Iranian Journal of Basic Medical Sciences
ijbms.mums.ac.ir

Phenotypic alterations in the immune system and tolerance induction in tumor-draining lymph nodes

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ARTICLE INFO

Article type:
Review

Article history:
Received: Aug 12, 2025
Accepted: Dec 9, 2025

Keywords:
Cellular reprogramming
Immune tolerance
Neoplasm metastasis
Sentinel lymph nodes
Tumor microenvironment

ABSTRACT

The cause of 90% of all cancer-related fatalities is metastasis. There are two main pathways for the spread of cancer cells: the blood and lymphatic systems. The underlying mechanism of lymphatic metastasis has been well established. However, our understanding of the molecular basis of lymphatic metastasis is still incomplete. Conceptually, cancer cells invade lymphatic vessels (LVs), passively disseminate towards lymphatic nodes, migrate to sentinel lymphatic nodes (SLNs; the first LNs to which cancer cells spread from the primary tumor), and then enter the bloodstream. Before arrival, cancer cells release specific soluble factors that modulate the SLN microenvironment, creating an immunosuppressive environment. After colonization, cancer cells suppress anti-tumor immunity by stimulating regulatory T cells, inhibiting dendritic cell and CD8+ T cell function, and promoting the release of immunosuppressive cytokines. SLNs serve as a microanatomical site for metastasis and play a crucial role in immune modulation. Developing new strategies to reverse tumor-induced remodeling of SLNs may reactivate immunity and reduce accumulation and metastasis. This review discusses the immunological changes induced by tumors in tumor-draining LNs (TDLNs). We also explore their reciprocal relationship and their impact on metastasis and LN immunity, demonstrating how a proper understanding of events occurring in TDLNs can create new opportunities for cancer immunotherapy.

▶ Please cite this article as:
Koohini Z, Karimi Kakh M, Rajabian Z, Koohini Z. Phenotypic alterations in the immune system and tolerance induction in tumor-draining Lymph nodes. Iran J Basic Med Sci 2026; 29:

Introduction

The lymphatic system, comprising lymphatic vessels (LVs) and lymph nodes (LNs), plays a crucial role in immune responses by facilitating the delivery of antigens and antigen-presenting cells to draining LNs. This system controls immune responses through pathways such as promoting antigen/DC trafficking through afferent LVs, displaying antigens in LN sinuses through lymphatic endothelial and LN stromal cells, and directing lymphocyte exit through efferent lymphatic pathways (1). The lymphatic system is crucial in clinical settings, and solid tumors often involve it. Tumor cells use afferent LVs to reach sentinel lymphatic nodes (SLNs), supporting invasion and metastasis. SLNs are the first sites of metastatic spread and are part of tumor-draining basins that are at risk of metastatic seeding (2). Tumor materials, including antigens and extracellular vesicles, are transported to tumor-draining lymph nodes (TDLNs) via afferent lymphatics. Stromal remodeling processes begin, affecting the structural changes and metastatic potential of TDLNs. Three fundamental events occur (Figure 1): extensive lymphangiogenesis, which expands lymphatic sinuses; dilation and differentiation of high endothelial venules (HEVs); and proliferation of fibroblastic reticular cells (FRCs), which disrupts antigen delivery to the paracortex LN. These processes contribute to early metastatic progression in the region (3). LNs can recruit lymphocytes for an immune response against tumors, acting as secondary lymphoid tissues and immune foci. However, they can also support immunosuppressive mechanisms and provide a favorable environment for cancer cell metastasis. This review focuses on the immunological changes induced by tumors in TDLN, their impact on metastasis and LN immunity, and how understanding these events can create new opportunities for cancer immunotherapy.

Migration of tumor cells to TDLN and formation of primary immune responses

Most human metastases of carcinoma and melanoma occur through the lymphatic system (4). The interaction between tumor cells, Extra cellular matrix (ECM), Tumor Associated Neutrophils (TANs), Tumor-associated macrophages (TAMs), and Cancer-associated fibroblasts (CAFs) triggers the secretion of vascular endothelial growth factors C and D, which mediate lymphangiogenesis, facilitating the migration of new vascular vesicles around the primary tumor and facilitating lymphatic spread due to the absence of a basement membrane in vascular vesicles (5).

Tumor cells can reach the SLN via blood vessels or LVs.

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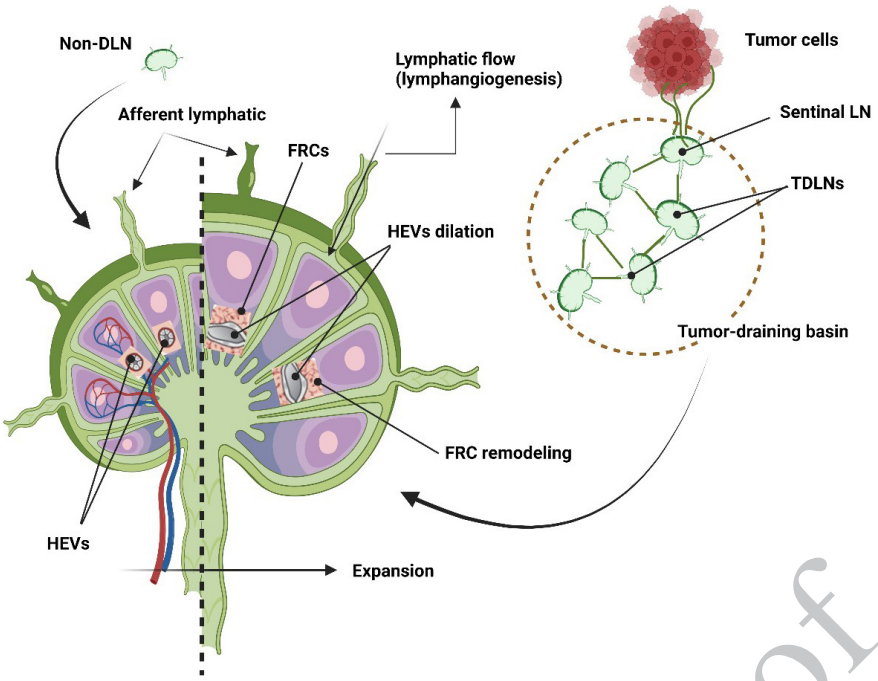

Figure 1. The tumor affects the LN through a network of LVs, which carry fluid, substances, lipids, and cells
The sentinel LN, located in a basin of TDLN susceptible to metastatic seeding, drains the LN. Tumor-derived material, like antigens and extracellular vesicles, is transported by afferent lymph. TDLNs enlarge and initiate stromal remodeling processes like lymphangiogenesis, HEV dilatation, and FRC proliferation, impacting TDLN structure and metastatic potential
LN: lymph nodes; LVs: lymphatic vessels; TDLN: tumor-draining LNs

The pattern via blood vessel migration is similar to that of leukocytes via HEVs and selectins. Migration via LV, which is more common, is mediated by the chemokine pathways CCR7 and CCR10, as well as the ligands CCL12 and CCL27 on tumor cells (6). Tumor cells can migrate toward the SLN individually or collectively, thereby forming micrometastases in the TDLN. These small clusters can remain dormant for years before transforming into overt and active metastases over time (Figure 2a) (7).

The LN is a crucial part of the lymphatic system, containing lymph that enters via afferent lymphatics, is filtered, and then exits via efferent lymphatics. It is divided into three regions: cortex, paracortex, and medulla. The cortex contains B cells and a follicular mantle, while the paracortex is filled with APCs and NK cells. The medulla is composed of sinuses and LVs that drain the LN (Figure 2b)

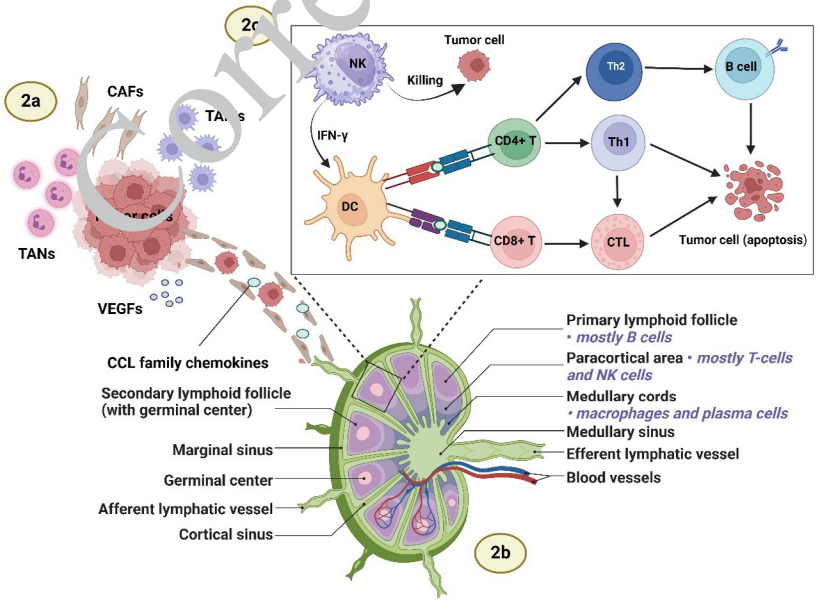

Figure 2. Migration of tumor cells to the TDLN and formation of primary immune responses
The tumor microenvironment, comprising tumor cells, extracellular matrix, TANs, TAMs, and CAFs, under the influence of hypoxia, acidosis, and nutrient deprivation, releases VEGFC and VEGFD, promoting lymphatic capillary growth. Chemokine receptors and attractants enable tumor cells to traverse lymphatic pathways (2a). Lymphatic lobules are divided into the cortex, paracortex, and medulla, with the cortex containing germinal centers and B-cells, and the paracortex containing antigen-presenting cells and T cells (2b). TAA can trigger anti-tumor immune responses, with tumor-infiltrating DCs transporting it to the TDLN. Activated NK cells kill tumor cells and secrete cytokines. TAA is then presented to naïve T cells, which differentiate into Th cells or CTL, causing cancer cell death (2c). TDLN: tumor-draining LNs; TANs: tumor associated neutrophils; TAMs: tumor-associated macrophages; CAFs: Cancer-associated fibroblasts; TAA: tumor-associated antigens; DCs: dendritic cells; CTL: cytotoxic T-Lymphocyte

(8). Tumor-associated antigens (TAAs) can trigger an anti-tumor immune response in TDLNs through three pathways. The first involves dendritic cells (DCs) capturing TAAs and activating naïve T cells. The second involves DCs infiltrating the tumor site, capturing TAAs at the primary site, and migrating to TDLNs to activate naïve T cells. The third pathway involves tumor cells directly presenting antigens to naïve T cells in TDLNs. NK cells, activated upon cancer cell arrival, kill tumor cells using perforins and secrete immune-stimulating cytokines like IFN-γ. TAAs are presented to naïve T cells in TDLNs, thereby activating CD4+ naïve T cells. Th2 cells induce cancer cell death through B cell-mediated mechanisms, while Th1 cells directly mediate cancer cell death (Figure 2c) (3, 9).

Gradual suppression of immune responses in TDLN

In examining immune cell phenotypic changes in TDLN, the observed alterations are more consistent with immune tolerance than with classical cellular exhaustion. In T cell exhaustion, typically arising from chronic antigen stimulation, is characterized by upregulation of canonical inhibitory receptors such as Programmed Cell Death Protein 1 (PD-1), T-cell Immunoglobulin and Mucin-domain containing protein 3 (TIM-3), Cytotoxic T-Lymphocyte Associated protein 4 (CTLA-4), and Lymphocyte-Activation Gene 3 (LAG-3), accompanied by metabolic deficits including reduced ATP levels, mitochondrial potential, and NADH/NAD^+ ratio (10). In contrast, microenvironment-induced immune tolerance can occur without significant energetic compromise and is often reflected in phenotypic reprogramming, expansion of regulatory B and T regulatory cells, tolerogenic dendritic cell profiles, and suppression of immunostimulatory cytokines such as IFN-γ and TNF-α (11). Consequently, the diminished antigen-presentation capacity or effector cytokine secretion observed in TDLN likely reflects active environmental modulation that promotes tolerance, rather than passive cellular fatigue.

Solid tumors often result in early lymphatic involvement in nonlymphoid tissues, which is often associated with a poor prognosis. Structural changes in the LN, as described above (Figure 1), can disrupt immune-cell function and significantly impair immune surveillance through dysfunctional immune responses (Table 1). Lymphatic factors transported from the tumor to the TDLN also appear to create a microenvironment that supports metastasis, immunosuppression, and immune tolerance.

Affecting T cells and DCs under TDNL microenvironment

SLN seems to be the first site for presenting TAAs. TAAs include soluble proteins or those trapped in exosomes secreted by tumor cells (12). The absence of immune responses in both mouse models and human tumors is attributed to the presence of CD8+ T-cell effector cells throughout tumor development. For instance, bladder cancer patients with involved LNs have higher percentages of IFN-γ/IL-17 double-positive CD8+ lymphocytes. However, the absence of an immune response can be attributed to reduced antigen-presenting mechanisms and active immune suppression (13). A study suggests that LN involvement may be due to decreased IFN-γ production and increased IL-4 production in CD8+ T-cell subsets (14). It has been reported that antigen-specific CD4+ T cells in TDLN become anergic as the tumor grows, and along with this occasion, CD8+ T cells become tolerant, and both T-cell types exhibit an increased rate of apoptosis in breast tumors, melanoma, hepatocellular carcinoma (HCC), and colorectal cancer (CRC) (15-19).

Ineffective T-cell activation in TDLNs can be linked to the presence of immature DCs, which play a crucial role in tolerance and suppression. In mouse tumors, immature DCs reduce T-cell priming and promote tumor immune escape by producing and secreting prostaglandin E2 (PGE2) and transforming growth factor-beta (TGF-β) (3). Resident and plasmacytoid DCs are found in human breast and gastrointestinal tumors, where they lose maturity

Table 1. An overview of the role of primary immune cells in tumor-draining LNs (TDLNs)

Cell type	Cell change in TDLN	Examples of tumor types	The role in tumor		Ref.
			Pro-Tumorigenic	Anti-Tumorigenic	21, 22, 26
Dendritic cells	Increased dendritic cell dysfunction	Melanoma Breast Carcinoma	Decrease of CD80, CD86 and CD40 Reduction in the uptake, processing, and presentation of antigen	Effective antitumor function in the absence of morphological and functional changes	15-19
CD8+ T cells	Impaired CD8+ T cells (number, function, proliferation)	Colorectal Carcinoma Hepatocellular Carcinoma Melanoma Breast Carcinoma	Functional impairment with increased inhibitory receptor expression and reduced granzyme secretion, tissue memory phenotype, and a reduction in the number associated with lower OS	Ag identification, proliferation, and increase in their number are associated with higher OS	27-30
Treg cells	Accumulation of FOXP3+ T cells	Colorectal Carcinoma Hepatocellular Carcinoma Breast Carcinoma	Suppression of effector T-cell proliferation and proinflammatory cytokine production, High expression of perforin and granzyme, increased invasion, migration, and survival of tumor cells, and Induction of T-regulatory phenotype. In some studies, an increase in their number is associated with a decrease in OS	Subset CD4+CD25-Foxp3+ with lower suppressive activity and higher effector properties (production of more IL-2 and IFN-γ)	38, 39, 41-44
NK cells	Altered phenotype and function	Breast Carcinoma Melanoma	Reduced penetration, acquisition of inhibitory phenotype, and decrease in toxicity function, degranulation, and cytokine production	Strong anti-tumor and anti-metastatic ability in case of active phenotype, and A higher frequency is associated with a better prognosis	49-51, 55, 58-60, 62-64
B lymphocytes	Altered phenotype and function	Breast Carcinoma Melanoma Pancreatic cancer HNSCC	Breg: Suppression of other effective immune cells in TME with regulatory function	Antibody production, antigen presentation, and direct tumor cell killing	

markers such as CD40, CD86, and CD83 and decrease production of inflammatory and stimulatory cytokines. In premetastatic SLNs, there is a marked decrease in CD8+ T cells and cytokine production. In contrast, an increase in immature myeloid cells with the phenotype Lin− HLA-DR− CD11b+ CD33+ and regulatory T cells (Tregs) is observed (19). Indoleamine 2,3-dioxygenase (IDO) is a key factor in the development of ineffective DCs in TDLNs, as it induces and expands immature DCs and functions as an immunosuppressive molecule (20). A DC subset of mice, characterized by the CD11C+ B220+ CD19+ phenotype, inhibits T-cell expansion by producing and secreting IDO (21). In melanoma patients, IDO is significantly increased in SLNs compared to NDLNs and is associated with poor patient survival (22). The data suggest a shift towards immune tolerance to TAAs in the SLN, limiting cytotoxic responses, and, due to lower HEV density in the TDLN, fewer naïve lymphocytes are recruited, reducing tumor immune efficacy.

The peripheral tolerance mechanism, a tumor escape strategy, is less researched than immune exhaustion. It involves inhibiting the innate immune system, which can occur in small, non-inflamed, non-necrotic, and low-mutation burden tumors, unlike immune exhaustion (23). In some tumors, peripheral tolerance can be induced, allowing tumor cells to evade immune responses, as observed in specific mouse models in which tumors structurally induce tolerance to tumor-derived antigens within TDLNs (24). Tolerance in TDLNs arises when apoptotic tumor debris releases neoantigens, which are captured by DCs and presented to CD8+ T cells in the LN. These DCs, tolerogenic DCs, modulate T-cell responses. Tolerogenic DCs interact with CD8+ T cells in TDLNs via TCR/MHC, CTLA-4/CD80, and PD-1/PD-L1 interactions, thereby inducing peripheral tolerance in certain tumors. TIM-3 also plays immunoregulatory roles in the Tumor microenvironment (TME) (25). A study found that the frequency of TIM-3+CD8+ T cells is linked to higher tumor grade and a higher mean fluorescence intensity (MFI) in patients with more than nine involved LNs. The MFI of TIM-3 in CD4+ T cells also correlates with the number of metastatic LNs. TIM-3 is expressed by CD4+, CD8+, and regulatory T cells in breast tissue-derived LNs, with expression on CD4+ and CD8+ T cells mainly associated with poor prognosticators such as the greater number of nodes (26). The study suggests that immune checkpoint blockers may be a suitable therapeutic option for patients with lymph node involvement or higher tumor grade. However, there is no conclusive evidence to confirm this occurrence (Figure 3).

Treg accumulation in TDLN

The immune response to tumors is influenced by immune tolerance, localized accumulation of suppressive myeloid cells, and their production of inhibitory cytokines. Current studies focus on Treg cells in the Intratumoral lymph node (ITLN) and the increased tumor burden, which leads to an increased accumulation of Treg cells in TDLNs (27). Reducing Treg cells in LNs in an inducible melanoma genesis mouse model enhances primary tumor control in the skin (28). Breast cancer patients show higher Treg cell frequencies in metastatic LNs than in non-metastatic LNs, exhibiting a Th1-like phenotype (T-bet high, GATA3 low) with high expression of immune checkpoint molecules, suggesting a suppressive function (27). A subset of CD4+Bcl6+CXCR5 high lymphocytes in breast cancer patients is Foxp3-positive (Forkhead Box P3). These cells, known as follicular regulatory (TFR) cells, are crucial for controlling follicular helper T cells (Tfh) cells, germinal center (GC) responses, and autoantibody production. However, their frequency remains consistent with tumor cell metastasis and progression. Another subgroup of Treg cells with a CD4+Foxp3+ CD127neg/low phenotype, constitutes a significant percentage of CD4+Foxp3+ T cells in the TDLN. The origin and function of these cells remain unclear; they are identified as either inactive Treg cells or active effector T cells that transiently express Foxp3 (29). On the other hand, a subset of T cells with the CD4+CD25-Foxp3+ phenotype was identified in the TDLNs of patients with breast and CRC. This subset produced IL-10 at higher levels than IL-2 and IFN-γ, but exhibited less suppressive and greater effector properties (30).

Treg cells suppress cytotoxic T-cell expansion and reduce cytotoxic activity by secreting TGF-β. Reduction of Treg cells leads to increased IFN-γ production by CD8+ T cells (31).

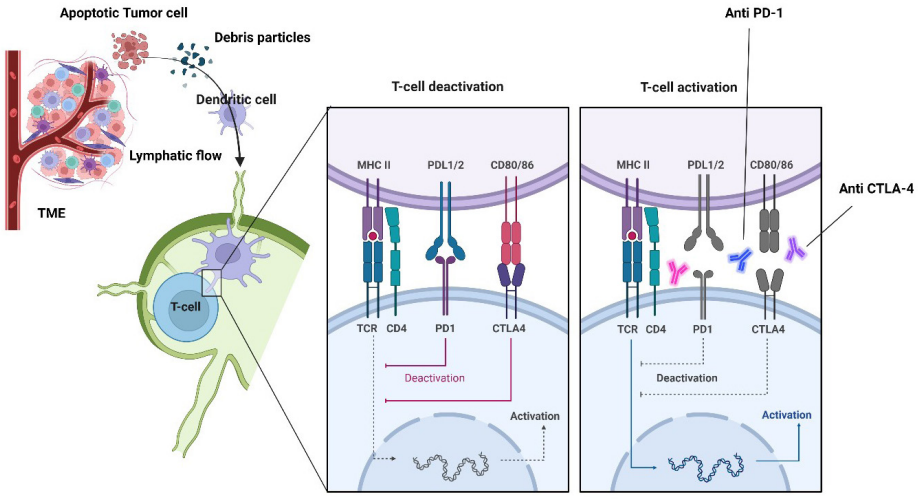

Figure 3. Environmental tolerance to tumor antigens
Tumors release cellular debris containing tumor neoantigens, which DCs can take up for presentation to naïve CD8+ T cells in the TDLN. In some tumors, tumor antigen presentation is tolerogenic due to insufficient immune activation or tumors modulating the LN environment. Checkpoint blockade with a-PD-1 or a-CTLA-4 can disrupt this tolerance process. DCs: dendritic cells; TDLN: tumor-draining LNs; CTL: cytotoxic T-Lymphocyte

Treg cell reduction restores LN structure, expands the T-cell zone, increases CCL21 expression, and promotes distinct HEVs throughout the LN, in addition to their direct effects on cytotoxic lymphocytes (32). Treg cells, more prevalent in individuals with involved LNs, may inhibit antitumor immune responses in the draining LNs, supporting the theory that LN Tregs disrupt immune surveillance, promoting tumor development and immune escape (33). It remains unclear which factors drive the accumulation of Treg cells in TDLNs. However, the accumulation of Treg cells in TDLNs appears to be influenced by antigen recognition and the cytokine environment. TGF-β plays a key role in the generation of suppressor Treg populations, as activation of naive CD4+ T cells in the presence of TGF-β induces FOXP3 expression and generates cells capable of suppressing the expansion of specific CD4+ T-cell subsets (34).

As found, Th2 and Treg cells are crucial in the development and maintenance of a suppressive TME, promoting tolerance and disease progression in LNs involved in metastasis. Activated lymphocyte subsets determine host-tumor interactions during anti-cancer responses; during tumor cell metastasis, immune responses shift from inflammatory to inhibitory, with cytokines such as IL-17 and IFN-γ decreasing.

Affecting NK cells in the TDLN microenvironment

NK cells are crucial for cytotoxic anti-tumor responses, which trigger robust IFN-γ production and secretion. They differentiate in the bone marrow and constitute 5–15% of peripheral blood cells. These innate immune cells are involved in immune surveillance and can initiate anti-tumor responses without TAA recognition, allowing for faster responses against tumors. Their activity depends on balancing activating and inhibitory receptors on their surface (35).

NK cells can infiltrate tumors, as evidenced by studies on breast cancer patients' TDLN. NK cells express the chemokine receptors CXCR3 and CD62L, suggesting that NK cell activation precedes tumor cell invasion (36). Increased blood flow and lymphangiogenesis may activate DCs, which, in turn, help attract NK cells via CXCR3 before tumor cell invasion (37). CXCL9 and CXCL10, ligands for CXCR3, have been detected in breast cancer tumors, suggesting that infiltrating NK cells traffic to LNs. These TDLN NK cells may activate resident LN NK cells, thereby improving control of tumor growth and metastasis. This study on breast cancer showed that the presence of infiltrating NK cells inhibits metastasis to multiple organs, while reducing or suppressing their number accelerates metastasis (38). Consistent with this, a study of melanoma patients found that the expression of activating receptors on TDLN NK cells negatively affects the percentage of tumor cells (39).

However, tumor cells can induce phenotypic and functional changes in NK cells, including decreased numbers, cytotoxicity, and tumor-penetrating ability, in patients with head and neck squamous cell carcinoma (HNSCC) (40). Phenotypic changes in NK cells in breast cancer are often associated with decreased levels of NKG2D and NCR activating receptors, which, together with impaired infiltrative NK function, hinder NK cells' ability to mount an effective anti-tumor response (41). The number of dysfunctional NK cells in breast cancer increases with tumor grade, possibly due to decreased tumor suppressive capacity and breakdown of cytotoxic activity (42). As the percentage of infiltrating cells increases in melanoma, NK-cell degranulation decreases (43). Tumor cells can cause defects in NK cell signaling pathways, including changes in the Jak/STAT pathway and reduced expression of Interferon-regulating transcription factor-1 (IRF1) and DNAX-activating protein of 10 KDa (DAP10), which are frequently observed in metastatic melanoma (44). IRF1 regulates IL-15 expression in stromal brain marrow cells, crucial for NK cell growth. DAP10, an adapter protein associated with the NKG2D receptor, initiates target-cell killing via NKG2D (45).

Effective B cells and regulatory B cells (Bregs) in TDLN

The host immune system plays a crucial role in successful anti-tumor function, with T and B lymphocytes being the most infiltrating cells. T cells have been extensively studied, and immunotherapy strategies based on them have gained attention. However, B cells have gained greater attention as viable T-cell replacements, as they can serve as effective treatments (46). T helper cells activate effective B cells during tumor challenge, thereby mediating humoral immune responses. B cells rapidly expand and express immunoglobulin genes in TDLNs (47). Generally, the function of effective B cells can be divided into four categories: 1) antibody production, 2) direct killing of cells, 3) suppressive functions, and 4) antigen presentation and cytokine production.

The effects of antibodies on tumors are dual and can vary widely depending on tumor type. IgG1 and IgG3 isotypes act strongly in antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP) and are closely associated with overall survival (OS) in melanoma patients with high titers (48). The pre-tumorous role of antibodies in tumors may be attributed to IgG4 and IgA isotypes. IgG4 acts very weakly in CDC, ADCC, and ADCP (49, 50). Additionally, IgA not only does not induce cell death but also supports Th2 responses (50). Furthermore, in tumors with low antigenic burden, such as pancreatic tumors, antibodies accumulate in complexes with antigens in TDLNs and are better captured and presented by DCs. This enhances the initiation of anti-tumor responses, as DCs alone are much more effective at capturing antigen-antibody complexes than antigens alone (51).

It has been reported that effector and Breg cells are present in the tumor microenvironment; however, there are mixed reports on how B cells contribute to tumor growth and how they counteract it. For example, in fibrosarcoma, removing B cells accelerates tumor growth (52), whereas in mice with tumors, CD8+ T cells that produce IFN-γ accumulate in the TDLN, and advanced colorectal tumors are better controlled (53). It has been reported that IgA+ IL-10+ PDL1+ plasma cells appear to function as regulatory cells that suppress T cells in prostate cancer (54). Additionally, tumor metastasis in breast cancer alters B cell populations toward resting, inactive, and unchanged phenotypes, and lymphatic involvement may increase the subset of Breg cells in non-metastatic LNs (55).

Another aspect of B-cell function in anti-tumor immunity is direct cellular killing. B cells can directly kill tumor cells expressing Fas by producing granzyme B (GZMB) or by expressing Fas ligand (FasL) (56), but these functions can

also contribute to tumorigenesis. Breg cells expressing Fas can destroy Fas-expressing T cells (57). It has been reported that melanoma and lung metastasis mouse models derived from breast cancer have higher numbers of Breg cells in TDLNs than in non-draining LNs (NDLN), which suppress effector T cells or induce Treg cells by producing suppressive cytokines, including IL-10, IL-35, IL-4, and TGF-β (58). In a conflicting report, the abundance of Breg cells in the TDLNs of patients with HNSCC is significantly associated with a favorable prognosis (59). The study suggests that breast cancer patients with abundant GAMB+ B cells in their TDLN have Breg cells that contribute to tumor cell killing. Still, these cells are not significantly associated with prognostic factors (60).

B cells can express MHC and CD80/CD86 in TDLNs, acting as antigen-presenting cells, a process that is crucial in tumors such as non-small cell lung cancer (NSCLC), which have low numbers of DC cells (61). In this regard, it has been reported that B cells in the TDLN of melanoma patients activate anti-tumor responses via CD4+ T cells (62). A study of breast tumor TDLNs found that high TNF-α expression (TNF-αhi) B cells were negatively correlated with LN involvement and HER2 expression, and that their frequency was negatively correlated with LN involvement. The frequency of TNF-αhi B cells also showed an inverse correlation with the frequency of FoxP3+ Tregs, which was associated with poor prognostic indicators. This highlights the importance of cytokine-producing B cells in antitumor immunity (63). Overall, the data on these topics suggest that B cells with antitumor response capabilities undergo functional changes, depending on the tumor type, and may also shift toward a regulatory phenotype that could support tumor progression. Among the contributing factors are hypoxia and the effect of Hif-1α on B cell function, acidosis caused by increased lactic acid and increased production of IL-10 by B cells, oxidative stress, cytokines including IL-10, IL-35, and TGF-β, and growth factors, as well as interactions with other cells. For example, in the co-culture of TDLN-derived B cells with Adipose-derived stem cells (ASC) isolated from the breast fat of normal women (nASCs) or women with breast cancer (cASCs), it was shown that cASCs can shift the cytokine production profile of B cells towards IL-10 production and induce a regulatory phenotype of B cells (64). Interpreting these results requires answering the question of which type of B cell is dominant in controlling the tumor: anti-tumor B cells or regulatory B cells? It seems that if the balance between regulatory and stimulatory B cells shifts toward regulatory B cells, the number of involved LNs will be higher, and the cancer will be associated with a worse prognosis (65).

Changes in stromal cells in TDLN

Lymphoid glands contain various differentiated stromal cells, including lymphoid tissue organizer cells (LTo), follicular dendritic cells (FDCs), fibroblastic reticular network cells (FRCs), and marginal reticular network cells (MRCs). LTo cells attract hematopoietic cells to the glands, while FDCs support B cell survival near B cell areas. MRCs produce chemokine CXCL13 to modulate LTo cell characteristics and functions (66). FRCs produce various extracellular matrix proteins, including type I and III fibrillar collagen, type IV collagen, laminin, fibronectin, and integrin, to create a network site for immune cell movement and enhance the structure of lymph glands, thus playing an essential role in maintaining HEV integrity and immune cell survival (67). A study of B16.F10 melanoma mice found that FRC cells in tumor-bearing mouse SLNs showed increased expression of genes involved in biological processes such as growth, metabolism, mitochondrial function, cell motility, and cell-cell adhesion. Transcriptional profiling also revealed increased expression of activation markers such as fibronectin 1, actin α2, S100A4, vimentin, muscle myosin light chain, and collagens, suggesting that FRC activation in SLNs supports lymph metastasis (68).

Cytokine and chemokine modulation in TDLN during cancer progression

Cytokine and chemokine signaling pathways not only aid in immune response formation but also serve as pathways for tumor cell growth and progression (Table 2). For example, in TDLNs of melanoma patients, increased expression of GM-CSF, IFN-γ, and IL-10 compared to NDLNs has been observed (66). In breast cancer, the expression of IL-12p40, IFN-γ, IL-10, and Foxp3 was significantly upregulated in SLNs infiltrated by the tumor (69). Neutralization of p40 by anti-p40 monoclonal antibodies resulted in the death of human breast cancer cells and led to positive regulation of CD4+ IFN-γ+ and CD8+ IFN-γ+ T-cell populations (70). IL-19, a cytokine produced by immune and non-immune cells, exerts its biological effects through the IL-20 receptor family. It is secreted by many cancer cells, including squamous cell carcinoma (SCC), renal cell

Table 2. Modulation of cytokines and chemokines in sentinel lymphatic nodes (SLN) during cancer progression

Cancer type	Cytokines/Chemokines	Effect	Ref.
Melanoma	GM-CSF	Proliferation and differentiation of DCs	66
	IFN-γ	Production of cytotoxic cells	
	IL-10	Dampens acquired Th1 cell cytokine production	
Breast cancer	IL-12P40	Down-regulation of human CD4+IFNγ+ and CD8+IFNγ+ T-cell populations	69-72
	IFN-γ	Production of cytotoxic cells	
	IL-19	Upregulation of TGF-β and CXCR4	
NSCLC	TGF-β	Decreased DCs number	73, 74
Melanoma	CCR8-CCL1	Tumor-Lymphatic endothelial cells chemotaxis	75
	CXCR4-CXCL12	Tumor-Lymphatic endothelial cells chemotaxis	
Gastric, Colorectal	CCR7-CCL19/MIP3β	Tumor-Lymphatic endothelial cells chemotaxis	76, 77

carcinoma (RCC), and infiltrative ductal carcinoma (IDC). Increased IL-19 production in tumor tissues alters TGF-β and CXCR4 expression, promoting metastasis and a poor clinical prognosis. Antibodies against IL-19 have been shown to suppress cancer growth, as cancer cells with the related receptor expression can proliferate, migrate, and metastasize (71). The decrease in the serum level of IL-19 in breast cancer patients compared to healthy individuals may be due to the use of systemic IL-19 in the tumor site, as it has been reported that patients with breast cancer with TDLN involvement have a lower IL-19 serum level compared to the NDLN group (72). In NSCLC, tumor-derived TGF-β reduces the number of DCs in SLNs (73). It has been shown that chemokine receptors such as CXCR3 and CXCR4 are regulated in various types of cancer animal models and are strongly associated with SLN metastasis (74). The chemokine CCL1 has been identified in LNs and lymphatic sinuses, and its receptor CCR8 is significantly regulated at the cellular level in human melanoma cells, providing a molecular basis for how CCL1 promotes the invasion of cancer cells into SLNs (75). Several receptor-ligand pairs, including CXCL12-CXCR4, CCL19-CCR7, and CCL21-CCR7, also effectively promote the invasion of LNs by cancer cells. These studies indicate that the cytokine/chemokine environment plays a crucial role in creating a pre-metastatic niche in SLNs (76, 77).

Metabolic reprogramming in TDLN

LNs contain high levels of fatty acids, making them a rich source of fat (78). Cancer cells undergo metabolic reprogramming toward fatty acid oxidation (FAO), enabling migration to LNs by activating metastasis-associated transcription factors and playing a crucial role in lymphangiogenesis (78). Studies show that metabolic reprogramming of CD8+ T effector cells towards FAO can inhibit these cells, thereby promoting tumor growth and metastasis in breast cancer (79). Treg cells use fatty acids for energy production, whereas effector T cells rely on glycolysis. They induce fatty acid uptake and choose FAO for the optimal suppressive function (80). FRCs in breast cancer increase oxidative phosphorylation (OXPHOS) and ATP production by overexpressing fumarate hydratase (FAH), a key enzyme in the tyrosine breakdown pathway, thereby producing metabolites like fumarate, which creates a suppressive tumor microenvironment (66). Co-culture of mouse immune cells with FRCs overexpressing FAH inhibits their activation in vitro, and oncometabolites such as fumarate, succinate, and 2-hydroxyglutarate create a favorable tumor microenvironment through epigenetic changes (81).

Enhancing antitumor responses by targeting TDLN

TDLNs disrupt immune responses and stromal remodeling despite the presence of TAA, thereby promoting metastasis. SLN involvement is crucial for tumor metastasis, making it a suitable target for therapeutic interventions. Metabolic changes in SLN cells create a favorable microenvironment for pre-metastatic progression. Inhibiting or restoring metabolic switches can reverse this microenvironment. Stromal cells in SLNs use lipids and the FAO pathway for energy and ATP production, so local suppression of FAO can prevent tumor cell invasion into TDLNs (82).

Another point that underscores the value of TDLNs is their use of immune modulators and cancer vaccines to enhance anti-cancer immunity. For example, lymphangiogenic immunotherapy in mouse melanoma enhances the activation of DCs, T cells, and NK cells by injecting cancer cells that overexpress VEGF-C before tumor cell invasion. Intranodal injection of TAA increases antigen presentation by DCs and improves vaccine efficacy (83). Checkpoint inhibition is a key approach in cancer treatment, and a better understanding of the mechanisms of immune checkpoint blockade (ICB) in TDLNs may play an essential role in the response to immunotherapy.

The initial hypothesis regarding anti-PD-1/PD-L1 was based on reversing exhaustion in CD8+ PD-1hi T cells. However, evidence indicates that CD8+ T cells accumulate in the TME and migrate from lymphoid organs to it. Inhibiting migration increases tumor growth with the fingolimod (FTY720) drug, suggesting TDLNs are a suitable site for ICB function (84). Another report on colon cancer in mice treated with anti-PD-1/PD-L1 has shown that the number of CD8+ T cells in the TDLN is significantly higher than in the NDLN, and that physical removal of the TDLN by surgery greatly reduces treatment efficacy (85). Single-cell RNA sequencing and TCR profiling reveal CD8+ T-cell clones expanding in tumors and normal tissues in patients undergoing anti-PD-L1 therapy, indicating the presence of blood-induced clones (86). Reversed CD8+PD-1+Ki67+ T cells appear in the peripheral blood of patients undergoing treatment with anti-PD-1 antibodies (87), and both pre-existing and newly infiltrating T-cell clones target PD-1 blockade to tumors (88). Anti-PD-1/PD-L1 therapy leads to peripheral expansion and the emergence of new tumor-targeting responses, suggesting that ICB activity extends beyond the tumor. This suggests peripheral activation and expansion of newly arising T-cell clones may be required for a robust response, and targeting SLNs or TDLNs could be a new approach to developing anti-cancer therapies.

Conclusion

Cancer metastasis occurs via the lymphatic system, in which tumor cells employ strategies such as secreting cytokines, chemokines, growth factors, ECM proteins, and suppressive factors to spread to distant sites. These strategies affect immune cells and TDLN stromal cells, creating a favorable microenvironment for invasion. However, an immune organ that initiates immune responses can also be a site for tumor cell survival and metastasis. TDLNs, intratumoral LNs, are reconstructed as tumors progress, reducing antitumor immunity. Immunotherapy aims to understand the relationship between stromal cells and lymphocyte populations in TDLNs to activate the host immune system and induce anti-tumor responses. Although most treatments focus on this issue, there is growing interest in developing therapies that target TDLNs and in emerging topics in tumor immunology, such as stromal remodeling and metabolic reprogramming.

As discussed in this article, TDLN stromal remodeling, including FRCs and HEVs, clearly influences immune dysfunction. FRCs in TDLN become enlarged, and extracellular matrix pathways and chemokine signaling, such as CCL21 and IL-7, are down-regulated, leading to reduced lymphocyte migration and impaired T-cell priming. HEVs also undergo lumen dilation, endothelial thinning, and decreased expression of the Peripheral Node Addressin (PNAd) marker, which is associated with

impaired lymphocyte recruitment. Therefore, targeting these stromal and vascular changes in TDLNs, for example, restoring FRC function, restoring homeostatic chemokine expression, and reprogramming HEVs could be a significant therapeutic focus. This approach may improve response to immunotherapies, reverse immune-tolerance pathways, and help design combination therapies that, in addition to targeting the tumor, also repair the TDLN environment.

In the last few decades, it has been shown that FRCs not only play a role in the structure and architecture of LNs but also that their metabolic activity contributes to the creation of a suppressive environment for T cells. By increasing the activity of metabolic pathways involved in glucose and fatty acid utilization, FRCs create conditions that favor T cell survival over effector function (89). FRCs also undergo "metabolic reprogramming" under tumor pressure, and pathways such as OXPHOS and FAO become more active. These changes result in the consumption of metabolic resources by the FRCs themselves, reduced production of antigens or lymphocyte-activating chemokines, and ultimately reduced energy and metabolic levels of T cells, resulting in reduced IFN-γ production, reduced $CD8^+$ priming, and increased T-cell activation threshold (90).

Given this evidence, redirecting metabolic pathways of FRCs—for example, suppressing FAO/fatty acid beta-oxidation or resetting the glucose: acidolysis ratio—could be an important therapeutic strategy to restore T-cell function in TDLNs. This strategy could include the use of FAO or OXPHOS inhibitors or the stimulation of the glycolysis pathway in FRCs to reallocate resources and create metabolic space for lymphocytes. Such an intervention—in combination with immunotherapy (e.g., PD-1 inhibitors) could lower the threshold for T-cell activation, improve $CD8^+$ priming, and facilitate lymphocyte trafficking into the node (including entry from HEV, trafficking through the FRC reticular network, and efficient egress). Ultimately, the goal is to transform TDLNs from a "metabolically suppressive environment" to an "immunotropic environment," in which T cells with sufficient energy, appropriate signaling, and a high functional profile engage in tumor responses.

Acknowledgment

The authors would like to thank all researchers and sources whose work contributed to the preparation of this review article.

Ethics Approval Statement

Ethical approval was not required for this study as it is a review article with no involvement of human or animal subjects.

Authors' Contributions

Z K conceived the study and drafted the manuscript. M KK and Z R assisted with data collection and figure creation. Z K also helped with table preparation and reviewed and edited the manuscript. All authors read and approved the final version.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Declaration

No AI tools were used in the preparation of this manuscript.

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