Urologia Internationalis

Review Article

Urol Int 2023;107:841–847
DOI: 10.1159/000532127

Received: March 21, 2023
Accepted: July 17, 2023
Published online: September 28, 2023

Urological Tumor: A Narrative Review of Tertiary Lymphatic Structures

Chong Shen[a] Dong-Li Zhang[a] Xiao-Long Cheng[b] Wei-Chuan Zhang[b] Jian-Jun Zhao[b]

[a]College of Clinical Medicine, Hebei University of Engineering, Handan, China; [b]Department of Urology II, Affiliated Hospital of Hebei Engineering University, Handan, China

Keywords
Tertiary lymphoid structures · Urology · Tumors · Immunotherapy · Markers

Abstracts

Background: Tertiary lymphoid structures (TLSs), as ectopic lymphoid-like tissues, are highly similar to secondary lymphoid organs and are not only involved in chronic inflammation and autoimmune responses but are also closely associated with tumor immunotherapy and prognosis. The complex composition of the urological tumor microenvironment not only varies greatly in response to immunotherapy, but the prognostic value of TLSs in different urological tumors remains controversial. ***Summary:*** We searched PubMed, Web of Science, and other full-text database systems. TLSs, kidney cancer, uroepithelial cancer, bladder cancer, and prostate cancer as keywords, relevant literature was searched from the time the library was built to 2023. Systematically explore the role and mechanism of TLSs in urological tumors. It includes the characteristics of TLSs, the role and mechanism of TLSs in urological tumors, and the clinical significance of TLSs in urological tumors. ***Key Messages:*** The prognostic role of TLSs in different urological tumors was significantly different. It is not only related to its enrichment in the tumor but also highly correlated with the location of the tumor. In addition, autoimmune toxicity may be a potential barrier to its role in the formation of TLSs through induction. Therefore, studying the mechanisms of TLSs in autoimmune diseases may help in the development of antitumor target drugs.

Introduction

As the global population ages, the incidence of urological tumors is increasing. According to the International Agency for Research on Cancer, there will be 4.08 million new cases worldwide in 2040, which has become one of the major life-threatening diseases [1]. At this stage, surgery is still the treatment of choice for solid urological tumors, but the high recurrence rate after surgery and resistance to chemotherapy and radiotherapy lead to a poor prognosis for urological tumors. Therefore, there is an urgent need for relevant and effective treatments to improve the clinical prognosis of urologic tumors. What is exciting is that with the success of immunotherapy in a variety of cancers over the last two decades, immunotherapy for urologic tumors has shown equally great benefits.

Autoimmune response is the body's response to various pathological stimuli, including chronic inflammation, tumors, allografts [2]. It was previously thought that this response process was mainly mediated by secondary lymphoid organs (SLOs), but recent studies have revealed that plastic tertiary lymphoid structures (TLSs) formed by

karger@karger.com
www.karger.com/uin

Correspondence to:
Jian-Jun Zhao, zhaojianjun1668@163.com

Karger

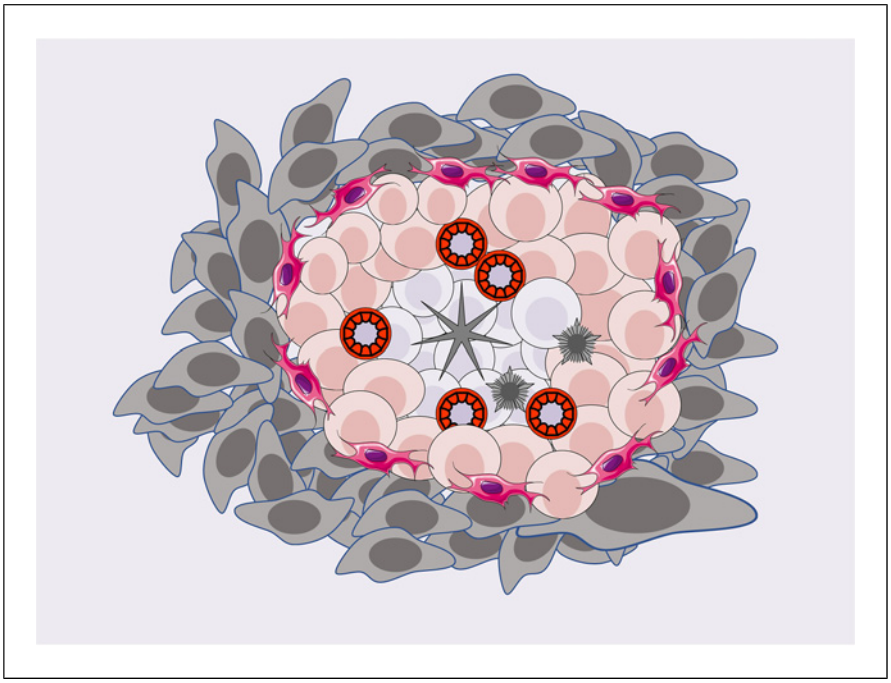

Fig. 1. Cellular composition of TLSs. The intermediate B cells are surrounded by T cells, and there are characteristic high endothelial vesicles in them. Fibroblast reticulocytes settle at the junction of tumor and T cells, while dendritic cells and follicular dendritic cells are scattered among them.

aggregation of immune cells in multiple tumor microenvironments can also orchestrate this response [3]. Moreover, TLSs have been found in almost all solid urological tumors [4–6]. The process of tumor progression induces autoimmune responses in the body through the release of multiple cytokines. This cascade of responses can promote the infiltration and aggregation of immune cells and the formation of TLSs to promote or inhibit tumor growth. However, the specific role of this lymphatic structure in urologic tumors is still poorly understood. Here, we compare the role of TLSs in urologic tumors and discuss the implications of these findings.

Tertiary Lymphoid Structures

Composition of TLSs

TLSs are collection of lymphocytes that are ectopically located outside of normal lymph nodes. They were initially thought to be raised in response to pathogenic microbial infection and chronic inflammatory stimuli [2]. In recent years, a growing number of studies have identified its presence in autoimmune diseases and cancers alike and may influence tumor development [2, 3]. Although the exact composition of TLSs is still unknown, they are mainly composed of high endothelial venules (HEVs), B-cell areas, T-cell areas, and dendritic cells (Fig. 1). It is often referred to as tertiary lymphoid tissue because it not only has a high degree of structural similarity to SLOs but also performs the functions of secondary lymphoid tissues to some extent [7]. In addition, their antitumor effects differ with each stage of maturation. Therefore, some scholars have classified TLSs according to their stages of maturation like:

1. Early TLSs
2. Primary TLSs
3. Secondary TLSs [8–10]

Unlike SLOs, TLSs lack peripheral fibrous cystic structures, arise secondary to them, and are not usually localized [11–13]. Now, as research continues, it has been found that the role of TLSs in tumors is dual. It is not only associated with good tumor prognosis [14–16] but also with poor prognosis in some tumors [17–19]. The cause of this phenomenon may not only be related to the type of tumor but also be highly correlated with the location and maturity of TLSs in the tumor [9, 10]. These studies above well illustrate that TLSs vary greatly among urological tumors and are the main cause of antitumor immune heterogeneity.

Molecular Characteristics of TLSs

Although the exact molecular mechanisms underlying the formation of TLSs are still unclear, a number of studies have found a strong link with the formation of SLOs, which are formed when lymphocytes spread and accumulate

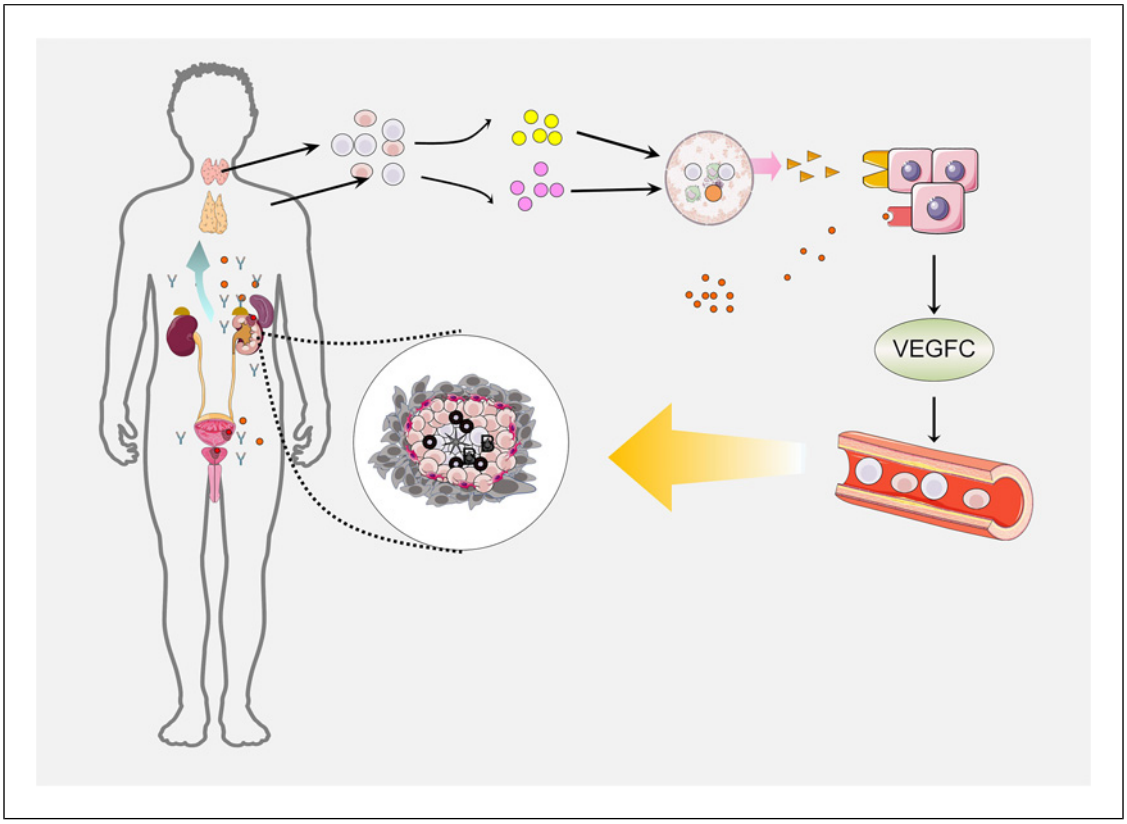

Fig. 2. Molecular characteristics of the formation of TLSs. Tumor cells continuously release antigen and inflammatory factors to stimulate lymphocytes and stromal cells to secrete CXCL13 and IL-7 and recruit lymphoid tissue-inducing cells (LTis). The formed LTis promote lymphocyte infiltration by HEVs through the expression of TLα1β2 and binding to receptors on stromal cells or lymphoid tissue organizer cells (LTOs), eventually forming TLSs.

outside the lymph nodes in response to various stimulating factors. For example, tumor cells continue to release antigens and inflammatory factors to promote lymphocyte infiltration, while lymphocytes and stromal cells recruit lymphoid tissue inducer cells by secreting CXCL13 and IL-7 [20]. Interestingly, CXCL13 has been found to act not only as a lymphocyte inducer but also as a marker for predicting the prognosis of treatment with immune checkpoint inhibitors (ICIs), which provides evidence that TLSs may be an important marker of good tumor prognosis [21]. The formation of lymphoid tissue inducer cells promotes the recruitment of lymphocyte infiltration by HEVs through the expression of TLα1β2 binding to receptors on stromal cells or lymphoid tissue organizer cells, ultimately forming TLSs [22] (Fig. 2). Notably, the presence of tumor necrosis factor (TNF) receptors on stromal cells and lymphoid tissue organizer cells has been found to act synergistically with TLα1β2 [23]. The above molecular mechanisms have also been validated in mouse models, such as Allen [24] who used anti-vascular endothelial growth factor receptor 2, anti-PD-L1, and LTβR therapies to induce HEV formation, increase intra-tumoral immune cell infiltration, and enhance cytolytic activity, leading to antitumor effects. However, as most of the studies are based on conjectures from animal experiments and have not been confirmed in humans, further confirmation for this information in humans is needed in the future, which has far-reaching implications for the development of relevant antitumor drugs.

The Role of TLSs

In most cancers, TLSs activate B-lymphocyte and T-lymphocyte antitumor immune responses to provide a favorable antitumor immune microenvironment. On the one hand, the special structure of TLSs without fibrous capsule encapsulation allows it to maximize contact with tumor-associated antigens and produce tumor-specific endogenous antibodies. On the other hand, the germinal centers of TLSs can clone and differentiate antigen-bound

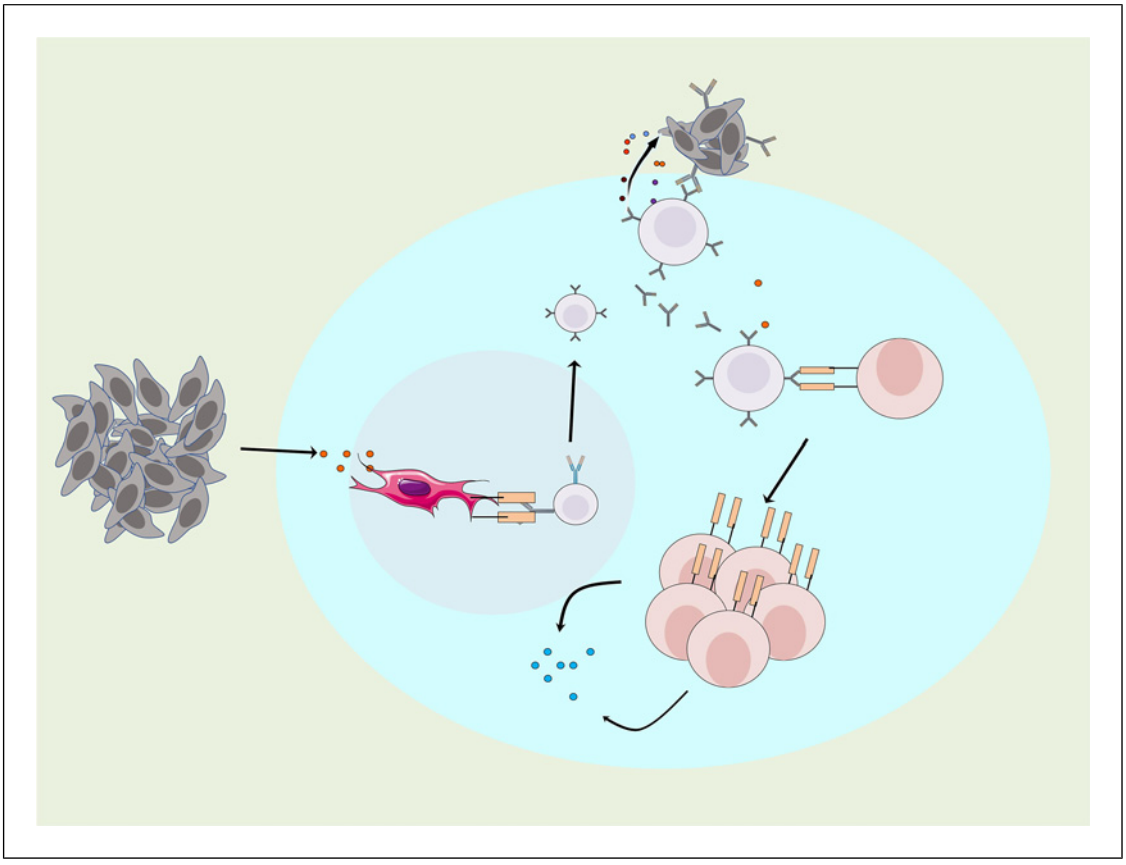

Fig. 3. Role of TLSs in the fight against tumors. TLSs in tumor cells activate B-lymphocyte and T-lymphocyte antitumor immune responses. Polyclonal IgA or IgG antibodies produced by tumor-associated B cells bind to the corresponding receptors on the surface of tumor cells and release granzyme B to inhibit tumor growth.

B cells and produce the corresponding antibodies [25]. In contrast, polyclonal IgA or IgG antibodies produced by tumor-associated B cells can bind to the corresponding receptors on the surface of tumor cells and release granzyme B to inhibit tumor growth (Fig. 3). Notably, in addition to producing cytokines and plasma cells, B cells can also act as antigen-presenting cells to deliver antigens to T cells to activate cytotoxic T cells and form memory T cells, which ultimately kill tumors by releasing interferon-γ (IFN-γ).

TLSs in Urological Tumors

Clear Cell Renal Cell Carcinoma

Clear cell renal cell carcinoma (ccRCC) is one of the most common malignancies of the urological tract. Although it has been most intensively studied, low early detection rate, rapid progression and high postoperative recurrence rates have led to consistently poor outcomes in early-stage ccRCC, while the lack of an effective therapeutic response to immunotherapy and targeted therapy in patients with advanced ccRCC has resulted in a 5-year survival rate of only 12% for advanced ccRCC [26, 27]. One of the main reasons for this is the complex composition of the immune microenvironment and its mechanisms of action due to the complex molecular characteristics and cellular morphological composition of ccRCC [28–30]. Currently, Cabrita et al. [31] have identified up to 12 signature genes that can be used for the identification of TLSs in tumors. Among them, CXCL13 not only acts as a B-cell chemokine but also positively correlates with the number of TLSs and good prognosis in renal cell carcinoma (RCC) [32]. Interestingly, high CXCL13 expression in ccRCC was positively correlated with poor prognosis, suggesting that CXCL13 could be used as an antitumor immunotherapy and prognostic marker. In addition, T-lymph in TLSs is found in most

solid tumors and its T-lymphocyte infiltration is positively associated with a good prognosis, but in ccRCC, it is associated with a poor prognosis. For example, Sobottka et al. [33] found that infiltration of TLSs and CD8+ T cells was negatively correlated with response to immunotherapy in 8 patients treated with ICIs by second-generation sequencing. This may be due to the T lymphocytes infiltrating the different stages of ccRCC. Further analysis of the dynamics of lymphocytes infiltrating ccRCC is necessary in the future to improve the stratified treatment of ccRCC patients. All of the above studies demonstrate the complexity of the immune microenvironment in ccRCC. The differences in the development of TLSs in ccRCC and the regulation of antitumor immunotherapy are not only reflected in the molecular features but are also closely related to the spatial location of lymphocyte infiltration. For example, Meylan et al. [34] found by spatial transcriptomic analysis that CXCL12-expressing fibroblasts in close contact with tumor cells could recruit plasma cells from TLSs into cancer nests and thus exert antitumor effects. In contrast, plasma cells promote the expression of CXCR4, the receptor for CXCXL12, and downregulate the expression of CXCR5, the receptor for CXCL13, which is a potential marker of poor prognosis in ccRCC [35]. In conclusion, all these data demonstrate that the induction of TLS formation is one of the important pathways for future ccRCC.

Urinary Bladder Cancer

Despite the effectiveness of ICIs in localized and metastatic muscle-invasive bladder cancer, 60–85% of patients remain nonresponsive. In contrast, TLSs are mainly involved in tumor immune pathways such as the PD-1 and PD-L1 immune checkpoint pathways. Currently, PD-L1 is the main predictive biomarker for the treatment of ICIs, but unfortunately, the sensitivity and specificity of related immunotherapy response markers such as PD-L1, IFN-γ, and tGE8 are low [36–38]. As a result, a great deal of research has been devoted to finding a new biomarker to improve the prediction of response to treatment with ICIs in bladder cancer. For example, Groeneveld et al. [39] found that high CXCL13 expression in patients receiving immunotherapy was associated not only with good immune response but also with better survival, suggesting that CXCL13 could be used as a prognostic marker for immunotherapy in bladder cancer. As with ccRCC, it has been found that spatial differences in TLSs are not only associated with antitumor immune responses but also highly correlated with prognosis. For example, van Dijk et al. [40] found that superficial TLSs with high expression of CD4+ T cells in bladder cancer were not associated with antitumor immune responses. On the other hand, TLSs have been found to be highly similar to the lymphoid aggregates formed by Hunner-type interstitial cystitis [41–43]. Therefore, whether there are partially nonfunctional superficial TLSs associated with bladder inflammation needs to be thoroughly investigated in future advances. In conclusion, although the various mechanisms of TLSs in bladder cancer are still unclear, identifying accurate biomarkers of response is one of the key issues that still needs to be addressed in the future with a view to opening up new avenues for the treatment of bladder cancer.

Prostate Cancer

The key to a response to ICIs is the strength of the immune cell infiltrate, and ICIs are not ideal for prostate cancer with poor immune infiltration. TLSs, a feature of immune cell infiltration, are found not only in normal prostate tissue but also in prostate cancer tissue [44]. Therefore, it is important to study its role in prostate cancer. García-Hernández et al. [45] found that different stages of prostate cancer not only had significantly different infiltration of TLSs but also had different cellular characteristics and molecular markers around their TLSs. For example, CXCL10-expressing epithelial cells are highly expressed in early-stage prostate cancer, while a high reduction of CXCL10+CD3+ T cells is found in advanced prostate cancer TLSs. This cell produces a vasopressor, CXCL10, which not only inhibits tumor angiogenesis but also induces CXCR3+ T cells and NK cells to clear tumor cells. However, high CXCR3A expression has been found to be associated with metastasis and invasion of prostate cancer [46]. This may be due to the destruction of TLSs in advanced prostate cancer resulting in a high reduction of CXCL10+CD3+ T cells and is an important reason for their low response to immunotherapy [47]. In conclusion, in the future, accurate stratification of prostate cancer patients with the help of cellular and molecular characteristics of TLSs and screening of patients with high response to immunotherapy will be of great significance in improving the survival of prostate cancer patients.

Summary and Outlook

Although TLSs have been identified in many cancers, their specific molecular mechanisms of formation remain unclear, which not only poses a significant obstacle to exploring the specific mechanisms of action of TLSs in tumors but also complicates the use of TLSs to predict the

prognostic role in different cancers. Therefore, it is necessary to conduct in-depth studies on the specific molecular mechanisms of TLS formation in conjunction with their cellular and molecular composition in the future, which will not only have far-reaching implications for revealing the predictive role of TLS in different diseases but also provide theoretical support for immunotherapy. In addition, although TLSs have been identified to play a certain adaptive immune response in antitumor, it is still unknown whether they have a synergistic or antagonistic effect with SLOs, and addressing this issue may be important for the future development of specific antitumor immune drugs. Finally, by understanding the immunotoxicity associated with TLSs, it may help identify targets for immunotherapy.

Conflict of Interest Statement

All authors declare that they have no competing interests.

Funding Sources

This study was supported by the Natural Science Foundation of Hebei Province (Grant No. H2021402018).

Author Contributions

C.S. wrote the manuscript and literature collection. D.Z. and X.C. performed literature quality screening. W.Z. contributed to picture drawing. C.S. and J.Z. reviewed, revised, and approved the final manuscript.

References

1 Bukavina L, Bensalah K, Bray F, Carlo M, Challacombe B, Karam JA, et al. Epidemiology of renal cell carcinoma: 2022 update. Eur Urol. 2022;82(5):529–42.
2 Kratz A, Campos-Neto A, Hanson MS, Ruddle NH. Chronic inflammation caused by lymphotoxin is lymphoid neogenesis. J Exp Med. 1996;183(4):1461–72.
3 Pitzalis C, Jones GW, Bombardieri M, Jones SA. Ectopic lymphoid-like structures in infection, cancer and autoimmunity. Nat Rev Immunol. 2014;14(7):447–62.
4 Giraldo NA, Becht E, Pagès F, Skliris G, Verkarre V, Vano Y, et al. Orchestration and prognostic significance of immune checkpoints in the microenvironment of primary and metastatic renal cell cancer. Clin Cancer Res. 2015;21(13):3031–40.
5 Pfannstiel C, Strissel PL, Chiappinelli KB, Sikic D, Wach S, Wirtz RM, et al. The tumor immune microenvironment drives a prognostic relevance that correlates with bladder cancer subtypes. Cancer Immunol Res. 2019;7(6):923–38.
6 Wolf MJ, Seleznik GM, Zeller N, Heikenwalder M. The unexpected role of lymphotoxin beta receptor signaling in carcinogenesis: from lymphoid tissue formation to liver and prostate cancer development. Oncogene. 2010;29(36):5006–18.
7 Dieu-Nosjean M, Goc J, Giraldo NA, Sautès-Fridman C, Fridman WH. Tertiary lymphoid structures in cancer and beyond. Trends Immunol. 2014;35(11):571–80.
8 Siliņa K, Soltermann A, Attar FM, Casanova R, Uckeley ZM, Thut H, et al. Germinal centers determine the prognostic relevance of tertiary lymphoid structures and are impaired by corticosteroids in lung squamous cell carcinoma. Cancer Res. 2018;78(5):1308–20.
9 Calderaro J, Petitprez F, Becht E, Laurent A, Hirsch TZ, Rousseau B, et al. Intra-tumoral tertiary lymphoid structures are associated with a low risk of early recurrence of hepatocellular carcinoma. J Hepatol. 2019;70(1):58–65.
10 Posch F, Silina K, Leibl S, Mündlein A, Moch H, Siebenhüner A, et al. Maturation of tertiary lymphoid structures and recurrence of stage ii and iii colorectal cancer. OncoImmunology. 2018;7(2):e1378844.
11 Ruddle NH. Lymphatic vessels and tertiary lymphoid organs. J Clin Invest. 2014;124(3):953–9.
12 Drayton DL, Liao S, Mounzer RH, Ruddle NH. Lymphoid organ development: from ontogeny to neogenesis. Nat Immunol. 2006;7(4):344–53.
13 van de Pavert SA, Mebius RE. New insights into the development of lymphoid tissues. Nat Rev Immunol. 2010;10(9):664–74.
14 Munoz-Erazo L, Rhodes JL, Marion VC, Kemp RA. Tertiary lymphoid structures in cancer: considerations for patient prognosis. Cell Mol Immunol. 2020;17(6):570–5.
15 Dieu-Nosjean M, Giraldo NA, Kaplon H, Germain C, Fridman WH, Sautès-Fridman C. Tertiary lymphoid structures, drivers of the anti-tumor responses in human cancers. Immunol Rev. 2016;271(1):260–75.
16 Galon J, Bruni D. Tumor immunology and tumor evolution: intertwined histories. Immunity. 2020;52(1):55–81.
17 Figenschau SL, Fismen S, Fenton KA, Fenton C, Mortensen ES. Tertiary lymphoid structures are associated with higher tumor grade in primary operable breast cancer patients. BMC Cancer. 2015;15:101.
18 Sautès-Fridman C, Lawand M, Giraldo NA, Kaplon H, Germain C, Fridman WH, et al. Tertiary lymphoid structures in cancers: prognostic value, regulation, and manipulation for therapeutic intervention. Front Immunol. 2016;7:407.
19 Masuda T, Tanaka N, Takamatsu K, Hakozaki K, Takahashi R, Anno T, et al. Unique characteristics of tertiary lymphoid structures in kidney clear cell carcinoma: prognostic outcome and comparison with bladder cancer. J Immunother Cancer. 2022;10(3):e003883.
20 Meier D, Bornmann C, Chappaz S, Schmutz S, Otten LA, Ceredig R, et al. Ectopic lymphoid-organ development occurs through interleukin 7-mediated enhanced survival of lymphoid-tissue-inducer cells. Immunity. 2007;26(5):643–54.
21 Sautès-Fridman C, Petitprez F, Calderaro J, Fridman WH. Tertiary lymphoid structures in the era of cancer immunotherapy. Nat Rev Cancer. 2019;19(6):307–25.
22 Cupedo T, Kraal G, Mebius RE. The role of cd45+cd4+cd3- cells in lymphoid organ development. Immunol Rev. 2002;189:41–50.
23 Mebius RE. Organogenesis of lymphoid tissues. Nat Rev Immunol. 2003;3(4):292–303.
24 Allen E, Jabouille A, Rivera LB, Lodewijckx I, Missiaen R, Steri V, et al. Combined antiangiogenic and anti-pd-l1 therapy stimulates tumor immunity through hev formation. Sci Transl Med. 2017;9(385):eaak9679.
25 Victora GD, Nussenzweig MC. Germinal centers. Annu Rev Immunol. 2022;40:413–42.
26 Atkins MB, Tannir NM. Current and emerging therapies for first-line treatment of metastatic clear cell renal cell carcinoma. Cancer Treat Rev. 2018;70:127–37.
27 Escudier B, Porta C, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, et al. Renal cell carcinoma: esmo clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(5):706–20.
28 Dizman N, Philip EJ, Pal SK. Genomic profiling in renal cell carcinoma. Nat Rev Nephrol. 2020;16(8):435–51.

29 Ma C, Xu W, Xu Y, Wang J, Liu W, Cao D, et al. Identification and validation of novel metastasis-related signatures of clear cell renal cell carcinoma using gene expression databases. Am J Transl Res. 2020;12(8):4108–26.
30 Xu W, Xu Y, Tian X, Anwaier A, Liu W, Wang J, et al. Large-scale transcriptome profiles reveal robust 20-signatures metabolic prediction models and novel role of g6pc in clear cell renal cell carcinoma. J Cell Mol Med. 2020;24(16):9012–27.
31 Cabrita R, Lauss M, Sanna A, Donia M, Skaarup Larsen M, Mitra S, et al. Tertiary lymphoid structures improve immunotherapy and survival in melanoma. Nature. 2020;577(7791):561–5.
32 Xu W, Ma C, Liu W, Anwaier A, Tian X, Shi G, et al. Prognostic value, dna variation and immunologic features of a tertiary lymphoid structure-related chemokine signature in clear cell renal cell carcinoma. Cancer Immunol Immunother. 2022;71(8):1923–35.
33 Sobottka B, Nienhold R, Nowak M, Hench J, Haeuptle P, Frank A, et al. Integrated analysis of immunotherapy treated clear cell renal cell carcinomas: an exploratory study. J Immunother. 2022;45(1):35–42.
34 Meylan M, Petitprez F, Becht E, Bougoüin A, Pupier G, Calvez A, et al. Tertiary lymphoid structures generate and propagate anti-tumor antibody-producing plasma cells in renal cell cancer. Immunity. 2022;55(3):527–41.e5.
35 Hargreaves DC, Hyman PL, Lu TT, Ngo VN, Bidgol A, Suzuki G, et al. A coordinated change in chemokine responsiveness guides plasma cell movements. J Exp Med. 2001;194(1):45–56.
36 Mariathasan S, Turley SJ, Nickles D, Castiglioni A, Yuen K, Wang Y, et al. Tgfβ attenuates tumour response to pd-l1 blockade by contributing to exclusion of t cells. Nature. 2018;554(7693):544–8.
37 Necchi A, Raggi D, Gallina A, Ross JS, Farè E, Giannatempo P, et al. Impact of molecular subtyping and immune infiltration on pathological response and outcome following neoadjuvant pembrolizumab in muscle-invasive bladder cancer. Eur Urol. 2020;77(6):701–10.
38 Powles T, Kockx M, Rodriguez-Vida A, Duran I, Crabb SJ, Van Der Heijden MS, et al. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the abacus trial. Nat Med. 2019;25(11):1706–14.
39 Groeneveld CS, Fontugne J, Cabel L, Bernard-Pierrot I, Radvanyi F, Allory Y, et al. Tertiary lymphoid structures marker cxcl13 is associated with better survival for patients with advanced-stage bladder cancer treated with immunotherapy. Eur J Cancer. 2021;148:181–9.
40 van Dijk N, Gil-Jimenez A, Silina K, van Montfoort ML, Einerhand S, Jonkman L, et al. The tumor immune landscape and architecture of tertiary lymphoid structures in urothelial cancer. Front Immunol. 2021;12:793964.
41 Lu K, Wei S, Wang Z, Wu K, Jiang J, Yan Z, et al. Identification of novel biomarkers in hunner's interstitial cystitis using the cibersort, an algorithm based on machine learning. BMC Urol. 2021;21(1):109.
42 Akiyama Y, Luo Y, Hanno PM, Maeda D, Homma Y. Interstitial cystitis/bladder pain syndrome: the evolving landscape, animal models and future perspectives. Int J Urol. 2020;27(6):491–503.
43 Akiyama Y, Maeda D, Katoh H, Morikawa T, Niimi A, Nomiya A, et al. Molecular taxonomy of interstitial cystitis/bladder pain syndrome based on whole transcriptome profiling by next-generation rna sequencing of bladder mucosal biopsies. J Urol. 2019;202(2):290–300.
44 Di Carlo E, Magnasco S, D'Antuono T, Tenaglia R, Sorrentino C. The prostate-associated lymphoid tissue (palt) is linked to the expression of homing chemokines cxcl13 and ccl21. Prostate. 2007;67(10):1070–80.
45 García-Hernández MDLL, Uribe-Uribe NO, Espinosa-González R, Kast WM, Khader SA, Rangel-Moreno J. A unique cellular and molecular microenvironment is present in tertiary lymphoid organs of patients with spontaneous prostate cancer regression. Front Immunol. 2017;8:563.
46 Wu Q, Dhir R, Wells A. Altered cxcr3 isoform expression regulates prostate cancer cell migration and invasion. Mol Cancer. 2012;11:3.
47 Hickman HD, Reynoso GV, Ngudiankama BF, Cush SS, Gibbs J, Bennink JR, et al. Cxcr3 chemokine receptor enables local cd8(+) t cell migration for the destruction of virus-infected cells. Immunity. 2015;42(3):524–37.