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LTβR Agonist and IFN-I Cooperatively Induce Antitumor Tertiary Lymphoid Structure Formation: Mechanisms and Therapeutic Prospects

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Abstract

This review systematically explores the antitumor strategy of combining lymphoxin beta receptor agonists with type I interferons to induce tertiary lymphoid structure formation, thereby transforming “cold” tumors into “hot” tumors. The article pointed out that this combination therapy can synergistically overcome the microenvironmental barriers of “cold” tumors: LTβR agonists provide structural scaffolds for the formation of tertiary lymphoid structures by activating tumor stromal cells, especially inducing high endothelial vein generation to promote lymphocyte homing; Type I interferon, on the other hand, provides powerful immune activation signals through its downstream signaling pathway, including promoting the recruitment and activation of B cells and T cells, enhancing the function of antigen-presenting cells, and driving B cells to differentiate into follicular-like B cells. Preclinical studies have confirmed that this strategy can effectively enhance the efficacy of existing therapies such as immune checkpoint inhibitors and chimeric antigen receptor T cells, and induce durable anti-tumor immune memory in neoadjuvant therapy, showing broad clinical translation prospects.

Keywords

tertiary lymphoid structures, LTβR agonist, type I interferon, tumor immunotherapy

1. Introduction: TLS – The Central Hub of Tumor Immunotherapy

1.1 Definition and Structural Features of Tertiary Lymphoid Structures (TLS)

Tertiary lymphoid structures are highly organized ectopic aggregates of immune cells that form in non-lymphoid tissues under conditions of chronic inflammation, including infection, autoimmune disease, and cancer. They structurally and functionally mimic secondary lymphoid organs (SLOs) [1]. TLS formation is a dynamic, continuous process, initiated by the release of chemokines induced by inflammatory signals and culminating in the establishment of functional germinal centers (GCs). Their structural core is precisely composed of the following components. High endothelial venules (HEVs) are specialized vascular “entry points” for the lymphocyte-specific homing into TLS. They characteristically express addressins like PNAd, providing a directed migration pathway for CCR7+ lymphocytes, particularly naive T cells and central

memory T cells. Within the TLS, immune cells exhibit distinct spatial compartmentalization. The T-cell zone is formed by a network scaffold of stromal cells expressing CCL19 and CCL21. This chemokine environment recruits and clusters dendritic cells and naive T cells via their receptor CCR7, serving as the critical site for antigen presentation and CD8+ T cell activation. The adjacent B-cell zone is primarily orchestrated by CXCL13. This chemokine recruits CXCR5+ B cells to form follicles and induces the differentiation and maintenance of the follicular dendritic cell (FDC) network, providing survival and proliferation signals for B cells. Under persistent antigen stimulation and with help from follicular helper T (Tfh) cells, a germinal center can form within the B-cell zone. Here, B cells undergo clonal expansion, somatic hypermutation (SHM), antibody class switch recombination (CSR), and affinity maturation, ultimately differentiating into long-lived plasma cells and memory B cells capable of secreting high-affinity antibodies, thereby establishing the foundation for long-term humoral immunity [1, 2].

The maturity of TLS is directly correlated with its immune function. Mature TLS, as the subtype with the highest functional capacity, is strongly associated with favorable patient prognosis, potent anti-tumor immunity, and superior response to immune checkpoint inhibitors (ICIs).

1.2 TLS and Clinical Prognosis: One of the Strongest Immune Biomarkers

The presence and maturity of TLS correlate with better prognosis in multiple cancer types and can serve as a biomarker for immunotherapy efficacy. In cancers such as melanoma, non-small cell lung cancer, breast cancer, head and neck squamous cell carcinoma (HNSCC), and pancreatic cancer, mature (GC-containing) TLS is strongly associated with longer overall survival and enhanced response to ICIs [1, 3, 4]. Among these components, B cells are essential for coordinating the anti-tumor immune response and achieving long-term protective immunity [5].

The presence of mature TLS containing CD23+ follicular dendritic cells is associated with improved objective response rates to ICIs in various human cancers, and this association is independent of CD8+ T cell density and PD-L1 expression [6].

1.3 Deficiencies of Single-agent TLS Induction

Endogenous lymphotoxin-α1β2 (LTα1β2) signals are low in intensity, unstable, and cell-contact dependent, insufficient to drive high-intensity, rapid tissue restructuring. To address these limitations, exogenous administration of an LTβR agonistic antibody (e.g., 4H8) can directly, at high concentration, and independently of cell contact, activate the Lymphotoxin-β receptor (LTβR) on tumor stromal cells, inducing TLS and HEV formation.

LTβR signaling primarily drives the activation of stromal cells like fibroblastic reticular cells (FRCs) and the construction of tissue architecture. It provides relatively weak direct stimulation for the activation, clonal expansion, and functional differentiation of immune cells themselves, particularly B and T cells. TLS induced by LTβR agonist monotherapy exhibits defects in B cell activation, expansion, and functional maturation [5]. This deficiency suggests that while LTβR activation provides the core framework for TLS, the formation and optimization of a functional germinal center (GC) reaction within the TLS requires the synergy of a potent immune-activating signal.

1.4 TLS Neogenesis: LTβR & IFN-I Synergy Drives Inducibility, Maturity, and Anti-tumor Immunity

The neogenesis of TLS recapitulates key steps in lymphoid organ development. It begins with an inflammatory recruitment phase mediated by cytokines like type I interferon (IFN-I), followed by a tissue organization phase dependent on the LTα1β2-LTβR signaling pathway triggering stromal formation, and finally a functional phase characterized by germinal center formation and local humoral immune responses [7]. LTβR signaling provides the necessary organizational scaffold for TLS formation, while IFN-I activation confers critical immune activity to the TLS. The synergistic action of both achieves the core properties of TLS: inducibility, functional maturity, and the ability to mediate anti-tumor immune responses.

2. LTβR Signaling and IFN-I Signaling: Independent Biological Functions and Core Pathways

2.1 The LTβR Signaling Axis: The Skeletal Organizer of TLS Genesis

The LTβR (lymphotoxin-β receptor) signaling axis is a key molecular pathway regulating lymphoid organ development and TLS formation. Its activation depends on the membrane-bound ligand LTα1β2 (composed of 1 LTα and 2 LTβ subunits) or the soluble ligand LIGHT. Upon ligand binding, LTβR primarily activates the intracellular NIK/IKKα signaling module, initiating the non-canonical NF-κB (p52/RelB) transcriptional program and moderately regulating the canonical NF-κB pathway [8]. This axis primarily acts on lymphoid tissue organizer (LTo) cells, vascular endothelial cells, and stromal cells within the tumor microenvironment, inducing lymphoid stromal cells to highly express adhesion molecules like VCAM-1 and ICAM-1, and to secrete key chemokines such as CCL19, CCL21, and CXCL13. This establishes the initial framework for immune cell recruitment and retention [9]. Concurrently, this signaling directly acts on vascular endothelial cells, inducing phenotypic remodeling, upregulating marker molecules like PNAd and MAdCAM-1, thereby driving the transformation of ordinary blood vessels into high endothelial venules (HEVs) with lymphocyte-homing functionality [1].

Through the induced chemokine gradients, LTβR signaling mediates the regionalized arrangement of lymphocytes within the TLS. CXCL13 recruits CXCR5+ B cells and mature Tfh cells to form the follicular area, while CCL19/21 recruits CCR7+ CD4+ T cells, particularly naive/central memory T cells and dendritic cells, homing them to the T-cell zone. This process ultimately results in spatial segregation, forming B-cell and T-cell areas [9]. Furthermore, the CXCL13-CXCR5 axis can induce B cells and LTi cells to express LTα1β2, which binds to LTβR on stromal cells/HEVs, establishing a positive feedback loop that sustains and strengthens the expression of chemokines and adhesion molecules, accelerating TLS maturation [1, 9]. Sustained LTβR non-canonical NF-κB signaling is crucial for maintaining the follicular dendritic cell (FDC) network and stromal cell survival. This mechanism prevents the disintegration of formed TLS structures, ensuring their long-term function [9].

2.2 The IFN-I Signaling Axis: Activating TLS Function

2.2.1 JAK1/TYK2-STAT1/STAT2-IRF9-ISGF3

Type I interferons (IFN-I), primarily including IFN-α and IFN-β, are key cytokines that initiate anti-tumor innate and adaptive immunity. Their signaling is mediated by IFNAR (IFN-α/β receptor, composed of IFNAR1 and IFNAR2 subunits). Upon IFN-I binding, IFNAR activates intracellular JAK1/TYK2 kinases, leading to phosphorylation of STAT1 and STAT2, which then bind with IRF9 to form the ISGF3 transcription complex. This complex translocates to the nucleus and binds to ISRE cis-elements, initiating the expression of hundreds of interferon-stimulated genes (ISGs), including various chemokines (e.g., CXCL9, CXCL10, CXCL11) and their receptors [10, 11].

2.2.2 Tolerance Breakage, APC Activation, and Chemokine - Driven Immune Cell Recruitment

IFN-I signaling is a key driver in breaking tumor immune tolerance and reshaping the immune microenvironment of cold tumors. Its core mechanism lies in potently activating the antigen cross-presentation capacity of cDC1s through its downstream transcription factors (particularly ISGF3 and IRF family members), causing them to upregulate MHC-I and more efficiently present tumor antigens to CD8+ T cells, initiating tumor-specific cytotoxic T lymphocyte (CTL) responses [11]. IFN-I broadly enhances the maturation and function of antigen-presenting cells, not only upregulating MHC-II and co-stimulatory molecule expression but also maintaining MHC-II synthesis and antigen processing functions in intracellular vacuolar compartments, thereby enabling DCs to continuously sample and present antigens to T cells [12]. Concurrently, STAT1 homodimers strongly induce the production of chemokines CXCL9, CXCL10, and CXCL11, forming a chemotactic gradient that efficiently recruits immune cells expressing CXCR3, such as CD8+ effector T cells, into the tumor microenvironment [13]. Additionally, IFN-I acts directly on immunosuppressive cells like MDSCs and Tregs, limiting their suppressive functions, thereby promoting CD8+ T cell anti-tumor activity [11].

3. Mechanism of TLS Induction by LTβR and IFN-I Synergy

LTβR agonists and type I interferon (IFN-I) synergistically induce the formation of anti-tumor tertiary lymphoid structures (TLS) through spatiotemporal coupling, pathway crosstalk, and cellular network interactions.

3.1 Complementary Chemokine Networks and Positive Feedback Cascades in Cellular Networks

The LTβR signal is primarily responsible for promoting the structural foundation of TLSs. This includes driving the formation of the structural scaffold, inducing the differentiation of high endothelial venules (HEVs), and orchestrating the organized recruitment of T cells and B cells to their respective functional zones via chemokines like CXCL13, CCL19, and CCL21, thereby achieving initial tissue organization and compartmentalization [9]. In a lung inflammation model, IFN-I can initiate this process through two synergistic pathways. On one hand, IFN-I induces lymphocytes (particularly early-recruited T cells) to express lymphotoxin alpha (LTα), which subsequently activates LTβR on stromal cells, driving their production of the key B-cell chemoattractant CXCL13 [14]. Blocking LTβR signaling completely suppresses TLS development and CXCL13 expression, confirming the pivotal role of this pathway [14]. On the other hand, IFN-I can be directly sensed by stromal cells, independently of LTβR signaling, inducing their expression of T-cell chemokines CXCL9, CXCL10, CCL19, and CCL21. Notably, although CCL19 is expressed, its absence in this model does not affect TLS formation, suggesting functional redundancy within the chemokine network [14].

Complementing the LTβR signal, the IFN-I pathway focuses on activating and amplifying cellular immunity. It can significantly enhance the activation of antigen-presenting cells (particularly cDC1s). By upregulating chemokines like CXCL9 and CXCL10, IFN-I actively recruits effector CD8+ T cells, Th1 cells, and NK cells from the peripheral circulation or draining lymph nodes into the TLS-containing tumor microenvironment [11,15]. The IFN-I signal-promoted activation of cDC1s facilitates antigen presentation to CD4+ T cells in the T-cell zone, inducing their differentiation into CXCR5+ T follicular helper (Tfh) cells. These Tfh cells migrate along the CXCL13 gradient towards the T-B border and into the B-cell follicles [3].

In the early stages of TLS formation, IFN-I not only creates the necessary inflammatory conditions within an immunosuppressive microenvironment, but the effector T cells it recruits can also upregulate the expression of LTα1β2 upon antigen stimulation [16]. This LTα1β2 can feedback onto LTβR on stromal cells, thereby further consolidating and amplifying the local chemokine gradient. Concurrently, the mature HEVs constructed by LTβR signaling provide an efficient portal for the various immune cells recruited by IFN-I to enter the tissue site [2].

These two signaling pathways exhibit a synergistic effect, jointly amplifying the expression of chemokines and adhesion molecules. The ultimate outcome of this multi-layered collaboration is the sustained recruitment of lymphocytes, the orderly arrangement of T-cell and B-cell zones, the full maturation of functional HEVs, and the refinement of the germinal center (GC) reaction mediated by Tfh cells and B cells. Consequently, scattered immune cell aggregates are transformed into mature TLSs possessing complete lymphoid organ structure and potent anti-tumor activity, achieving a high degree of coupling between the core processes of structural construction and immune activation.

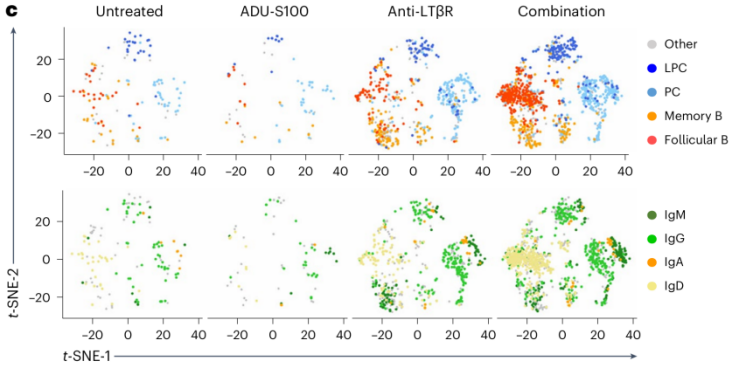
Furthermore, low concentrations of IFN produced in response to TNF are sufficient to increase STAT1 expression, thereby priming immune cells like macrophages to exhibit enhanced responsiveness to subsequent IFN-I signals during early infection [10]. This priming mechanism may also be applicable to the initial phase of TLS formation, where IFN-I in the microenvironment can increase the sensitivity of resident immune cells to subsequent activation signals.

3.2 STING/LTβR Combination Drives B-cell Maturation in TLS

STING (stimulator of interferon genes) agonists bind to the STING protein and activate downstream signaling pathways, ultimately promoting the nuclear translocation of interferon regulatory factor 3 (IRF3), thereby inducing the robust production of type I interferons. As shown in Figure 1, mouse experiments with a STING agonist (ADU-S100) confirmed that the combination of an LTβR activator and IFN-I can promote

the differentiation of memory B cells towards a follicular B-cell-like phenotype. In Figure 1 (top panel), t-SNE visualization shows the abundance of intratumoral B cell subsets across four treatment groups (untreated, ADU-S100, Anti-LTβR, combination therapy). The combination therapy group exhibited a significant increase in follicular B cells, memory B cells, and plasma cells, forming dense, well-defined cell clusters—a hallmark of TLS. In contrast, B cell populations in the monotherapy groups were sparse and dispersed, indicating incomplete TLS induction. Figure 1 (bottom panel) further demonstrates enrichment of IgG produced by plasma cells and IgD involved in maintaining follicular B cell homeostasis in the combination therapy group [2]. This shift towards class-switched, high-affinity antibodies is a key functional output of the germinal center reaction, strongly suggesting that combined activation drives the functional maturation of B cells within the TLS.

Figure 1: Synergistic induction of B cell subsets and immunoglobulin class switch by combined STING and LTβR activation [2].



4. Anti-tumor Immune Effects of Synergistically Induced TLS: From Local Activation to Systemic Response

4.1 In Situ Immune Activation: Tumor-specific T/B Cell Clonal Expansion and Killing

As an immune fortress within the tumor, the core function of a TLS is to achieve in situ antigen presentation and efficient lymphocyte activation [2]. In mature TLSs induced by the synergistic action of an LTβR agonist and IFN-I, CXCL13+ follicular dendritic cells (FDCs) and CD11c+ dendritic cells (DCs) capture tumor antigens. With the assistance of cytokines like IL-6 and IL-12, they activate CD4+ T cells to differentiate into CXCR5+Bcl6+ T follicular helper (Tfh) cells [17]. Tfh cells interact with B cells through CD40L-CD40 signaling, driving the germinal center (GC) reaction, manifested by high Ki-67 expression in B cells, activation-induced cytidine deaminase (AID)-mediated somatic hypermutation (SHM), and antibody class switching (from IgM to IgG) [18]. Simultaneously, CD8+ T cells activated in the T-cell zone of the TLS receive co-stimulatory signals, differentiating into effector cells (Teff) that highly express granzyme B (GZMB) and perforin, which directly infiltrate the tumor parenchyma to execute killing [18]. Single-cell sequencing has confirmed that the clonal diversity of T cells within TLSs is significantly higher than in the periphery, and TCR sequences show a high match with tumor neoantigens, proving tumor-specific clonal expansion [19].

4.2 Immune Memory Formation: Long-lasting Anti-tumor Immunity and Prevention of Recurrence

In mouse models of pancreatic cancer (KPC) and breast cancer (Py230), an experimental design involving initial combination therapy (to induce TLS formation), followed by surgical resection of the primary tumor, and finally tumor re-challenge in mice, simulated the clinical scenario of post-operative prevention of recurrence [2, 4]. Mice receiving the combination neoadjuvant therapy exhibited 100% long-term survival, with re-inoculated tumor growth completely inhibited or regressed, indicating the mice developed robust, durable anti-tumor immune memory [4]. Tumor growth was also significantly inhibited in naive recipient mice receiving serum from donors that underwent combination therapy, demonstrating that humoral immune memory can provide protection via passive antibody transfer [4].

4.3 Tumor Microenvironment Remodeling

The synergistic strategy achieves comprehensive remodeling of the TME through TLS formation. The LTβR signal acts directly on endothelial cells, inducing the differentiation of high endothelial venules (HEVs, MECA-79+), which replace the original leaky tumor vasculature, significantly improving the infiltration efficiency of lymphocytes (especially naive lymphocytes) [20]. The IFN-γ and TNF-α enriched within TLSs inhibit the expansion of myeloid-derived suppressor cells (MDSCs) and impair the suppressive function of regulatory T cells (Tregs) [15]. Tumors that were originally "immune-desert" or "immune-excluded" and lacked T-cell infiltration are transformed into "immune-hot" tumors rich in CD8+ T cells, B cells, and DCs following TLS formation. This transformation occurs concurrently with the upregulation of PD-L1 expression, creating conditions for subsequent immune checkpoint blockade (ICB) therapy [21].

5. Preclinical Models and Translational Evidence

In models of pancreatic ductal adenocarcinoma (PDAC), melanoma (B16-OVA), colorectal cancer (MC38), and breast cancer, combination therapy with an LTβR agonist (e.g., C91) and IFN-I (or a STING agonist as an IFN-I inducer) has demonstrated potent anti-tumor activity superior to monotherapies. In the KPC pancreatic cancer model, monotherapy with either LTβR agonist or IFN-I only slightly delayed tumor growth, whereas the combination therapy induced widespread TLS formation and led to tumor regression [2].

6. Future Perspectives

6.1 Golden Combinations for Combination Therapy

Based on the function of TLSs as niches for maintaining T cell stemness, the combination of an LTβR agonist + IFN-I + PD-1/PD-L1 inhibitor is considered a powerful triple therapy. The induced TLS provides a supportive microenvironment for T cells, particularly TCF1-expressing precursor exhausted T cells (Texprog) with stem-like properties. This helps maintain their stemness and prevents their differentiation into terminally exhausted T cells (Texterm) with irreversible functional impairment. This population serves as a key reservoir capable of proliferating and differentiating into effector cells following PD-1 blockade [2, 22]. Additionally, LTβR + IFN-I + cancer vaccine/oncolytic virus can strengthen antigen supply [23]; LTβR + IFN-I + CAR-T leverages the homing properties of TLSs: HEVs can significantly promote CAR-T cell infiltration into the tumor parenchyma, and concentration gradients of chemokines like CXCL13 facilitate efficient infiltration of CAR-T cells engineered to overexpress corresponding chemokine receptors (e.g., CXCR5) [2, 24]. The supportive microenvironment within the TLS, composed of activated APCs, Tfh-type cytokines (e.g., IL-21), and antibodies produced by B cells, provides co-stimulation for CAR-T cells, prevents exhaustion, and may generate synergistic anti-tumor effects through mechanisms like antibody-dependent cellular cytotoxicity (ADCC) and epitope spreading [1, 5].

6.2 Innovations in Delivery Technology

To overcome the challenges of the short half-life and systemic toxicity of IFN-I, novel delivery systems such as thermosensitive hydrogels, lipid nanoparticles (LNPs), and biodegradable scaffolds are being developed for intratumoral, localized release [25]. These systems can confine IFN-α/β or STING agonists to the tumor site, enabling sustained, low-dose release to mimic chronic inflammatory signals (beneficial for TLS initiation) while avoiding the immunosuppression or toxicity associated with acute inflammation, effectively preventing systemic cytokine storms [25]. Combined with agonistic antibodies targeting LTβR, these approaches hold promise for achieving safe and effective TLS-inducing therapies in the clinic.

7. Conclusions

LTβR agonist with IFN-I can synergistically induce the formation of functional tertiary lymphoid structures (TLS). The LTβR signaling pathway mainly constructs the physical framework of TLS, for example, driving the formation of high endothelial venules; while the IFN-I signaling pathway provides critical immune activation signals. Together, they can effectively convert cold tumors into hot tumors,

showing better anti-tumor effects than single therapy in preclinical models and enhancing the efficacy of existing immunotherapies.

This study clarifies the synergistic mechanism of two core pathways in TLS generation: structural construction and functional activation. The LTβR pathway is responsible for the initial formation and maintenance of tissue structure, while the IFN-I pathway drives the activation and recruitment of immune cells. They enhance each other through positive feedback loops, providing an integrated theoretical framework for understanding the dynamic generation of in-situ tumor immune structures. This strategy offers a new direction for improving the response to solid tumor immunotherapy. It has two main application pathways: first, as a sensitizer for therapies such as immune checkpoint inhibitors, to improve treatment response rates by remodeling the tumor immune microenvironment; second, for neoadjuvant/adjuvant therapy, aiming to induce long-term immune memory and reduce the risk of recurrence. In addition, the maturity of TLS can serve as a potential biomarker for predicting the efficacy of immunotherapy.

Future research will focus on exploring its optimized combinations with existing therapies, such as combining with PD-1 inhibitors, cancer vaccines, or CAR-T cell therapies, to achieve synergistic effects. At the same time, developing novel technologies that enable local and sustained drug delivery is key to overcoming the systemic toxicity of cytokines and promoting their clinical translation.

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