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Review

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Tertiary lymphoid structures as unique constructions associated with the organization, education, and function of tumor-infiltrating immunocytes

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Abstract: Tertiary lymphoid structures (TLSs) are formations at sites with persistent inflammatory stimulation, including tumors. These ectopic lymphoid organs mainly consist of chemo-attracting B cells, T cells, and supporting dendritic cells (DCs). Mature TLSs exhibit functional organization for the optimal development and collaboration of adaptive immune response, delivering an augmented effect on the tumor microenvironment (TME). The description of the positive correlation between TLSs and tumor prognosis is reliable only under a certain condition involving the localization and maturation of TLSs. Emerging evidence suggests that underlying mechanisms of the anti-tumor effect of TLSs pave the way for novel immunotherapies. Several approaches have been developed to take advantage of intratumoral TLSs, either by combining it with therapeutic agents or by inducing the neogenesis of TLSs.

Key words: Tertiary lymphoid structure (TLS); Tumor-infiltrating immunocyte; Tumor microenvironment (TME)

1 Introduction

Tumor-infiltrating immune cells are key factors that hold the balance of the tumor microenvironment (TME), greatly affecting tumor progression and clinical outcomes (Giraldo et al., 2019; Lei et al., 2020). Numerous attempts have been made to manage tumors by modifying the immune states of the TME, either through immune checkpoint blockade (ICB) on dysfunctional T cells (Hodi et al., 2010; Pardoll, 2012) or through the transfusion of ex vivo engineered T cells (Tran et al., 2016; Gee et al., 2018; Depil et al., 2020). However, emerging evidence indicates that effector cells never fight alone during immune response. Based on their presence in the TME, the localization, organization, and other cell types of the immune cell lineage can all greatly alter the tumor-associated immune response. It is worth pointing out that the compartmentalized organization defined by the physical separation of immune/non-immune clusters could independently determine the outcome of tumor sufferers. Ectopic aggregated but orderly organized immune cells are termed as tertiary lymphoid structures (TLSs) (Aloisi and Pujol-Borrell, 2006; Pitzalis et al., 2014), which are representative constructions of the mentioned context. The conspicuous performance of TLSs in tumors has been noticed (Sautès-Fridman et al., 2019), but the way they contribute to the function of tumor-infiltrating immunocytes by proper organization and education remains poorly understood. Aiming to shape the existing ideas about novel strategies of tumor management, in this paper, we briefly review the composition, organization, and prognostic value of TLSs, as well as the potential mechanism through which they educate tumor-infiltrating immunocytes.

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2 Inconsistent immune performance in tumor-associated TLSs

The immune cells within the TME have been proved to be key factors in carcinogenesis, tumor progression, and cancer prognosis (Giraldo et al., 2019; Hinshaw and Shevde, 2019; Lei et al., 2020). The existing findings indicate that tumor-antagonizing or tumor-promoting functions are not only restricted to the immune cell types. It has been revealed that the same cell populations might perform opposite functions in certain conditions; however, the reasons for the unpredictability of these tumor-infiltrating immune cells have not been elucidated.

Among the various kinds of immune cells, B cells are considered to be the most controversial type. These cells are now recognized as key players in the core immune network, whose quantity could increase at a late tumor stage and result in a dual effect on recurrence and tumor progression (Bindea et al., 2013). A comprehensive analysis based on 69 studies covering 19 cancers stated that half of the cases possessed a positive association between tumor-infiltrating B cells (including plasma cells (PCs)) and the clinical outcome, whereas the remainder showed negative (9.3%) or neutral (40.7%) effect (Wouters and Nelson, 2018). Since the biases induced by cancer type, pathologic factors, or technical approaches have been removed, the inherent characteristics of the tumor-infiltrating B cells deserve increased attention. The transcriptome and proteomic analysis of ICB-treated melanoma and renal cell carcinoma cohorts revealed unique functional states of B cells in responders, which appeared more memory-like (Amaria et al., 2018; Helmink et al., 2020).

A similar paradox was also presented by follicular helper T (Tfh) cells, which robustly predicted breast cancer survival or responsiveness to chemotherapy (Gu-Trantien et al., 2013) but was also reported to be negatively associated with hepatocellular carcinoma (HCC) survival (Shalapour et al., 2017).

Additional findings showed that patients with both T and B cells infiltrated into tumors were more likely to possess favorable prognosis than those with only T or only B cells. The co-occurrence of cluster of differentiation 8-positive ($CD8^+$) T cells and $CD20^+$ B cells within tumors was found independently associated with improved survival (Cabrita et al., 2020). Moreover, tumor-infiltrating $CD8^+$ T cells, the well accepted positive prognostic factor, only exhibited their cytotoxic capacity and prognostic value if B cells were also augmented within the tumor (Kroeger et al., 2016; Wouters and Nelson, 2018). Tumors rich in B cells were more likely to be infiltrated with increased levels of naive and memory T cells that were supposed to do well in anti-tumor response (Cabrita et al., 2020). It has been recently acknowledged that immune cells alone are incapable of proper function, as it is their coordinated action that is critical for both the physiological and pathological processes. The complex network of interactions bridges the gaps among diverse immune cells, as well as non-immune cells (Garner and de Visser, 2020).

The varied effect of multiple kinds of immunocytes triggered by their co-localization and cooperation reaches the concept of TLSs. These are well-organized aggregates of immune cells in non-lymphoid tissues that are subjected to long-lasting inflammatory response, including chronic infection, autoimmune disease, as well as tumors (Sautès-Fridman et al., 2019). TLSs are composed of an inner $CD20^+$ B cell-zone mantled with $CD3^+$ T cell-zone, anchored with dendritic cells (DCs) and vessel structure, similar to the lymphoid follicles in secondary lymphoid organs (SLOs) (Aloisi and Pujol-Borrell, 2006; Drayton et al., 2006).

TLSs provide an appropriate niche for communication among diverse immune cells. The unencapsulated structure of TLSs enables sufficient interactions between immune cells and the surrounding microenvironment (Braun et al., 2011). It is reasonable to speculate that the contradictory property of certain immune cells might be attributed to the formation and organization of TLSs to some extent. Supporting evidence shows that only when organized into TLSs, did B cells predict better prognosis and higher response rate to immunotherapy (Castino et al., 2016; Petitprez et al., 2020). B cells outside TLSs are likely to inhibit anti-tumor immunity and contribute to tumor growth (Germain et al., 2014; Cabrita et al., 2020). Similarly, T cells located inside or outside TLSs, or those sporadically infiltrated in tumors without TLSs, showed a distinct transcription signature and molecular phenotype, with the latter group of T cells exhibiting dysfunctional preference (Cabrita et al., 2020). Meanwhile, $CXCL13^+CD4^+$ Tfh cells, one of the major components of TLSs, always indicate extensive immune

infiltration within the tumor, intense response to chemotherapy, and longer survival (Gu-Trantien et al., 2013). $CXCL13^+CD4^+$ and $CXCL13^+CD8^+$ T cells could hardly enhance the ICB effect without forming TLSs (He et al., 2022). In brief, TLSs facilitate coordinated antitumor response by involving the combined actions of mainly T cells, B cells, and DCs (Germain et al., 2014; Goc et al., 2014; Carmi et al., 2015; Kroeger et al., 2016).

3 Composition and organization of TLSs in cancer

As introduced previously, intratumoral TLSs maintain an active immune response (Hiraoka et al., 2015). Moreover, the cooperation among the affiliates is well-organized. Although still partly unclear, the current understanding of the generation of TLSs was mostly referred to SLOs considering the anatomical resemblance (Drayton et al., 2006). This process is initiated with the colonization of lymphoid tissue inducer (LTi) cells that interact with lymphoid tissue organizer (LTo) cells by lymphotoxin signaling (de Togni et al., 1994; Mebius et al., 1997; Dejardin et al., 2002; Yoshida et al., 2002; Veiga-Fernandes et al., 2007). The abovementioned interactions promote the expression of adhesion molecules (e.g., vascular cell adhesion molecule 1 (VCAM1), intercellular adhesion molecule 1 (ICAM1), mucosal vascular addressin cell adhesion molecule 1 (MAdCAM1), and peripheral lymph node addressin (PNAd)) and the production of chemokines (e.g., chemokine (C-C motif) ligand 19 (CCL19), CCL21, and chemokine (C-X-C motif) ligand 13 (CXCL13)), which further leads to vascularization and immune cell recruitment (Gunn et al., 1998; Ngo et al., 1999; Suzuki et al., 1999; Ansel et al., 2000; Luther et al., 2003). However, it has been described that the induction of TLSs was not restricted to lymphotoxin signaling, and several immune cell populations, such as group 3 innate lymphoid cells (ILC3), B cells, T helper 17 (Th17) cells, effector $CD8^+$ T cells, and M1 macrophages, were found to be surrogate LTi cells (Lochner et al., 2011; Peters et al., 2011; Guedj et al., 2014; Carrega et al., 2015; Peske et al., 2015). Similarly, certain stromal and immune cells were thought to act as potential surrogate LTo cells (Bénézech et al., 2010; Barone et al., 2016; Rodriguez et al., 2021).

Even with certain distinctions during the initiation of TLSs and SLOs, the main chemokines involved in the downstream process are shared between these two structures. Among the significant chemokines, CXCL13 performs as a crucial element due to its full participation throughout the TLS organization. As a typical marker of TLSs, the expression of CXCL13 can also be utilized for prognosis prediction. Patients with CXCL13 deletion suffer a significantly higher risk of relapse (Bindea et al., 2013). CXCL13, also defined as B lymphocyte chemoattractant, has been proved to be sufficient to mediate B cell recruitment, together with the downstream process for lymphoid neogenesis, including but not limited to vessel differentiation, chemokine induction, T/B segregation, and germinal center (GC) formation (Luther et al., 2000). Moreover, CXCL13 has also been reported as a unique marker for tumor antigen-specific $CD4^+$ and $CD8^+$ T cells, as well as good prognosis (Groeneveld et al., 2021; He et al., 2022).

One of the main sources of CXCL13 points to Tfh cells, indispensable in forming extrafollicular and GC responses, where they are crucial for humoral immunity (Gunn et al., 1998; Allen et al., 2007; Kerfoot et al., 2011). CXCL13-producing Tfh cells have also been defined as a positive prognostic factor in several tumors, more or less profiting from its promotion for TLS organization (Gu-Trantien et al., 2013; Li et al., 2021). In fact, CXCL13-producing antigen-specific Tfh cells, which are necessary and sufficient for TLS formation, effectively dampen colorectal cancer (CRC) development with assistance of B cells (Overacre-Delgoffe et al., 2021). In addition, certain $CD8^+$ T subsets and stromal cells also turned out to be the origin of CXCL13, accompanied by antigen presenting capacity (van de Pavert et al., 2009; Workel et al., 2019; Wu et al., 2020; He et al., 2022). Interestingly, these CXCL13-producing $CD8^+$ T cells are always recognized as exhausted $CD8^+$ T cells ($CD8^+$ Tex) owing to the highly expressed inhibitory immune checkpoint molecules (such as programmed cell death protein-1 (PD-1), cytotoxic T lymphocyte-associated protein-4 (CTLA-4), T-cell immunoglobulin domain and mucin domain-containing molecule 3 (TIM-3), lymphocyte activation gene-3 (LAG-3), and T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT)) (Thommen et al., 2018; Dai et al., 2021; Jin et al., 2021). Unlike the previously

accepted poor prognostic value of $CD8^+$ Tex in tumors, the accumulation of $CD8^+$ Tex favors the clinical outcome in CRC, melanoma, and breast cancer, when accompanied with Tfh (Niogret et al., 2021). In addition, other chemokines such as CXCL12, CCL19, CCL21, and tumor necrosis factor (TNF) also contribute to lymphoid tissue organogenesis by supporting the infiltration of B cells, T cells, and DCs (Luther et al., 2002; Furtado et al., 2014). CCL21 was also shown to be beneficial for the formation of more and larger TLSs (Luther et al., 2002).

Alongside B and T cells that dominate in TLSs, DCs also matter in TLS formation and function. Follicular dendritic cells (FDCs) localized within GC are critical for the selection of memory B cells, while mature dendritic cell-lysosomal-associated membrane proteins (DC-LAMPs; also present as a special marker for tumor-associated TLSs) that are predominantly distributed in the T cell zone act as the major type of antigen-presenting cells (APCs) to facilitate the generation of tumor-reactive T cells (Wykes et al., 1998; di Pucchio et al., 2008; Schmitt et al., 2009; Goc et al., 2014). DC is generally required for early Tfh differentiation, indicating its indispensable role in the initial step of TLS formation (Choi et al., 2011; Goenka et al., 2011; Kato et al., 2015; Krishnaswamy et al., 2017). What is more, the formation and maintenance of TLSs are greatly dependent on antigen recognition. As long as the antigens are thoroughly eliminated, TLSs will generally disintegrate (Geurtsvankessel et al., 2009; Halle et al., 2009). The enrichment of mature DC in TLSs also displayed a potential promotive effect on T cell infiltration, activation, and cytotoxic orientation; moreover, the transmission of $CD4^+$ T cell-derived help signals consequently contributed to long-term survival (Schoenberger et al., 1998; Yang et al., 2006; Goc et al., 2014; Eickhoff et al., 2015; Hor et al., 2015; Lee et al., 2017; Weinstein et al., 2017).

4 Prognostic value of TLSs in cancer

Accumulating evidence suggests the magnified anti-tumor immune response in TLSs. Meanwhile, a favorable prognostic and predictive impact of TLSs has been well presented in many kinds of solid tumor (Sautès-Fridman et al., 2019). Also, the prognostic value of TLSs was found to be independent of tumor stage as well as other survival factors (Hiraoka et al., 2015; Posch et al., 2018). Studies focusing on tumor ICB therapy have preliminarily revealed the correlation between TLSs and the response to ICB. For multiple tumors including melanoma, CRC, non-small cell lung cancer (NSCLC), and so on, patients with intratumoral TLSs, sometimes featured with enriched B cells or $PD\text{-}1^{hi}$ dysfunctional $CD8^+$ T cells, could better respond to ICB therapy (Buisseret et al., 2017; Johansson-Percival et al., 2017; Cabrita et al., 2020; Helmink et al., 2020; Petitprez et al., 2020).

The biological advantages of TLSs manifest as an increased opportunity for tumor-specific immune cells to encounter the matched antigens. On the other hand, the enhanced immune response benefits from the collaboration among diverse immune cells. It is well known that the fate of Tfh cells, also defined as tumor-specific $CD4^+$ T cells in TME, can be regulated by B cells and B cell-recognized neoantigens. Afterwards, the primed Tfh cells enhance the activation and cytotoxic function of $CD8^+$ T cells by producing interleukin-21 (IL-21) for an anti-tumor effect (Cui et al., 2021; Niogret et al., 2021). In turn, the recruitment of Tfh cells is partly due to CXCL13 expression by intratumoral $CD8^+$ T cells (Niogret et al., 2021). Furthermore, the sufficient antigen-driven interaction between $CD4^+$ T cells and DC produces CCL3/4 to directly attract $CD8^+$ T cells and increase the possibility of optimal stimulation of antigen-specific $CD8^+$ T cells (Castellino et al., 2006).

The exact mechanisms for boosting the immune reactivity of TLSs still remain elusive. The prevailing ideas can be roughly summarized into three main groups. (1) Some effector cells are preferred to be recruited into TLSs, such as ILC3 (Carrega et al., 2015), natural killer T (NKT) cells (Bénézech et al., 2015), and effective PCs (Lochner et al., 2011), which participate in the organization of TLSs. (2) Local priming derived from TLSs orients naive populations to have a particular status, forming the evidence that naive T cells can be attracted into TLSs and maturate into CTLs (Lee et al., 2006; Garner and de Visser, 2020), and the resident stem-like $CD8^+$ T cells are likely to enter dysfunctional terminal state that can sustain antigen stimulation for the maintenance of TLSs (Jansen et al., 2019). Meanwhile, B cells within TLSs are more likely switched into memory B cells,

and prefer to maturate toward IgG-producing PCs that boost ICB response by labeling tumor cells with IgG (Helmink et al., 2020; Kinker et al., 2021; Meylan et al., 2022), and also promoting $CD8^+$ T cells infiltration (Castino et al., 2016). Without TLSs, however, B cells would function suboptimally and more likely acquire suppressive function (Siliņa et al., 2018; Cillo et al., 2020; Ruffin et al., 2021). It could be interpreted that TLSs-resident B cells are well embraced by T cells and DCs, and protected from immunosuppressive stimuli by tumor cells (Germain et al., 2014; Siliņa et al., 2018; Cabrita et al., 2020). (3) Existing effector populations could be reeducated to gain novel characteristics. Th17 cells, one type of surrogate LTi cells, could be induced into Tfh-like population with upregulated CXCL13 expression for TLS induction (Lochner et al., 2011; Peters et al., 2011). At the same time, Tfh cells could possess cytotoxic ability as functional Th1-oriented cells under the education of TLSs (Goc et al., 2014; Noël et al., 2021). Even Tfh cells that locate in distinct sites diverge along their differentiation trajectory, with Tfh outside GC proliferating continuously while GC-resident Tfh stopping proliferation soon after differentiation but performing better in vesicle organization and exocytosis (Yeh et al., 2022). The previously defined "dysfunctional" $CD8^+$ Tex cells have been found as a highly proliferative and dynamically differentiating subset in the TME (Li et al., 2019), indicating their unique role in tumor-associated immune response. $CD8^+$ Tex cells always locate within tumor sites thanks to tumor antigen-specific priming, and these cells can be educated by stroma-derived transforming growth factor-β (TGF-β) to secrete Tfh/B cell-recruiting CXCL13 to assist with the formation of TLSs exactly inside tumors (Workel et al., 2019). On the other hand, the "exhausted" phenotype of $CD8^+$ T cells caused by continuous stimulation could counteract with the help of $CD4^+$ T cells. It has been reported that antigen-activated $CD4^+$ T cells could improve the clonal expansion of effector $CD8^+$ T cells and strengthen tumor-reactive $CD8^+$ T cells by downregulating coinhibitory receptors, increasing migration-related chemokine receptors, and boosting the generation of the cytotoxic effect (Bennett et al., 1997; Ridge et al., 1998; Janssen et al., 2003; Shedlock and Shen, 2003; Ahrends et al., 2017).

As a matter of fact, the composition and function of TLSs vary along with tumor progression, and their presence will not necessarily subvert the immunosuppressive state of the TME, exemplified as highly inflamed tumors (Sautès-Fridman et al., 2019). There are many factors that determine the phenotype of TLSs, including but not limited to their quantity, location, composition, and degree of maturation. Visually, the morphology of TLSs can differ significantly according to their location, even within the same tumor sample (Munoz-Erazo et al., 2020), but whether they differ in biological function remains unclear. What is already known is that the location of TLSs is a determinant of their anti-tumor ability. The favorable prognostic value of intratumoral TLSs has been confirmed in HCC, while the adverse effect of tumor-adjacent TLSs has also been established. The tumor margin area is prone to be in an inflamed condition, which potentially alters TLS to become a refuge for tumor stem cells that might cause late recurrence (Calderaro et al., 2019).

It is reasonable to presume that not only the density and location, but also the composition and degree of maturation of TLSs could significantly impact their function. Evidence shows that the integration of TLS density and TLS maturation can better predict tumor prognosis than each parameter separately (Posch et al., 2018). To our knowledge, there are mainly three stages during TLSs maturation. At the initial stage, immature TLSs are segregated aggregates of recruited T and B cells. In the intermediate maturation stage, follicular DCs penetrate into the niches. Finally, GCs are organized within the structure and distinguish mature TLSs. The maturation of TLSs not only affects the activation, proliferation, and affinity maturation of B cells, but also determines the therapeutic response and proggnostic value of TLSs (Berek et al., 1991; Germain et al., 2014; Siliņa et al., 2018). In other words, only TLSs with GCs are active and functional.

5 Clinical application and therapeutic induction of TLSs

In view of the given anti-tumor effect of mature TLSs, these fascinating structures could turn into ideal therapeutic targets for a variety of solid tumors.

Since it has been well documented that the presence of mature TLSs always predicts better prognosis in the vast majority of solid tumors (Sautès-Fridman

et al., 2019), the strategy for these patients is to make full use of the anti-tumor effect of TLSs. Large clinical cohorts have revealed the positive correlation between TLSs and canonical tumor therapy. Better response to neoadjuvant therapy, which leads to increased pathological complete response, was found to be significantly associated with higher TILs in breast cancer, regardless of the molecular subtypes (Song et al., 2017; Denkert et al., 2018). The application of ICB in sarcoma, melanoma, and renal cell carcinoma was reinforced by the presence of tumor-associated TLSs (Cabrita et al., 2020; Helmink et al., 2020; Petitprez et al., 2020).

With regard to the other group of the patients who lack mature TLSs within the tumor sites, different attempts aiming to trigger the induction of TLSs have been made. Considering that lymphatic vessels are essential for immune cell trafficking, it is reasonable that the major attempts to promote TLS formation began with the induction of high endothelial venules (HEVs) to promote immune infiltration, which has proved feasible (Jiang, 2020). This was achieved by applying lymphotoxin (Lee et al., 2006; Mounzer et al., 2010), vascular targeted LIGHT (an alias for TNF superfamily member 14 (TNFSF14)) (Johansson-Percival et al., 2017), or a combination of antiangiogenesis with programmed death-ligand 1 (PD-L1) blockade (Allen et al., 2017). HEVs surrounding or passing through TLSs function as gateways for lymphocyte traffic into tumors, as well as scaffolds for lymphoid structure formation (Martinet et al., 2011; Asrir et al., 2022). The existing research shows that a high density of HEVs inside tumors independently assures longer survival and lower risk of relapse (Martinet et al., 2011; Bindea et al., 2013). Besides, the tumor destruction achieved by Treg depletion was partly attributed to the formation of induced HEVs (Joshi et al., 2015; Colbeck et al., 2017). The above evidence elevates the accessibility and feasibility of targeting HEVs to induce TLS formation for tumor treatment. However, most of these attempts were limited to animal studies; hence additional clinical studies are in urgent need. It is encouraging that progress has been achieved in other clinical trials. Certain patients might benefit from canonical therapy, exemplified by hepatoblastoma patients carrying an adenomatous polyposis coli (APC) germline mutation, who could acquire better prognosis by cisplatin-induced TLSs (Morcrette et al., 2019). In addition, the application of human papillomavirus (HPV) vaccine and allogeneic pancreatic ductal adenocarcinoma vaccine successfully increased the infiltration of effector T cells, which further organized as TLSs to improve survival (Lutz et al., 2014; Maldonado et al., 2014).

It should be noted that, since the potent immune reactivity of TLSs provides their ability to antagonize tumor cells, concomitant autoimmunity should not be overlooked. Limited studies have revealed a risk of lymphocyte leakage for TLS formation caused by ICB therapy. The enrichment of cytotoxic cells within ectopic TLSs led to muscle fiber degeneration, identified as PD-1 myopathy (Matsubara et al., 2019). As a management of autoimmune toxicity caused by immunotherapy, the application of corticosteroids could markedly impair the formation and function of TLSs (Siliņa et al., 2018; van Dijk et al., 2020), leaving us with an elaborate risk-benefit ratio that needs careful evaluation.

6 Conclusions and prospects

It is beyond doubt that TLSs possess promising prognostic and predictive values in cancers. They provide a chance for various immune cells to be well orchestrated to maximize the immune response (Fig. 1). Meanwhile, the effect of TLSs acting on tumor-associated immune response is also plausible, which is susceptive to their localization, stage of maturation, and other factors. The flexibility of TLSs also offers us opportunities to manipulate their formation by adjusting certain conditions to achieve the desired therapeutic goal. To this end, a lot of research has been put forward and made preliminary achievements. Follow-up efforts are still needed for a more detailed understanding and a more effective use of tumor-associated TLSs for anticancer therapy.

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Author contributions

Jing CHEN was responsible for reference searching and manuscript writing, and Lie WANG and Jian CHEN for

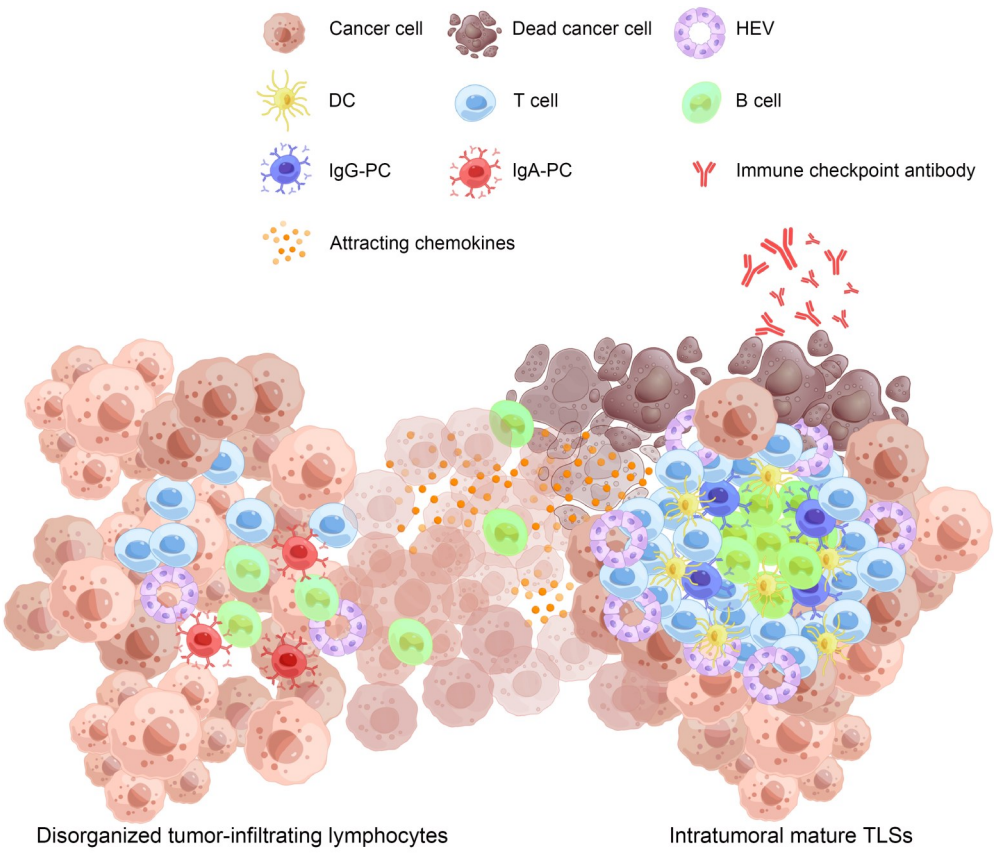

Fig. 1 Composition and potential function of TLSs in cancer. The above schematic represents immune cells infiltrated within the tumor site in two main forms. (1) Disorganized distribution within the tumor: scattered immune cells induced by tumor antigens are oriented to tumor-promoting phenotypes, represented as dysfunctional T cells and IgA-PC. (2) Assembled as TLSs within the tumor: TLSs are organized with an inner B cell-zone, mantled by the T cell-zone, with DC spreading over the structures. Surrounding HEVs act as gateways for chemo-attracted immunocytes entering the site. TLSs augment the collaboration of the aggregated immunocytes, leading to tumor-antagonizing status mainly mediated by effector T cells and IgG-PC. The presence of TLSs greatly boosts ICB therapy and efficiently disrupts tumor cells. TLS: tertiary lymphoid structure; HEV: high endothelial venule; DC: dendritic cell; IgG-PC: IgG-producing plasma cell; IgA-PC: IgA-producing plasma cell; ICB: immune checkpoint blockade.

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Compliance with ethics guidelines

Jing CHEN, Jian CHEN, and Lie WANG declare that they have no conflict of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

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