

Beyond the tumor microenvironment: Orchestrating systemic T-cell response for next-generation cancer immunotherapy (Review)

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Abstract. Immune checkpoint blockade therapy has revolutionized cancer treatment, yet its clinical efficacy remains limited to a subset of patients with specific tumor types. The present review provides a comprehensive analysis of T cell-mediated antitumor immunity from both local and systemic perspectives, with particular emphasis on CD8⁺ T cells as primary effectors. The review discusses how the complex trafficking between the tumor microenvironment (TME), surrounding lymphoid tissues and peripheral circulation creates multiple opportunities for tumors to evade immune surveillance. Within the TME, T-cell exclusion mechanisms, antigen specificity and the spectrum of T-cell exhaustion states, from progenitor exhausted T cells to terminally exhausted T-cell phenotypes, are reviewed. Beyond the local TME, the crucial roles of tumor-draining lymph nodes and tertiary lymphoid structures in maintaining sustainable antitumor immunity, as well as the significance of circulating T cells as both biomarkers and therapeutic targets, are analyzed. This systemic perspective provides insights into the dynamic nature of antitumor

immunity and suggests potential strategies for next-generation immunotherapies, including combination approaches targeting multiple immune compartments to achieve optimal therapeutic outcomes.

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1. Introduction

Immune checkpoint blockade (ICB) therapy has demonstrated marked clinical efficacy, albeit limited to a subset of patients with specific solid tumor types, such as melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma and urothelial carcinoma. Extensive research has been conducted to elucidate the characteristics of responding patients and the underlying mechanisms, aiming to identify suitable candidates for precision therapy and potential therapeutic targets to overcome resistance (1). A previous study demonstrated that ICB therapy efficacy is associated with an immunologically ‘hot’ phenotype of tumors (2). However, individual parameters, including programmed death ligand 1 (PD-L1) expression, tumor mutational burden (TMB) and T-cell infiltration (3), have proven insufficient as predictive biomarkers for ICB response. Furthermore, given that the immune response is an inherently systemic process, localized ICB administration often fails to achieve complete tumor elimination through immune-mediated mechanisms, such as cytotoxic T-cell activation and infiltration, which are critical for targeting and destroying tumor cells (4,5).

As with all immune responses, antitumor T cells undergo a sequential process of priming, activation, circulation, recruitment, infiltration, effector function, and ultimately, resolution

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or memory formation. The intricate trafficking network among the local tumor microenvironment (TME), surrounding lymphoid tissues and peripheral circulation provides multiple opportunities for tumors to abrogate effective antitumor immunity, necessitating comprehensive strategies to address all immune escape mechanisms for successful antitumor immune responses (6).

The recent advancement in multi-omics analysis has provided deeper insights into the complexities of antitumor immunity. Therefore, focusing on CD8⁺ T cells as the principal effectors of antitumor immune responses, the present review examines the comprehensive tumor ecosystem beyond the local TME, with particular emphasis on the dynamic and systemic nature of antitumor immunity, to provide direction for future basic and translational research.

2. T cells in the TME

The TME is a complex ecosystem consisting of immune and stromal cells, along with bioactive molecules that influence tumor progression and immune responses (Fig. 1) (7). Key components include T cells, tumor cells, cancer-associated fibroblasts (CAFs), myeloid-derived suppressor cells and tumor endothelial cells (TECs). Additionally, the extracellular matrix (ECM) and stromal molecules, such as collagen, chemokines, cytokines and signaling molecules, significantly impact tumor growth and T-cell function (Fig. 2). Among these, CD8⁺ tumor-infiltrating lymphocytes (TILs) are established prognostic biomarkers and form the foundation of most immunotherapies (8). However, their therapeutic efficacy is limited by their inherent heterogeneity in composition, phenotype and function, which complicates their correlation with treatment outcomes.

Exclusion. Although high TIL levels generally predict better therapeutic outcomes (9), immune-excluded tumors exhibit poor responses due to T cells being trapped in the tumor stroma, unable to penetrate the tumor core. This phenomenon, often mediated by CAFs and TECs, results in limited T cell-tumor contact and suboptimal ICB efficacy (10-12). CAFs, originating from diverse sources such as mesenchymal cells, epithelial-mesenchymal transition and stromal activation, exhibit functional plasticity (13). CAFs polarize into inflammatory CAFs, which secrete immunosuppressive cytokines, or myofibroblastic CAFs, which create physical barriers through ECM remodeling (14). A small subset of CD74⁺ CAFs can also present antigens, directly modulating immune responses (15).

Similarly, TECs impede T-cell infiltration through abnormal vascular responses, including reduced adhesion molecule expression. Abnormal responses of blood vessel TECs to inflammatory cytokines and decreased expression of adhesion molecules impede T-cell recruitment and infiltration (16,17). Studies have demonstrated that high inflammation coupled with low vasculature correlates with optimal ICB responses, as confirmed by two independent investigations (18,19). Lymphatic TECs further exacerbate immune exclusion by attracting C-X-C chemokine receptor type 4 (CXCR4)⁺ T cells away from tumors via C-X-C motif chemokine ligand 12 (CXCL12) signaling (20). Collectively, these stromal cells establish chronic inflammatory niches that hinder effective

immune responses. Recently, research (21) in hepatocellular carcinoma has revealed that pericancerous macrophages cross-present antigens to CD103⁺ CTLs via the endoplasmic reticulum-associated degradation machinery-mediated cytosolic pathway, subsequently activating the NLRP3 inflammasome in macrophages, thereby promoting the progression of hepatoma and immunotherapy resistance.

Specificity. T-cell specificity, driven by T-cell receptor (TCR) recognition of major histocompatibility complex-I:antigen complexes, underpins T-cell activation and antitumor immunity. TMB and neoantigen availability strongly correlate with ICB efficacy in immunologically ‘hot’ tumors such as melanoma and lung cancer (22-24). Conversely, in ‘cold’ tumors with low TMB, treatments such as chemotherapy, radiotherapy and tumor vaccines can enhance antigenicity, converting cold tumors into hot ones (25-28).

Despite these advances, most T cells in the TME are bystander T cells (Tbys) that lack tumor antigen recognition but still influence immune responses (29). Studies suggest that expressing Tby-specific antigens in tumor cells could harness their antitumor potential (30-32). By contrast, antigen-specific T cells (Tas), which recognize tumor neoantigens, are the primary effectors in immunotherapy (33). These cells often exhibit exhaustion due to chronic stimulation (34), characterized by markers such as CD39 (31,35,36,37), CD103 (38-40) and programmed cell death protein 1 (PD-1) (41,42). Emerging markers such as CXCL13 (43-47) and CD137 (48,49) further refine Tas identification and therapeutic targeting. Notably, the predominant expression of exhaustion markers among Tas markers emphasizes the critical need to address T-cell exhaustion in therapeutic strategies to maintain clonal expansion and effector function (50).

Exhaustion. Chronic antigen exposure in tumors induces T-cell exhaustion, marked by impaired proliferation, reduced cytokine production and elevated inhibitory receptor expression (51,52). T-cell exhaustion represents a complex process orchestrated by dynamic alterations and dysregulation in signaling pathways, transcription factors [including T cell factor 1 (TCF1), T-box expressed in T cells and thymocyte selection-associated high mobility group box protein (TOX)], epigenetic programs and metabolic adaptations (53,54). Exhausted T cells (Tex) comprise a heterogeneous population exhibiting a spectrum of phenotypic and functional characteristics (55). This spectrum is anchored by two distinct states: Progenitor Tex (Tex-prog), which maintain stem-like and proliferative properties, and terminally differentiated Tex (Tex-term).

Tex-prog. Tex-prog cells are characterized by high expression of TCF1 (56,57), a transcription factor essential for maintaining stemness and proliferative capacity. These cells respond well to ICB (58-62) and IL-2 (63-65) therapies. Tex-prog cells are considered primary mediators in chronic infection and ICB response (66-69), serving as primary mediators of long-term immune responses (70). The presence of the cells correlates with improved survival in melanoma and other cancer type. Notably, CXCL13⁺ T cells also exhibit Tex-prog characteristics (71).

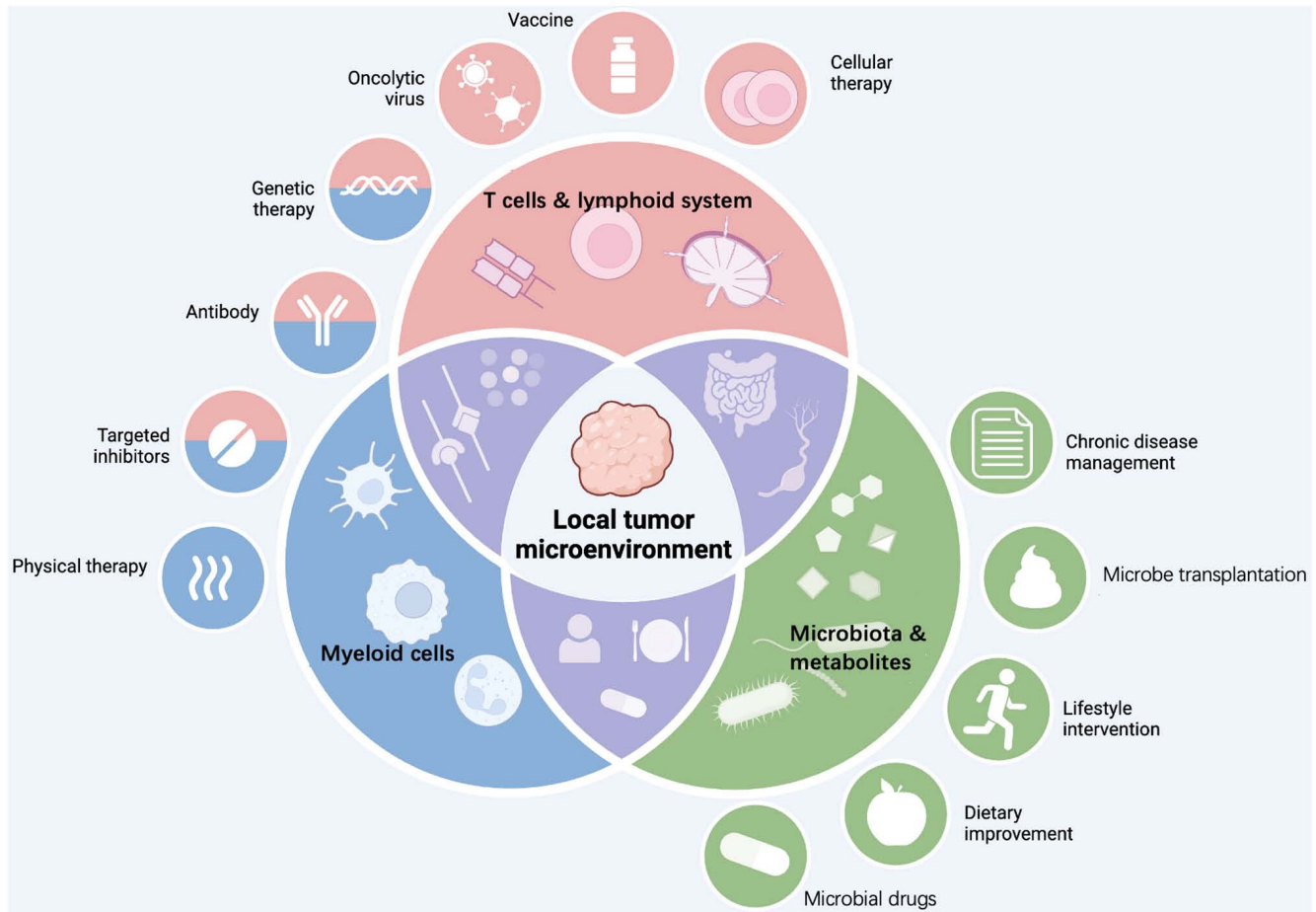


Figure 1. Local TME. This diagram illustrates various therapeutic and intervention approaches related to the local TME. It is divided into three main sections: T cells and lymphoid system, myeloid cells, and microbiota and metabolites. Each section encompasses different modalities such as vaccines, oncolytic viruses, cellular therapies, genetic therapies, antibodies, targeted inhibitors, physical therapies, chronic disease management, microbe transplantation, lifestyle interventions, dietary improvements and microbial drugs. These approaches aim to modulate the local TME for cancer treatment and management. TME, tumor microenvironment.

Tex-term. Tex-term, defined by TOX activity (72-75) and multiple inhibitory checkpoints [e.g., PD-1 and lymphocyte activation gene 3 (LAG3)] (76-78), exhibit irreversible epigenetic changes, rendering them resistant to ICB (69). Under hypoxic conditions, Tex-term suppress immune responses via CD39-adenosine signaling (79), contributing to immunotherapy resistance. Strategies targeting Tex-term-associated pathways, such as P-selectin glycoprotein ligand-1 (80) and CD39 (81,82), are under investigation.

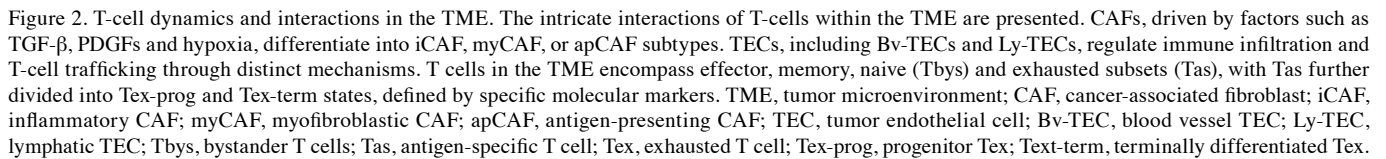
Intermediate Tex (Tex-int cells). Tex-int cells occupy an intermediate state between functional effector T cells and Tex-term. These cells retain proliferative capacity and respond robustly to ICB, serving as a 'stem-like' reservoir for sustained immune responses (68,69). The abundance of these cells correlates with improved clinical outcomes, making them promising targets for combination therapies such as vaccines and chimeric antigen receptor (CAR)-T cells (53).

Key mechanisms regulating T-cell exhaustion. T-cell exhaustion results from persistent antigen stimulation and is regulated by a complex interplay of signaling pathways (71), transcription factors and epigenetic programs. Factors such as mechanistic target of rapamycin (mTOR), transforming growth factor- β (TGF- β) and PD-1 signaling influence transcriptional regulators, such as basic leucine zipper transcription factor

ATF-like (BATF), TOX and TCF1, which maintain a delicate balance between T-cell activation and exhaustion (83,84). Briefly, upstream molecular pathways, such as mTOR and TGF β (85), PD1 signaling (86) and IL-10 stimulation (87), orchestrate the activities of transcription factors myeloblastosis (88), activator protein 1 (61,89), BATF (90-92), BTB and CNC Homology 2 (BACH2) (90), special AT-rich sequence-binding protein 1 (93), interferon regulatory factor 4 and nuclear factor of activated T cells cytoplasmic 1 (91,92,94). Multiple aspects of a T cell are kept in a fine balance by these regulators; for example, methylcytosine dioxygenase TET2 guards against BATF3-induced CAR-T cell proliferation and ensuing genomic instability (95,96). With a more complete understanding of this epigenetic programming, it is possible to fine tune T-cell immunity and exhaustion while keeping proliferative responses and general inflammation in check.

3. Systemic T-cell response

T cells in lymph nodes. The systemic T-cell response to ICB is driven by two key mechanisms: The expansion of pre-existing T-cell clones and the infiltration of new clonotypes, a process termed clonal rejuvenation (97). Pre-existing clones provide a rapid antitumor response, while new clonotypes, undetectable



tdLNs. *tdLNs* are critical for antitumor immunity (104) and serve as both initial metastatic sites and primary locations for T-cell activation. The presence of these lymph nodes correlates with ICB efficacy (105), systemic immune responses (106) and improved survival (107). Mechanistically, *tdLNs* (108) support antitumor immunity

TLSSs. TLSSs are organized immune cell aggregates that form in chronic inflammatory conditions, including cancer (119-121). Structurally resembling SLOs, TLSSs support *de novo* and ongoing immune responses, promoting T-cell activation and B-cell-mediated antibody production (122). Their presence is associated with favorable outcomes across

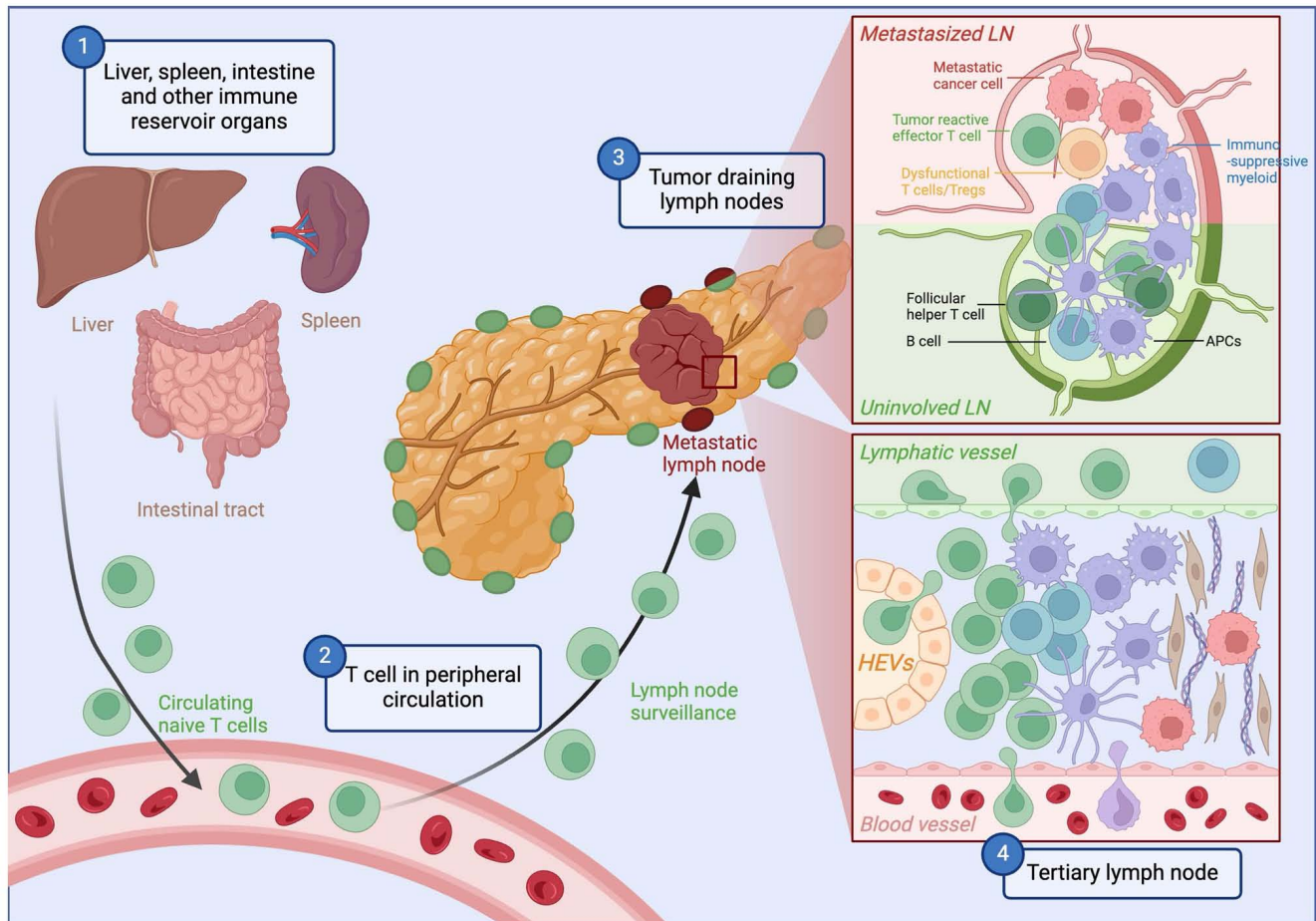


Figure 3. T-cell trafficking and immune interactions. T-cell trafficking and immune interactions within the tumor microenvironment and immune reservoirs are presented. Naive T cells circulate from organs such as the liver and spleen to the lymph nodes for surveillance. In the lymph nodes, metastatic cancer cells interact with effector T cells, which may be suppressed by Tregs and immunosuppressive myeloid cells. Tumor-draining lymph nodes and TLSs are key sites of immune activation, with lymphatic and blood vessels enabling immune cell migration between compartments. LN, lymph node; APC, antigen-presenting cells; Treg, regulatory T cell; TLS, tertiary lymphoid structure; HEV, high endothelial venule.

multiple cancer types, including breast (123), colorectal (124) and pancreatic (125,126) cancer.

TLS formation is driven by chemokines such as CXCL13, and their maturity, ranging from early lymphocyte aggregation to fully developed germinal centers, impacts their prognostic value (127-129). Mature TLSs are linked to better outcomes, while immature TLSs may correlate with a poor prognosis in certain cancer types, such as lung and breast cancer (130-132). Emerging therapeutic strategies aim to enhance TLS formation (133-136) and maturation while mitigating tumor-promoting inflammation.

The heterogeneity in TLS maturation, categorized into early (lymphocyte aggregation), primary (follicular dendritic cells without mature DCs) and secondary stages [active germinal centers (GCs)] (137), is evident across cancers and assessed via markers such as CD138⁺ plasma cells (138) and CD23⁺ GC B cells (139). For example, esophageal cancer shows 26.9% TLS-negative, 30.2% immature and 42.9% mature cases, with mature TLSs featuring proliferative/memory B cells, plasma cells and CD4⁺ Th17 cells (140). Liver cancer exhibits 53% TLS-negative cases, 26% lymphoid aggregates, 16% primary and 5% secondary follicles, with the latter two linked to reduced recurrence risk (141). In squamous lung cancer, mature TLSs with GCs predict prognosis unless

diminished by corticosteroids during neoadjuvant chemotherapy (128,142). Similarly, melanoma highlights B-cell markers (activation-induced cytidine deaminase and CD21) for mature TLSs and prognostic insights (143), while colorectal cancer emphasizes the significance of follicular dendritic cells and mature B cells (144).

However, TLSs may correlate with poor outcomes in some cancer types (145,146), such as renal cell carcinoma and pancreatic ductal adenocarcinoma, potentially due to TLS-associated Tregs (147), IL-10-secreting B cells (148), immune complexes, or tumor-promoting inflammation and angiogenesis (149,150). Emerging therapies aim to foster TLS neogenesis/maturation while mitigating inflammatory TMEs using cytokines, antibodies, immune checkpoint inhibitors, cellular therapies and synthetic scaffolds (151).

Lymphocytes in circulation

Total lymphocytes. The peripheral blood reflects systemic immune status, with lymphocyte composition serving as a key biomarker for antitumor immunity. Baseline lymphopenia, observed in various cancer types (152), such as metastatic breast cancer, correlates with disease burden and treatment outcomes. While systemic chemotherapy often suppresses peripheral immunity, localized treatments can preserve

immune function and synergize with ICB (153). Post-treatment lymphocyte counts are predictive of ICB response, with higher levels correlating with improved outcomes in melanoma, lung cancer and renal cell carcinoma (RCC) (154). Relative lymphocyte count demonstrates significant prognostic value in melanoma (155,156), non-small cell lung cancer and RCC (157).

TCRs. Circulating TCR diversity is a critical determinant of antitumor immunity (158). Reduced TCR diversity is linked to aggressive disease and a poor prognosis (159,160), while dynamic TCR remodeling occurs in response to therapy (161-163). Post-treatment TCR expansion, particularly in CD8⁺ T cells, predicts ICB efficacy (164,165). However, high pretreatment TCR clonality may indicate poor outcomes in breast and lung cancer (163,166). The presence of polyclonal effector CD8⁺ T cells responding to a limited number of immunodominant mutations, with individual neoantigens corresponding to specific effector T-cell clones, appears fundamental to ICB response (167). TCR diversification, particularly of CD4⁺ blood T-cell clones prior to ICB administration, confers therapeutic benefit in lung cancer (168,169), RCC (170) and urothelial cancer (171). TCR profiles also correlate with immune-related adverse events (irAEs) (172,173).

T-cell phenotype. The functional status of circulating T cells significantly impacts cancer immunity (174). Memory T cells, particularly central memory T cell (Tcm) and effector memory T cell (Tem) subsets, are associated with favorable outcomes, while Tregs and Tex-term often indicate a poor prognosis (175-177). Treatment-induced activation of cytotoxic T cells and interferon- γ (IFN γ) production (174) are key markers of ICB response. Elevated PD1⁺/CD8⁺ T cells and natural killer (NK) cells (178) predict better outcomes, whereas increased Tregs and naive T cells correlate with a poor prognosis.

The composition of lymphocyte subsets reflects distinct functional signatures defined by specific phenotypic markers, with memory T-cell phenotypes generally linked to favorable clinical outcomes. Key prognostic indicators include the Tcm/effector T cell ratio (179), CD8₊ Tem marked as C-C chemokine receptor type 7 (CCR7)/CD45RA/CD27/CD28⁺ (180,181), and CD4⁺ memory T cells characterized by positivity for CD45RO/CCR7 and the absence of CD62L (182). Elevated baseline CD274 expression on T cells is also a significant prognostic marker (183). CD4⁺ T-cell subsets include central memory (CD45RA/CD62L⁺), effector memory (CD45RA/CD62L⁻) and non-senescent (CD57⁻) cells (184). Baseline PD1⁺ T cells and activated NK cells indicate antitumor immunity (185), while CD25⁺/FOXP3⁺/CD4⁺ Tregs are negative prognostic factors (182,184), with PD1 expression on Tregs linked to susceptibility to ICB-mediated activation and potential tumor hyperprogression (186). Tex-term (PD1⁺/T-cell immunoreceptor with Ig and ITIM domains⁺/LAG3⁺ and CD28/CD57⁺/killer cell lectin-like receptor subfamily G member 1⁺) (180,187,188) and PDL1⁺ NK cells further highlight the complexity of immune dynamics in the TME (157).

Treatment-induced immune changes, particularly early T-cell activation and proliferation marked by Ki-67 expression in PD1⁺/CD8⁺ Tex (189-193), cytotoxic activity, IFN γ activation and effector memory phenotypes (194,195), are critical indicators of ICB efficacy. A higher PD1⁺/CD8⁺ to

PD1⁺/CD4⁺ T-cell ratio (173,196) and increased NK cell populations (197) correlate with favorable outcomes, whereas Treg induction predicts a poor prognosis (198). CD4⁺ Tem (CD27⁺/FAS⁻/CD45RA⁻/CCR7⁺) play a vital role (199), and post-treatment T cell immunoglobulin and mucin domain-containing protein 3-positive Tex show tumor-specific prognostic value, being unfavorable in NSCLC and RCC, but favorable in esophageal squamous cell carcinoma (157,200). These findings suggest their utility as biomarkers for immune activation rather than as direct effectors. In hepatocellular carcinoma, an inflammatory signature involving PDL1, CD8A, LAG3 and signal transducer and activator of transcription 1 correlates with better outcomes, while macrophage-associated gene patterns show no prognostic significance (201). A composite biomarker panel, including mitochondrial activation (peroxisome proliferator-activated receptor γ coactivator 1 and reactive oxygen species) and specific T-cell populations (CD8⁺/PD-1^{hi} and CD4⁺ T cells), has demonstrated high predictive accuracy for PD-1 blockade therapy outcomes (area under the curve, 0.96) (202).

Response and irAEs. irAEs are associated with enhanced therapeutic responses and prolonged survival times (203,204) in ICB-treated patients. Specific immune cell subsets, such as CXCR3⁺/CD8⁺ Tem and CD11c⁺ APCs, are linked to both efficacy and toxicity (205,206). Elevated Th17 (207) and Th1 (208) cells, coupled with reduced Treg levels, predict irAEs, while CTLA4 (209) insufficiency exacerbates these effects. Biomarkers such as post-treatment TCR clonality and peripheral immune profiles hold promise for optimizing treatment efficacy while minimizing irAEs (206,210).

4. T-cell therapeutics

Systemic inflammation. Systemic inflammation plays a pivotal role in regulating T-cell responses during immune defense against malignancies. Pro-inflammatory mediators, such as IL-1 β , TNF- α and IL-6, create an inflammatory environment that facilitates APC-mediated T-cell activation and expansion. While this process is essential for initiating immune responses against infections and cancer, chronic inflammation can lead to T-cell exhaustion (211), marked by reduced effector functions and increased expression of inhibitory receptors such as PD-1 and CTLA-4.

Therapeutic strategies targeting systemic inflammation aim to enhance T-cell functionality while preventing exhaustion. Approaches include use of cytokine inhibitors (e.g., IL-6 or TNF- α antagonists) to mitigate excessive inflammation and checkpoint inhibitors to restore T-cell activity (212). Emerging therapies such as selective adjuvants that activate Toll-like receptors and metabolic interventions targeting T cell-specific pathways offer promising avenues to sustain T-cell function without inducing chronic inflammation, particularly in cancer immunotherapy contexts (213).

PD-1 blockade therapy. PD-1 blockade therapy has transformed cancer treatment by reinvigorating T cell-mediated antitumor immunity. PD-1, an immune checkpoint expressed on T cells, suppresses T-cell activation to maintain self-tolerance, but is exploited by tumors for immune evasion via the PD-1/PD-L1 axis (214). Monoclonal antibodies targeting this

pathway, such as nivolumab and pembrolizumab, have achieved marked clinical success across various cancer types (215-217), such as non-small cell lung cancer, head and neck squamous cell carcinoma, and melanoma. Although these therapies provide durable responses and improved survival, they can cause irAEs, necessitating careful management (218,219). Combining PD-1 inhibitors with other immunotherapies or conventional treatments has shown promise in overcoming resistance and achieving synergistic effects (220-223).

Vaccine technologies. Advances in vaccine technologies have significantly enhanced T cell-mediated antitumor immunity. Cancer vaccines targeting tumor-associated antigens stimulate specific T-cell responses by mimicking natural infections (224-227). The addition of adjuvants, such as CpG oligodeoxynucleotides, further amplifies innate immune responses, supporting T-cell activation and proliferation (228-231). Combining cancer vaccines with checkpoint inhibitors has demonstrated synergistic effects, improving T-cell responses and tumor clearance (225,232,233). Personalized cancer vaccines, tailored to individual tumor antigenic profiles, represent a promising breakthrough by generating broad-spectrum T-cell responses while minimizing immune escape. These developments mark a significant step forward in precision immunotherapy (234).

mRNA-based therapies. mRNA-based therapies have emerged as a powerful tool in cancer immunotherapy, leveraging the ability of mRNA to encode tumor-specific antigens and stimulate targeted immune responses. Advances in delivery systems, such as lipid nanoparticles, have improved mRNA stability and protection against degradation (235-237). Structural modifications, including nucleoside alterations, enhance translation efficiency while minimizing immunogenicity (238-241). Co-delivery of immunomodulatory molecules encoded by mRNA further amplifies T-cell responses and counters immunosuppression (242). Clinical trials, particularly in melanoma, have demonstrated the efficacy of personalized mRNA vaccines in eliciting robust T-cell responses, underscoring their potential in cancer treatment (243-245).

Nano delivery systems. Lymphoid tissue-targeted nano delivery systems offer an innovative approach to enhancing T-cell functionality in cancer immunotherapy. Engineered nanoparticles, modified with ligands targeting lymphoid tissue receptors (e.g., CCR7 and CXCR5), enable precise delivery of immunomodulatory agents (246-249). Encapsulation of cytokines, such as IL-2 and IL-12 (250-253), within these nanoparticles enhances local T-cell responses while minimizing systemic side effects. Recent advancements include delivering checkpoint inhibitors directly to lymphoid tissues, addressing T-cell exhaustion in the TME (254-257). By concentrating therapeutic agents at desired sites, these systems improve treatment efficacy and reduce adverse effects, representing a promising direction for cancer immunotherapy.

Oncolytic viruses (Ovs). OVVs present a novel strategy to enhance T cell-mediated antitumor responses by selectively infecting and lysing cancer cells. This process triggers pro-inflammatory responses that activate adaptive immunity

while sparing healthy tissue (258). OVVs can also be engineered to express immunomodulatory genes, such as IL-12 and granulocyte-macrophage colony-stimulating factor, which enhance T-cell recruitment and activation within the TME (259-262). Combining OVVs with other immunotherapies, particularly checkpoint inhibitors, has shown synergistic effects in overcoming tumor-induced immunosuppression (263). This dual mechanism, namely direct tumor lysis and immune activation, positions OVVs as a promising component of combination immunotherapy strategies.

5. Perspective

The present review underscores the intricate interplay between local and systemic factors in T cell-mediated antitumor immunity. Within the TME, T cells face challenges such as physical exclusion, functional exhaustion and immunosuppression. The distinction between Tex-prog and Tex-term has emerged as a key factor influencing immunotherapy outcomes. Beyond the tumor site, systemic immune responses mediated by lymphoid structures and circulation are critical for sustaining effective antitumor immunity.

Recent advancements in T-cell biology have paved the way for novel therapeutic strategies, including mRNA-based therapies, targeted nano delivery systems and engineered oncolytic viruses. These innovations, coupled with improved biomarkers, such as TCR repertoire analysis and circulating T-cell phenotyping, enable more precise patient stratification and treatment optimization.

Looking ahead, several challenges remain. Balancing therapeutic efficacy with irAEs requires deeper insights into the molecular mechanisms distinguishing beneficial from harmful immune responses. Additionally, the role of systemic immunity, particularly lymphoid structures and circulation, warrants further exploration. Combination therapies targeting both T cells and the TME hold significant potential but need systematic evaluation. Finally, personalized immunotherapy, incorporating patient-specific factors, such as tumor antigens and immune status, promises to enhance treatment outcomes. Future clinical trials should consider stratifying patients according to Tex-prog and Tex-term profiles to optimize immunotherapy outcomes. Additionally, therapeutic interventions that promote the formation and maturation of TLSs in selected tumor types warrant systematic evaluation.

In conclusion, the rapid evolution of T cell-based cancer immunotherapy offers exciting opportunities to overcome current limitations. By advancing our understanding of immune dynamics and leveraging emerging technologies, more effective and personalized treatment strategies can be developed, ultimately expanding the benefits of immunotherapy to a broader patient population.

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Authors' contributions

XL, JH and CL wrote the draft. YZ and WW reviewed and revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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