



## PERSPECTIVE

# Deep insight into the B-cell associated tertiary lymphoid structure and tumor immunotherapy

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Bod et al.<sup>1</sup> recently published a study in *Nature* that garnered attention to B cell-associated anti-tumor immunity and immunotherapy of melanoma and other tumors<sup>1</sup>. As a promising supplemental immunotherapy to mainstream methods that target T and natural killer (NK) cells, B cell-associated anti-tumor immunotherapy is promising, especially for patients who have failed treatment or are resistant to immune checkpoint inhibitors. Knowledge pertaining to B cell functions and associations with tertiary lymphoid structures (TLSs) requires further investigation to provide a thorough understanding of their roles in tumor immunity. The perspective herein focused on B cell roles in TLSs and associated anti-tumor activities to facilitate clinical application of this new treatment option.

## Tumor-associated B cell types and functions

The roles of B cells in various stages and histologic types of malignancies are not fully understood. Some tumor-associated B cells may be indispensable allies of T cells in fighting cancer cells and are the main cell type in the initiation and maintenance of anti-tumor responses, especially in the form of TLSs<sup>1</sup> (Table 1).

## Plasma cells

The role of plasma cells in tumor immunity is controversial. In high-grade ovarian cancer, CD20+ B, CD4+ T, CD8+ T, and plasma cell invasion is associated with better survival<sup>2</sup>. However, B cell-generated antibodies deposited at the tumor site can form immune complexes, activate receptors *via* Fc $\gamma$ , and recruit myeloid cells and macrophages. B cells also secrete pro-angiogenic factors and immunomodulatory cytokines, and thus accelerate tumor progression<sup>2</sup>.

## Antigen-presenting B cells

B cells can act as antigen-presenting cells (APCs) and contribute to activating naive CD4 T cells. In lung cancer patients, activated B cells marked by CD69+HLA-DR+CD27+CD21+ are associated with the CD4+ effector T cell response, indicating a catalytic role of antigen-presenting B cells in anti-tumor immune responses<sup>3,4</sup>.

## Regulatory B cells (Bregs)

Bregs are a subpopulation of B cells with unique immunomodulatory and immunosuppressive properties. Bregs have an important role in peripheral tolerance<sup>2</sup>. Bregs inhibit dendritic cell (DC) differentiation, as well as Th1 and Th17 cell proliferation, and induce differentiation of Tregs by secreting IL-10. The secretion of IL-10 and TGF- $\beta$  by Bregs inhibits CD8+ T cell activation, proliferation, and production of effectors, such as IFN- $\gamma$ , TNF- $\alpha$ , and granzyme B, in cancer patients. Clearance of Bregs and elimination of inhibitory cytokines, such as IL-10 secreted by Bregs, are possible strategies against B cells<sup>2</sup>, but these strategies are in the early stages of investigation.

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**Table 1** Role of B cells and TLS in tumor immunity and immunotherapy

B cell type and TLS	Specific cell types	Tumor progression	Anti-tumor immunity	Prognosis	Tumor type	Mechanism
Plasma cells	Non-specific plasma cells		Antibody dependent anti-tumor functions	Better survival	High-grade ovarian cancer	<ul style="list-style-type: none"> <li>• Antibody-dependent cellular phagocytosis</li> <li>• Antibody dependent cell-mediated cytotoxicity</li> </ul>
	Non-specific plasma cells	Accelerate tumor progression				<ul style="list-style-type: none"> <li>• Form immune complexes, activate receptors through Fcγ</li> <li>• Recruit myeloid cells and macrophages</li> <li>• Secrete pro-angiogenic factors and immunomodulatory cytokines</li> <li>• Induce myeloid-derived suppressor cell (MDSC) generation</li> </ul>
Antigen-presenting B cells	IgA-type plasma B cells		Antagonize cancer growth	Increased IgA has a better prognosis	High-grade ovarian cancer	<ul style="list-style-type: none"> <li>• IgA wrap the surface of tumor cells for recognition by immune cells;</li> <li>• Coordinate control of the response between tumor, and T and B cells</li> </ul>
	mIgG1/BCR mutation plasma B cells (unique to Asians)		Enhance anti-tumor immunity	Prolong colorectal patient survival	Colorectal cancer	<ul style="list-style-type: none"> <li>• Promote the recuperation of tumor cells</li> <li>• Lead to antigen uptake by Fcγ receptors on dendritic cells (DCs)</li> <li>• Enhance DC presentation</li> </ul>
Regulatory B cells (Bregs)	Antigen-presenting B cells		Presentation of tumor-derived antigens to CD4+ and CD8+ T cells.		Lung adenocarcinoma	Enrichment of CD4+ T follicular helper cells and B cells related to germinal center formation
	CD69+HLA-DR+CD27+CD21+ B cells		Anti-tumor immune response		Lung cancer	Associated with CD4+ T cell response
Memory B cells	B cells expressing leucine tRNA synthetase (LARS) 2		Enhanced regulatory functions		Colorectal cancer	Mitochondrial metabolism is enhanced in LARS-expressing B cells, regeneration of NAD+. NAD+-dependent deacetylase sirtuin 1 (SIRT1) enhances binding ability to the Tgfb1 promoter region by deacetylating the transcription factor, PAX5.
	Bregs	Tumor progression				<ul style="list-style-type: none"> <li>• Induce differentiation of Tregs</li> <li>• Inhibit DC differentiation, and Th1 and Th17 cell proliferation</li> <li>• Inhibit CD8+ T cell activation, proliferation, and production of effectors</li> </ul>
Memory B cells	Memory B cells		Induce tumor regression		Lung cancer	<ul style="list-style-type: none"> <li>• Present antigens to local T cells</li> <li>• Maintain the level of effector activity in tertiary lymphoid structures (TLSs)</li> </ul>

**Table 1** Continued

B cell type and TLS	Specific cell types	Tumor progression	Anti-tumor immunity	Prognosis	Tumor type	Mechanism
	Memory B cells	Tumor progression			Lymphoma	<ul style="list-style-type: none"> <li>Entry of B cells into germinal centers is associated with acquisition of malignant features.</li> <li>Abnormal memory B cells are the originating cells of diffuse B cell lymphoma</li> </ul>
Tumor-infiltrating B cells	Cluster tumor-infiltrating B cells	Tumor progression	Predictor of disease prognosis	Predict the response of ICI treatment		<p>Clustered infiltration and number of B cells in TLSs</p> <ul style="list-style-type: none"> <li>Provide nutrients for tumor cells</li> <li>Produce IL-10, TGF-<math>\beta</math>, IL-35, IL-21, and TNF-<math>\beta</math></li> <li>Inhibiting CD8+ CTL and NK cell function</li> <li>Secrete the neurotransmitter, GABA</li> </ul>
	Scatter tumor-infiltrating B cells	Tumor progression				<ul style="list-style-type: none"> <li>STING agonist-promoted normalization of tumor blood vessels lead to TLS formation.</li> <li>Oncolytic viral therapies promoting cytokines and chemokines, favoring recruitment of all participants interacting in mature</li> <li>TLSs and TNF-<math>\alpha</math> of the LIGHT family also promote TLS formation when efficiently delivered to tumor blood vessels</li> <li>Immune checkpoint blockade therapy</li> <li>Tfh cell differentiation leading to the production of tertiary lymphoid structures</li> </ul>
	TLS		Positive tumor prognosis and immunotherapy, delay in tumor progression, and enhance antigen proliferation		<ul style="list-style-type: none"> <li>Melanoma</li> <li>Soft tissue sarcoma</li> <li>Kidney cancer</li> <li>Breast cancer</li> <li>Lung cancer</li> <li>Colorectal cancer</li> </ul>	
	ICOSL+ B cells in TLSs		Activate complement-dependent cytotoxicity to kill tumor cells		Breast cancer after chemotherapy	Complement regulatory protein CD55 regulates production of this cell population
	T-cell immunoglobulin mucin-1 (TIM1)-positive B cells		Promotes the anti-tumor immune response		Melanoma	Enhances effector T cell action, inhibits tumor growth
	CD20+CD27+IgD-subtype-converted B cells		Anti-tumor effect		Triple-negative breast cancer	Upregulate expression of BCR pathway molecules (FOS and JUN) and the germinal center chemokine regulator (RGS1), and activates CD69 and TNF $\alpha$ signaling <i>via</i> NF $\kappa$ B

## Memory B cells

Memory B cells are a dynamic population of mature B cells that re-enter the germinal center and TLSs in response to persistent tumor antigens. Memory B cells present antigens to local T cells and cause tumor regression. This effect may be particularly important in TLSs, where T cells receive activation signals and maintain effector activity<sup>3,4</sup>. Of note, memory B cell function in lymphomas may be reversed. Entry of B cells into germinal centers is associated with acquisition of malignant features and is required for disease progression. Additionally, diffuse B cell lymphomas originate in abnormal memory B cells.

## Tumor-infiltrating B cells

Tumor-infiltrating B cells scatter within tumors or cluster in well-structured mature TLSs, which suggests different functional statuses. As an important part of TLSs in tumor tissues, clustered infiltration and the number of B cells in TLSs are positively correlated with a good prognosis in the majority of tumor patients and predicts the response of patients to immune checkpoint inhibitor (ICI) treatment<sup>2,5</sup>. However, the infiltrated but scattered B cells easily release cytokines after interacting with other cell types in the tumor to inhibit T cell activity while promoting tumor growth. These B cells also provide nutrients for tumor cells by promoting neoangiogenesis, which facilitates tumor progression.

## Controversial roles of B cells in tumor immunity

The role of B cells in tumor-associated immunity is controversial. B cells have differing roles during tumor stages. In an analysis of 69 studies, > 50% of the studies that included 19 tumor types concluded that tumor infiltration by B cells is associated with a positive prognosis compared to < 10% of studies that exhibited the opposite trend<sup>6</sup>.

### Anti-tumor activity of B cells

Anti-tumor B cell functions mainly rely on the following methods. First, B cells present anti-tumor-associated antigens (TAAs) to CD4+ and CD8+ T cells. However, the specific

underlying mechanism has not been elucidated. It was recently reported that in tumor antigen-specific B cells promote differentiation of tumor-specific CD4+ T follicular helper cells and control tumor growth in lung adenocarcinoma by secreting the cytokine, interleukin-21, thereby enhancing the CD8+ T cell response and producing granzyme B<sup>7</sup>. Second, tumor-infiltrating B cells exhibit antigen-driven clonal expansion, class switching, and affinity maturation in the cancer microenvironment to change the antigen targets and increase the inhibitory effect on cancer cells. In triple-negative breast cancer (TNBC), increased CD20+CD27+IgD- subtype-converted B cells upregulate the expression of BCR pathway molecules (FOS and JUN) and the germinal center chemokine regulator (RGS1), then activate CD69 and TNF $\alpha$  signaling *via* NF $\kappa$ B<sup>8,9</sup>. Third, tumor-infiltrating B cells promote the recuperation of tumor cells, lead to antigen uptake by Fc $\gamma$  receptors on DCs, and enhance DC presentation. In high-grade ovarian cancer, IgA produced by IgA type B cells wrap the surface of tumor cells for recognition by immune cells and coordinate control of the response between tumor, and T and B cells to antagonize ovarian cancer growth<sup>10</sup>. Patients with B cell infiltration and increased IgA had a better prognosis<sup>10</sup>. In a similar fashion, the mIgG1/BCR mutation, which is unique to Asians, enhances anti-tumor immunity and significantly prolongs colorectal cancer patient survival<sup>11</sup>. Fourth, tumor-infiltrating B cells activate complement-dependent cytotoxicity (CDC) to kill tumor cells<sup>12</sup>. A breast cancer study showed that a population of ICOSL+ B cells in TLSs after chemotherapy has an important role in anti-tumor immune responses, and the complement regulatory protein, CD55, regulates production of this cell population, which in turn determines whether tumor B cells have an immune-promoting or immunosuppressive role<sup>12</sup>. Fifth, tumor-infiltrating B cells exert anti-tumor effects mediated through antibody-dependent cellular phagocytosis (ADCP) and antibody dependent cell-mediated cytotoxicity (ADCC). Sixth, tumor-infiltrating B cells secrete IFN- $\gamma$  and IL-12 for cytotoxic immune responses, kill tumor cells *via* granzyme B and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and exert tumor-immunosuppressive effects through the tumor immune microenvironment and immunomodulation.

### Roles of B cells in tumor progression

B cell infiltration is associated with a poor prognosis in patients with renal cancer and glioblastomas, suggesting that B cells

promote tumor progression<sup>6</sup>. B cells produce IL-10, TGF- $\beta$ , IL-35, IL-21, and TNF- $\beta$ , thereby exerting a tumor-promoting effect by activating the complement cascade, differentiating into Bregs, and inhibiting CD8+ CTL and NK cell function. Moreover, B cells synthesize and secrete the neurotransmitter, GABA, which induces macrophages to secrete IL-10<sup>13</sup>. Furthermore, some antibodies produced by plasma B cells and the immune complexes formed by TAAs induce MDSC generation, which in turn inhibits anti-tumor immunity.

## B cells in TLSs and the role in tumor immunotherapy

T-cell immunoglobulin mucin-1 (TIM-1) on the surface of B cells has an important role in B cell-mediated anti-tumor immunotherapy<sup>1</sup>. In the B16F10 melanoma model, conditional knockout of other co-inhibitory molecules, such as PD-1, TIM-3, TIGIT, and LAG-3 on B cells, has little effect on tumor burden, whereas selective knockout of *Havcr1*, which encodes TIM-1, effectively inhibits tumor growth and enhances effector T cell actions. Therefore, inhibition of TIM-1 on B cells enhances the T cell response and promotes the anti-tumor immune response<sup>1</sup>. This B cell-associated anti-tumor immunotherapy has great prospects, especially for patients who have failed treatment or are resistant to T cell-specific ICIs. Furthermore, B cells and associated TLSs might also have important value in anti-tumor immunotherapy (**Table 1**).

### B cell infiltration and TLS formation

B cells also have important roles in the establishment of TLSs and anti-tumor immunity<sup>14-16</sup>. A TLS is usually composed of B cells forming the internal core, T cells wrapping the B cell region, and B and T cells forming the main structure<sup>17</sup>. The likelihood of T follicular helper (Tfh) cells among T cells is relatively high, but Th1 cells, cytotoxic CD8+ T cells, or Tregs may also be present. TLSs also contain other cell populations, such as DCs, including CD21+ FDCs, which are essential for germinal center formation and B cell affinity maturation, and CD83+ DCs (DC-LAMP+ DCs), which are mainly localized in the T cell region. Additionally, CD68+ macrophages in a TLS might have a role in clearing apoptotic cells. In addition to the above cellular components, a large number of stromal cells act similar to follicular reticular cells in secondary lymphoid tissues by anchoring TLSs to chronic inflammatory

sites. Furthermore, high endothelial venules provide a route for lymphocytes to enter a TLS<sup>17</sup>. By analyzing a large number of clinical cohort samples, it was shown that B cell infiltration and TLS formation are positively correlated to the response to immunotherapy. Specifically, immunotherapy is more effective when TLSs in tumor tissue show B cell-forming clumps<sup>14,16,18,19</sup>.

### TLS formation, maturation, and anti-tumor immunotherapy

Given that the presence of a TLS is associated with a positive prognosis for many tumors, researchers have induced the formation of TLSs by locally expressing TLS-associated cytokines or chemokines in tissues. For example, stimulator for interferon gene (STING) agonist promotes normalization of tumor blood vessels, which leads to TLS formation. Oncolytic viral therapies may have a similar role in promoting cytokines and chemokines, favoring recruitment of all participants interacting in mature TLSs with the advantage of enhancing antigen proliferation. TNF- $\alpha$  of the LIGHT family [tumor necrosis factor superfamily member 14 (TNFSF 14)] also promotes TLS formation when efficiently delivered to tumor blood vessels using vascular targeting peptides. Immune checkpoint blockade therapy also induces TLS formation in tumors. T cell genetic engineering enhances Tfh cell differentiation, leading to the production of TLSs in nearly all tumors, which is associated with a significant delay in tumor progression. These results suggest that TLS formation can be utilized as an immunotherapy strategy.

An important factor leading to TLS assembly, or at least a strategy to form TLSs, involves the differentiation of activated CD4+ T cells into Tfh cells. In an ovarian cancer model, Tfh cells produce a chemokine environment that promotes spontaneous assembly of TLSs, including secretion of LIGHT and production of IL-21, which activate B cells in response to CXCL13 produced by Tfh cells. Independent studies in pre-clinical models of colorectal cancer confirmed the critical role of Tfh cells in TLS. There may be various ways to coordinate these lymphoid structures, but the roles of CXCL13 and Tfh cells appear to be particularly important, at least in terms of germinal center formation and maintenance. The discovery and in-depth study of TLSs have led to deeper insight into anti-tumor immunity and may provide a knowledge base by which to develop new and more effective tumor immunotherapies<sup>17,20</sup>.

## Unresolved issues involving TLSs in tumors

Some urgent issues need to be resolved in the current research on TLSs. The first issue is the lack of TLS markers. Most studies have used different molecular panels to define and describe TLSs, and more efficient and simple methods are needed to evaluate TLSs. Second, our understanding of the cellular and molecular processes that drive TLS formation was derived from models of autoimmune diseases and chronic infections. An understanding of TLS formation in tumors is lacking. The third issue is how mature TLSs form. TLS development undergoes continuous stages of maturity and is divided into early, primary, and secondary, of which secondary TLSs are mature. The fourth issue is the heterogeneity of TLSs<sup>14,16,18</sup>. TLSs have significant heterogeneity within a cancer type, as well as within cancer lineages. For example, in a breast cancer study, TLSs were not detected in brain metastases. In melanoma, the maturity of the TLS varies among regions, and TLSs in germinal centers are the most mature. In a sarcoma study, TLSs were classified as early, primary, or secondary follicular TLSs because of significant heterogeneity, of which 61% were early TLSs<sup>18,19</sup>. Fifth, the TLS itself has various types. Tissue-specific expression of CXCL13 induces aggregation of B cells lacking an FDC network. Expression of TNF and CXCL12 induces a TLS with B cells mainly supplemented by a small number of T cells and DCs. CCL19 and CCL21 induce aggregates of similar composition, whereas CCL21 induces large structures<sup>17</sup>.

## Future perspectives

It is likely that analysis of tumor tissue components, especially B cells and their associated TLSs after tumor resection in patients, can be used to quantitatively predict the efficacy of further immune checkpoint therapy and develop new immunotherapies. Such biomarkers are simpler, more economical, and more feasible than analyzing the tumor cell mutation burden. Another attractive strategy is B cell activation for TLS formation and maturation. Research focusing on TLS induction *via* complex technologies, including novel biomaterials, STING, oncolytic viral therapies, TNF- $\alpha$ , immune checkpoint blockade therapy, and T cell genetic engineering, is ongoing and preclinical models have achieved promising preliminary results. Although these findings fall short of the reproducibility and robustness needed to enter mainstream cancer treatment, existing data have highlighted B cells and their roles in

TLSs and associated anti-tumor activities to facilitate clinical development of new effective treatment options.

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## Conflict of interest statement

No potential conflicts of interest are disclosed.

## Author contributions

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