of different types of extracellular vesicles. Our group identified apoptotic exosome-like vesicles (ApoExo) as a novel type of extracellular vesicles released by endothelial cells through caspase-3 dependent pathways. ApoExo are smaller than classical apoptotic bodies, ranging from 30 to 100nm. Their protein, mRNA and microRNA contents differ from those of classical apoptotic bodies and classical exosomes (100, 102, 103). They are characterized by the presence of active 20S proteasome, perlecan LG3 C-terminal fragment and long non-coding RNAs. We showed that ApoExo are released in the bloodstream after hindlimb and renal ischemic injury resulting in higher circulating levels. In a model of vascular rejection in mice, allograft recipients injected with ApoExo showed increased TLS formation within the allograft (**Figure 2**). ApoExo injection prompted egress of γδ T cells from the spleen to the allograft leading to increased intragraft IL-17 expression, complement deposition and enhanced production of autoantibodies (34) (**Figure 2**). Mice genetically deficient in γδ T cells showed significantly less TLS formation, decreased autoantibody production and diminished allograft inflammation (**Figure 2**). Contrary to ApoExo, injection of apoptotic bodies did not foster TLS formation nor autoantibody production. The mechanism by which ApoExo activate γδ T cells and favor their homing to sites of injury remains to be fully characterized. Our results identify the proteasome activity of ApoExo as a pivotal signal regulating trafficking of γδ T cells to sites of vascular injury (34). Injection of ApoExo devoid of proteasome activity failed to induce TLS biogenesis and autoantibody formation in this system (**Figure 2**). Collectively, these recent findings identify ApoExo as novel inducers of γδ T cells activation and TLS formation and provide new clues into the mechanisms of cross talk between tissue injury and TLS biogenesis. The scope of future investigations will be to identify whether activation of γδ T cells by ApoExo is antigen specific or derives from innate signaling triggered by Toll-like receptor ligands or nonprotein mediators.

CONCLUSION

TLS are increasingly attracting interest because of their capacity to sustain local adaptive immune responses in a variety of disease

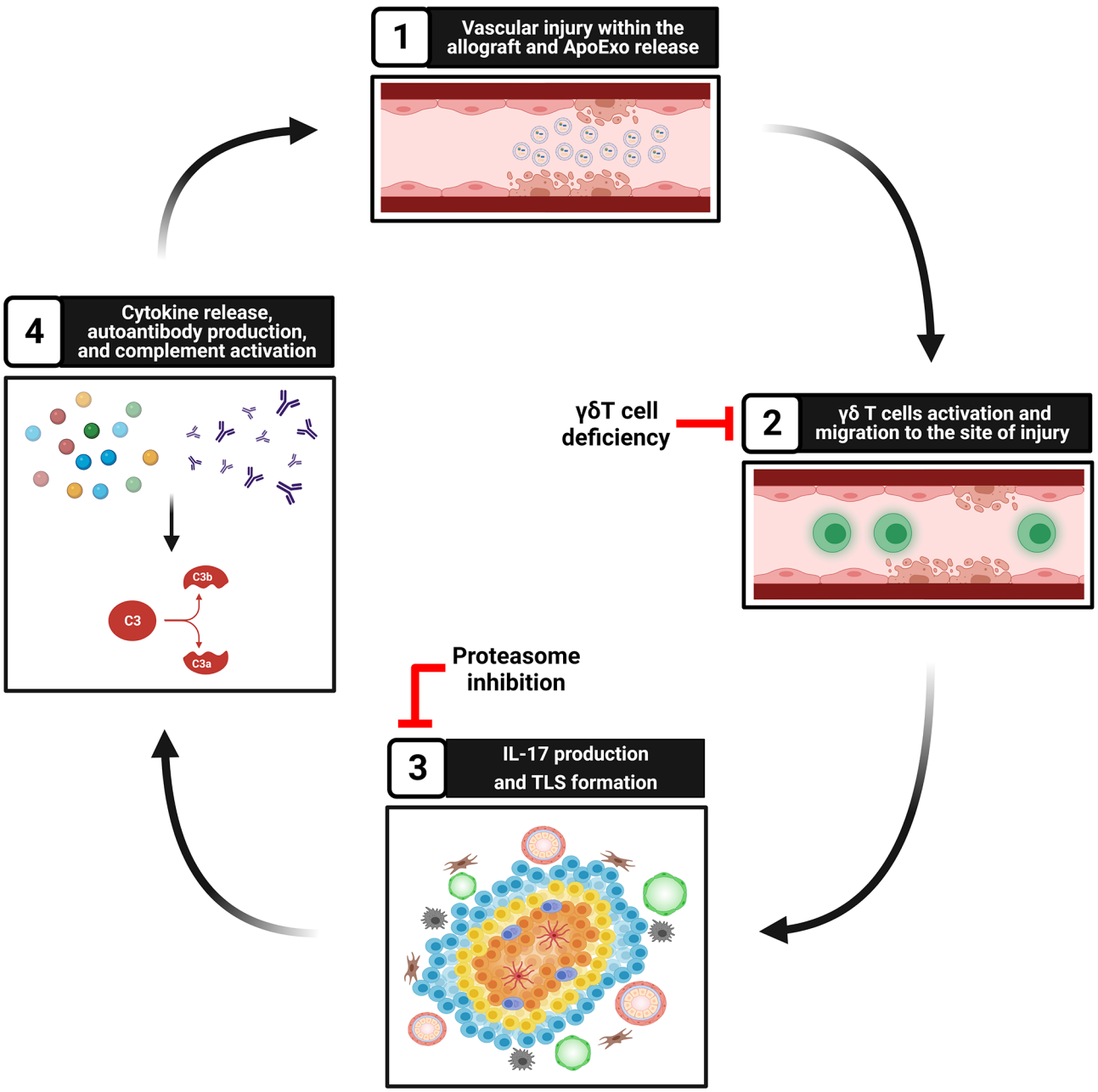

FIGURE 2 | Tissue injury, ApoExo release, and TLS formation. Step 1: Vascular injury and apoptosis of endothelial cells foster the release of apoptotic exosome-like vesicles (ApoExo) carrying active 20S proteasome. Step 2: ApoExo activate γδ T cells that migrate to the site of injury. Genetic deficiency of γδ T cells decreases TLS formation and autoantibody production. Step 3: γδ T cells produce IL-17 and favor the formation of tertiary lymphoid structures at sites of injury. Inhibition of proteasome activity within ApoExo blocks TLS biogenesis and autoantibody formation. Step 4: Tertiary lymphoid structures produce proinflammatory cytokines and autoantibodies, therefore favoring complement activation and further vascular injury.

states. Not only do TLS correlate with the severity and chronicity of tissue injury, they are increasingly recognized as pivotal players in maladaptive tissue remodeling, autoimmunity and inflammation. Although anti-tumor immune responses triggered and propagated from TLS are important pathways for controlling tumor growth, TLS are often associated with maladaptive autoimmune reactivity and tissue destruction in an array of autoimmune, alloimmune and chronic inflammatory diseases. The identification of ApoExo released by dying apoptotic cells as novel inducers of TLS biogenesis provides new insights into the mechanisms of cross talk that contribute to TLS formation at sites of injury.

AUTHOR CONTRIBUTIONS

MD, IK, and M-JH wrote the manuscript. All authors contributed to the article and approved the submitted version.

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