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Review Article

The Tumor Microenvironment and Tumor-infiltrating Lymphocytes in Solid Tumor: A Comprehensive Review

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Abstract

The tumor microenvironment is a dynamic cellular landscape critical to cancer progression. Within it, tumor-infiltrating lymphocytes hold a dual role, contributing to both tumor suppression and progression. This review synthesized current knowledge on tumor-infiltrating lymphocytes, emphasizing their prognostic significance and therapeutic potential. By dissecting their interactions within the tumor microenvironment and with cancer cells, we sought to uncover the complexities of the immune response in cancer and explored the future direction of immunotherapeutic strategies.

Introduction

The tumor microenvironment (TME) is a complex and dynamic network essential to the pathogenesis of cancer. It encompasses a diverse array of cell types, including cancer cells, immune cells, stromal cells, and extracellular matrix components,[1] all of which collectively contribute to the progression or suppression of cancer. Within this intricate network, tumor-infiltrating lymphocytes (TILs) play a crucial role in the host's immune defense against cancer. TILs comprise a heterogeneous array of T cells, B cells, and natural killer cells (NKs).[2] However, their functionality and efficacy in targeting tumor cells are profoundly modulated by the intricate interactions within the TME.

Beyond their established role in prognostic evaluation, TILs have emerged as promising targets for immunotherapy. The seminal work by Rosenberg *et al*. in isolating and expanding these lymphocytes from tumor tissues has marked a significant milestone in cancer treatment.[3,4] Nonetheless, despite extensive research underscoring the importance of TILs in the oncogenesis and progression of tumors, ambiguities remain regarding the precise cellular makeup, the spatiotemporal dynamics within the TME, and the exact mechanisms by which TIL-based therapies modulate tumor immunity.

This review sought to elucidate the intricate interplay between the adaptive and innate immune components within the TME, with a particular focus on the T and B cell interactions central to the adaptability of the host's immune response. By consolidating recent advancements in the field, we aim to enhance the understanding of TIL spatial distribution and their immunomodulatory roles, thereby providing a comprehensive overview of TILs as pivotal components of the TME and their burgeoning potential in immunotherapeutic applications.

Overview of TIL dynamics in the TME

Within this TME network, lymphocytes are categorized based on their response mechanisms into adaptive and innate systems. Adaptive cells, such as T cells, B cells, and NKs, are defined by their antigen specificity and capacity to develop immunological memory. Innate immune cells like macrophages, neutrophils, and dendritic cells offer rapid, albeit non-specific defensive mechanisms.[1] This section will distil recent research on the composition of TILs and unpack the intricacies of their infiltration and differentiation within the TME.

T cell populations: diversity and functionality

T cell differentiation within TILs varies depending on the cancer type and the influence of the TME. These cells can either suppress or promote tumorigenesis. T cell subsets are typically identified by their T cell receptor (TCR) and lineage markers CD4 and CD8. The αβ TCRs, categorized into $CD4^+$ and $CD8^+$ cells based on their major histocompatibility complex (MHC) class I and II restriction, form the dominant composition within the TIL population.[5] Recent studies have revealed non-traditional T cell subsets, offering fresh insights due to their unique functions and impacts on the TME's dynamics. For instance, significant proportions of T cells within lung tumors have been identified, highlighting the diversity and functional significance of T cell populations in cancer.[6,7]

Keywords: Tumor-infiltrating lymphocytes; Tumor microenvironment; Immunotherapy; Cellular interactions; Prognostic value; Therapeutic targeting.

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TCR αβ$^+$ T population

The TCR αβ$^+$ population in the TME exhibits several distinct subsets that diverge from those found in peripheral blood due to tumorigenesis. CD8$^+$ T cells and CD4$^+$ T cells play significant roles in antitumor immunity, with their functionality influenced by the TME. Research has shown that CD4$^+$ T cells are crucial in tumor immunity,[8] with their activation or suppression altering cytokine levels and tumor growth dynamics. For instance, Friedman *et al*. demonstrated the importance of CD4$^+$ T cells in tumor immunity by observing a reduction in interferon gamma (IFN-γ) levels upon blocking MHCII with human leukocyte antigen DR (HLA-DR) antibodies.[8] Furthermore, Ben-Avi *et al*. found that while melanoma-infiltrating lymphocytes were enriched with CD8$^+$ T cells, TILs from non-small cell lung cancer contained a higher proportion of CD4$^+$ T cells.[9] Additionally, ERBB2IP has been identified as a new target for tumor rejection, and reactivation of CD4$^+$ T cells with an ERBB2IP mutation can lead to dramatic regression in liver and lung cancers.[10]

Apart from these, double-positive TCR αβ$^+$ cells (DPTs) have been identified in lung cancer,[11] breast cancer,[12] kidney cancer,[5,13] and melanoma,[14] representing the functional characteristics of both CD4$^+$ and CD8$^+$ T cell populations.[15] DPTs express activation markers such as HLA-DR, CD38, 4-1BB, CD137, and Ki-67, as well as inhibitory markers including programmed cell death protein 1 (PD-1), T-cell immunoglobulin and mucin-domain containing-3, and T cell immunoreceptor with Ig and ITIM domains (TIGIT). Additionally, DPTs produce conventional cytokines found in memory cells, such as interleukin (IL) 4, IL5, and IL13.[12,14,16] Found in prostate cancer and lung cancer as well,[17,18] double-negative T cells are implicated in immune regulation and suppression,[17,19] playing pivotal roles in adoptive cellular therapies.[20] Their regulatory-like phenotype and the distinctions from normal tissue counterparts offer insights into their function and potential alterations during tumor infiltration.[5]

Naïve T population

Mature naïve T cells, characterized by specific transcriptional factors, recirculate between secondary lymphoid organs,[21] and are separated by the expression of transcriptional factors such as C-C chemokine receptor type 7, lymphoid enhancer-binding factor 1, and transcription factor 7.[22] Mature naïve T cells, characterized by specific transcriptional factors, recirculate between secondary lymphoid organs.[23,24]

Th population

Derived from naïve CD4$^+$ T cells, Helper T (Th) cells support the immune response by enhancing CD8$^+$ T cell functions through cytokine secretion.[1] Th cells are associated with favorable outcomes in various cancers and are classified based on their cytokine production profiles,[25] liver cancer, biliary carcinoma,[26,27] non-small cell lung cancer,[28] nasopharyngeal carcinoma,[29] triple-negative breast cancer,[30] head and neck squamous carcinoma.[31]

Th cells are further classified by the production of lineage-specific cytokines. For instance, Th1 and Th2 cells dominantly secrete IFN-γ, IL1, and IL2, while Th17 cells are identified by the secretion of IL17.[32] Studies in hepatocellular carcinoma patients undergoing neoadjuvant anti-PD-1 trials have highlighted the role of CXCL13$^+$ Th cells in the response to immune checkpoint blockade within T cell-rich tumors.[33] Furthermore, research has demonstrated that CD4$^+$ Th cells facilitate the induction of antitumor responses by cytotoxic T lymphocytes (CTLs) through their interaction with classical type 1 dendritic cells *ex vivo*, indicating a positive correlation with prognosis.[34]

In addition to conventional Th cells, a population of T follicular helper cells has been identified in recent studies by their expression of the C-X-C chemokine receptor type 5 (CXCR5).[5]

Effector memory T (TEM) cells and tissue-resident memory (TRM) cells

T_{EM} and T_{RM} are independent prognostic indicators. High levels of T_{EM} correlate with favorable cancer stages. Studies on colorectal cancer (CRC) have revealed that higher levels of infiltrating T_{EM} are associated with low-grade tumor stage, limited invasion, and reduced lymph node metastasis. Furthermore, T_{RM} have been linked to a favorable prognosis in various tumor types, with the CD103$^+$ T_{RM} subtype facilitating enhanced tumor homing through integrin expression on the cell surface. T_{EM} have been identified as independent prognostic indicators of cancer and studies on CRC have revealed that higher levels of infiltrating T_{EM} are associated with low-grade tumor stage, limited invasion, and reduced lymph node metastasis.[35]

CTLs

Predominately, the CD8$^+$ TCRαβ$^+$ T cell population, known as CTL, in the TME recognizes and destroys cancer cells displaying abnormal tumor antigens. Their presence often correlates with a positive prognosis in cancer patients. High levels of antitumor cytokines and cytotoxic molecules, including IFN-γ, tumor necrosis factor (TNF) α,[36] granzyme B, and PRF1,[22] are associated with CTL activity. On the other side, they exhibit high expression levels of inhibitory receptors, including PD-1, T cell immunoglobulin and mucin-domain containing-3, TIGIT, and lymphocyte-activation gene.[5] CTLs provide long-term protection through memory cells, which have been shown to correlate with an overall positive prognosis in CRC and breast cancer.[35,37] Recent single-cell sequencing (sc-seq) reveals the existence of CD4$^+$ cytotoxic lymphocytes, expressing granzyme B,[38] MX1,[22] and TNF.[37]

Mucosal associated invariant T (MAIT) population

Despite the cell surface biomarkers of CD4 and CD8, MAIT are conventional conserved innate-like T subset. Despite their crucial role in regulating immunity and inflammation due to microbiota-derived signals,[39] MAIT populations also show a significant impact on anti-tumor immunity. However, MAIT cells exhibit heterogeneity and dysfunctionality, with impaired infiltration into liver tumors. Interactions with CSF1R$^+$PD-L1$^+$ tumor-associated macrophages in the adjacent liver microenvironment play a key role in MAIT cell dysfunction.[40] In addition to non-small cell lung cancer (NSCLC) patients, MAIT cells transition to an exhausted tumor-promoting phenotype, with circulating MAIT subsets serving as predictors for responsiveness to anti-PD-1 immunotherapy.[41]

TCR γδ$^+$ T population

Apart from traditional T-cell subsets, TCR γδ$^+$ T cells hardly express CD4 or CD8 cell surface biomarkers. γδ$^+$ T cells induce antitumor effects specifically on cancer cells without affecting normal cells. Their genetic structure allows for easy therapeutic interventions. These cells can recognize a wide range of antigens, including lipids, phospho-antigens, and peptides, in both MHC-dependent and -independent manners, making them effective against tumors with low mutational loads and downregulated MHC.[42] Furthermore, they have shown significant potential in immunotherapy, particularly in combination with immune checkpoint blockade, as they exhibit exhaustion in the TME and respond similarly to immune checkpoint inhibitors as conventional T cells.[43]

T cell exhaustion

Continuous antigen stimulation leads to a progressive decline in multiple functions of T cells, characterized by impaired proliferation and cytotoxicity, as well as upregulation of various inhibitory factors such as PD1, lymphocyte-activation gene 3 (*LAG-3*), TIGIT, T-cell immunoglobulin and mucin-domain containing-3, TIGIT and lymphocyte activation gene 3-like protein.[44,45] This phenomenon, known as T cell exhaustion, has been observed in various cancers, progressing from a pre-exhaustion state to a dysfunctional cell state.

Exhausted T (Tex) population

The exhausted $CD8^+$ T cell population comprises progenitor stem-like Tex cells and terminal Tex cells.[46] The balance between these subsets is critical for an effective antitumor immune response.[46,47] Progenitor stem-like exhausted T cells retain the ability for specific immune responses, self-renewal, and differentiation into T_{EX} cells while exhibiting high expression of the transcription factor 1 and the chemotactic receptor CXCR5.[46] T_{EX} cells, predominantly express inhibitory cell surface receptors and transcription factors associated with cytolytic functions such as IFN-γ and granzyme B.[5,37]

Recent research by Liangtao Zheng *et al*. has inferred state-transition paths from a naïve to an exhausted state, elucidating the pan-cancer single-cell landscape.[37] Exhausted T cells, particularly CD8+ T cells, account for a significant proportion of potentially tumor-reactive T cells and display high heterogeneity. The paths leading to exhaustion involve both T_{RM} and T_{EM}. In $CD4^+$ T cells, potentially tumor-reactive T cells are predominantly follicular Th cells that exhibit dual functionality as Th1 cells.

Moreover, increased expression of CX3C chemokine receptor 1, a biomarker of T cell exhaustion and differentiation, is consistently accompanied by decreased expression of PD1, LAG-3, and TIGIT.[48] CX3C chemokine receptor 1-negative cells have been shown to impede tumor proliferation and improve survival rates. Another crucial regulator is TOX, which plays a significant role in the formation of T_{EX} and the expression of inhibitory receptors on T cells.[5] T cells lacking TOX have lost their functions,[49–51] suggesting that exhaustion may, to some extent, serve to protect T cells from tumor cell-induced injury or activation-induced cell death.[5]

Understanding the mechanisms of cell exhaustion may pave the way for novel directions in tumor immunity, such as enhancing immunotherapy by preserving the functionality of T cells before they become dysfunctional.

Regulatory T (Treg) population

Treg cells, also known as tumor-promoting $CD4^+CD25^+FoxP3^+$ T cells, are the terminal $CD4^+$ T population. They have garnered considerable attention due to their ability to inhibit the tumor-specific immune response of CTLs.[52] Their actions include modulating NK cell homeostasis and indirectly supporting cancer cell survival via interactions with stromal cells.[1]

Tregs not only secrete immunosuppressive cytokines such as IL10, IL35, and transforming growth factor-β (TGF-β), but also exert inhibitory effects on the tumor immune environment by depleting nutrients, IL2, and inducing cytolysis.[52] Persistently expressing CTLA4, Tregs competitively suppresses T cell activation by binding to CD80 and CD86 on antigen-presenting cells (APCs).[53] Evidence suggests that tumor-infiltrating lymphocytes, particularly $Foxp3^+$ Tregs in the tumor microenvironment, contribute to disease progression, invasion, and metastasis.[54] Six studies on gastric cancer and CRC have found a correlation between high levels of Tregs and improved survival rates.[55] However, technical challenges in quantifying cells adjacent to Tregs may have influenced these findings, as it is currently impossible to simultaneously evaluate.[55]

B cell population and their controversial roles

B cells contribute to tumor immunity through antigen presentation, antibody production, and cytokine secretion.[56] Similar to dendritic cells (DCs), B cells possess antigen-presenting functions. Activated B cells ($CD69^+HLA\text{-}DR^+CD27^+CD21^+$) in non-small cell lung cancer have been found to present tumor-associated antigens to $CD4^+$ T cells, highlighting the role of B cells as APCs. Additionally, plasma cells, a subtype of B cells responsible for antibody production, are present in tertiary lymphoid structures surrounding tumors.[57] The coexistence of $CD8^+$ T cells, $CD20^+$ B cells, and plasma cells is significantly associated with a favorable prognosis. In high-grade ovarian cancer, this combination is correlated with a 10-year survival rate close to 65%.[5]

Contrarily, regulatory B cells (Bregs) are associated with a poor prognosis.[58,59] Bregs inhibit tumor immune responses through the secretion of IL10 and TGF-β. IL10 affects the differentiation of DCs, leading to the suppression of T cell proliferation and promoting their differentiation into Tregs.[59] Studies in ovarian cancer and liver cancer have shown that IL10 secreted by Bregs significantly suppresses tumor-specific T cell responses.[58,60] However, in breast cancer and tongue squamous carcinoma models, Bregs inhibit the differentiation of $CD4^+$ T cells into Tregs through TGF-β.[61,62]

Innate lymphoid cell (ILC): Emerging players in tumor immunity

ILCs, including NK cells and various subtypes, are recognized for their significant roles in maintaining immune homeostasis.

NK cells

NK cells, lacking antigen-specific B or T cell receptors due to the absence of recombination-activating genes,[63,64] are positively associated with survival rates and negatively correlated with disease progression.[5] They exhibit antitumor immunity by releasing granzyme and perforin and activating TNF-related apoptosis-inducing ligand.[63,64] NK cells also produce chemotactic factors such as chemokine (C-C motif) ligand 5 (CCL5), XCL1, and XCL2 to activate conventional DCs, affecting tumor immunity.

ILCs

While NK cells are typically associated with positive survival outcomes, the roles of ILC subtypes in cancer are complex and varied. Some ILCs promote tumor defense, while others potentially aid in tumor escape. Although poorly understood, ILCs are believed to exhibit high plasticity and display contradictory roles in tumor immunity.[65] Type I ILCs function similarly to NK cells by producing IFN-γ.[66] Type II ILCs express IL33 receptors ST2 and CD127, and upon activation, they also express PD-1.[67,68] Type III ILCs show contradictory manifestations in tumor immunity, promoting the formation of protective tumor-related tertiary lymphoid structures through TNF-α and IL22.[69] However, a study on lung squamous carcinoma found that the transformation from type I and type II ILCs contributes to tumor immune escape, correlating with tumor growth and poor prognosis.[5]

Interestingly, a novel cell population known as innate-like T cells with high cytotoxic potential (ILTCKs) has been identified. ILTCKs are characterized by high expression of NK1.1, CD49a, and CD103.[70] They exhibit unique tumor-elicited immune responses and share similarities with ILCs. While conventional T cells mainly recognize neoantigens, ILTCKs can respond to unmutated antigens in the absence of APCs.[71]

The multidimensional interactions of TILs within the TME

TME represents a multifaceted ecological system, encompassing not only malignant cells but also an array of immune cells, vasculature, and components of the nervous system. This intricate milieu acts as a battleground where the immune system and cancer cells dynamically interact. Within this framework, the composition of the TME and the presence of immune biomarkers hold significant prognostic value for tumor evaluation and treatment outcome.[72,73] The heterogeneity and functionality of TILs are particularly varied across different cancer types. For instance, in liver cancer, TILs present distinct clonality and exhaustion patterns, pivotal for understanding their role in tumor progression.[45]

Cellular interaction in the TME

The immune milieu within the TME profoundly influences the functionality of TILs. During the incipient stages of oncogenesis, cancer cells may evade innate immunity, leading to the development of functionally compromised T and B cells.[74,75] Additionally, nutrient scarcity within the TME compels TILs to assume metabolic adaptations conducive to tolerogenic phenotypes, thereby diminishing their antitumor efficacy.[76] Furthermore, Myeloid-derived suppressor cells exert suppressive actions on T cell proliferation and the activation of NK and T cells, while simultaneously enhancing regulatory Treg functions.[77] In breast cancer, tumor-associated fibroblasts contribute to intratumoral vascularization and the recruitment of immune cells.[78]

A pivotal study on the Tumor Immune Microenvironment in primary liver cancer identified five distinct subtypes through single-cell RNA sequencing, delineating immune activation, suppression, exclusion, and residence phenotypes, each mediated by different cellular clusters and genomic characteristics.[79]

Chemokines, cytokine, and TIL recruitment

The cytokine milieu within the TME provides indirect insight into the interactions between the TME and TILs. In hepatocellular carcinoma by Chew *et al*., tumor escape is predominantly facilitated by immunosuppressive chemokines released by T cells within the TME, while therapy resistance correlates with immune neglect in regions lacking T-cell infiltration.[80–82]

Cytokines are instrumental in modulating immune checkpoints, including CTLA-4 on T cells, which attenuates T cell activation, and PD-1 on tumor cells, promoting immune suppression.[72] Conversely, PD-1 expressed by tumor cells interferes with immune-suppressive pathways.[83] Teng *et al*. introduced a classification of the TME into four types based on the presence of TILs and PD-L1 expression,[84] aiding in predicting the tumor's response to therapies targeting PD-1/PD-L1 pathways and serving as a valuable prognostic tool.

The TME can both hinder and support the function of TILs. Factors such as local immunosuppression, the presence of Tregs, and the secretion of various cytokines and growth factors can dramatically alter the activity of TILs within tumors. Chemokines such as CXCL10 and CCL5 play a pivotal role in recruiting TILs to the tumor site, enhancing the infiltration of T cells and NK cells, thereby increasing tumor cell death.

Clinical values of TILs

TILs have fundamentally transformed the approach to clinical prognosis and immunotherapy for hematologic cancers. However, the diversity of solid tumors necessitates utilizing TILs with broad specificity. Recent advancements in understanding the TME, immune exhaustion, and immune checkpoints have paved the way for applying TIL clinical regimens.

Prognostic value

The composition and number of TILs are critical to tumor prognosis.

T cell population

A systematic review and meta-analysis focusing on laryngeal squamous cell carcinoma (LSCC) revealed that TILs, particularly stromal TILs, play a favorable prognostic role for overall survival (OS) and disease-free survival (DFS). High levels of CD8+ TILs were associated with prolonged OS and DFS, reinforcing the importance of TILs as biomarkers in cancer prognosis.[85] Daniele Fanale *et al*. demonstrated the significant prognostic value of TILs in cancers like ovarian cancer.[86] High densities of TILs, particularly CD8+ cytotoxic T cells, are often associated with better survival outcomes. This comprehensive analysis, encompassing 11 studies with 1,398 patients, confirmed the strong prognostic value of TILs for OS and DFS in LSCC. The findings highlight the significance of immune infiltrates in the TME of head and neck squamous cell carcinoma and suggest their potential as standardized and validated biomarkers in routine pathology reports.[85] The identification and validation of biomarkers that can accurately predict patient response to immune checkpoint blockade therapies are crucial for developing personalized treatment strategies and potentially increasing the success rate of these therapies. The meta-analysis underscores the need to standardize TIL assessment in clinical pathology, especially for patients with LSCC. Assessing TILs using hematoxylin-eosin-stained tumor sections or immunohistochemistry could provide valuable insights into patient prognosis and guide treatment strategies.[85]

B cell population

While immunotherapy research typically focuses on T cells, mounting evidence shows that tumor-infiltrating B cells and plasma cells, collectively referred to as tumor-infiltrating B lymphocytes, play a crucial and synergistic role in tumor control. They have significant predictive and prognostic implications in many cancers, despite the conventional emphasis on T cells in immunotherapy. The presence of T cells and myeloid cells in the TME is a prerequisite for infiltrating B cells, whose dysfunction with CXCL13 activates the recruitment of B cells and plasma cells in the TLS.[87] TIL-Bs promote antitumor immune responses through their unique antigen presentation mechanisms, contribute to the formation of immunologically active tumor microenvironments, and possess the potential to counter immune editing and address tumor heterogeneity. This offers hope for developing new treatment approaches and more effective immunotherapy options for cancer patients.

Therapeutic targeting

For solid tumors, TILs play critical roles in innate and adaptive antitumor immunity. Studies have shown that combination therapy can increase the infiltration of lymphocytes, including CD8+ T cells, into the TME compared to monotherapy with anti-PD-L1 or β-lap, highlighting the impact of therapeutic interventions on TILs.[88,89] Traditional chemotherapy has evolved into more targeted approaches focusing on specific cells within the TME. Immune checkpoint blockade therapies, like those targeting CTLA-4 and PD-1, have shown significant clinical benefits but are effective in only a subset of patients.[72] The identification of relevant biomarkers is crucial to

determine patient responsiveness to these therapies.

The advent of immune checkpoint blockade therapy marked a significant shift in cancer treatment by targeting specific immune cells within the TME. By blocking receptor-ligand interactions like CTLA-4 and PD-1, these therapies aim to enhance T-cell activation and function. Despite their potential, a majority of patients remain unresponsive, highlighting the need for precise biomarkers to predict treatment efficacy.[1]

Therapeutic implications and future directions

With the technical development of sc-seq and spatially resolved transcriptomics, numerous studies have demonstrated more potential for TILs and indicated future directions. In NSCLC patients undergoing neoadjuvant PD-1 blockade combined with chemotherapy, sc-seq identified distinct NSCLC tumor microenvironment transcriptomes correlated with therapy response, offering novel biomarkers and potential strategies to overcome immunotherapy resistance, despite limitations of small patient sample size and combination therapy.[90] Another study on NSCLC identified mutation-associated neoantigens (MANA)-specific T cell clones in neoadjuvant anti-PD-1-treated non-small cell lung cancers, revealing unique transcriptional programs. MANA-specific CD8 T cells exhibit features of tissue-resident memory cells but display incomplete cytolytic activation, providing insights into overcoming resistance to PD-1 blockade.[50]

Despite significant developments in TIL treatment, it has been observed that TIL activity and numbers decrease, and their antitumor functions are limited or even altered during the infiltration process. Enhancing lymphocyte infiltration, identifying therapeutic targets, and selecting TILs could provide more possibilities for antitumor immunity. There are 43 ongoing clinical trials of TILs and related drugs (Table 1), which will further implicate the clinical application of TILs in the future. Future research should focus on unraveling the complex interactions within the TME and harnessing this knowledge for therapeutic benefit.

Conclusions

TILs, especially T cells, are integral to orchestrating effective immune responses against tumors. Advances in technologies like sc-seq and spatiomics have enhanced our understanding of TILs. This review emphasized the pivotal role of TILs, discusses their potential as therapeutic targets and prognostic markers, and underscores the need for further research to unravel the complex interactions within the TME for effective cancer immunotherapy.

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Author contributions

Study concept and design (XZ, SJ), acquisition, analysis and inter-

Table 1. Comprehensive overview of clinical trials on tumor infiltrating lymphocyte therapy for advanced solid tumors

NCT number	Study title	Study status	Interventions
NCT05035407	T cell receptor (TCR) gene therapy targeting Kita-kyushu lung cancer antigen 1 (KK-LC-1) for gastric, breast, cervical, lung and other KK-LC-1 positive epithelial cancers	Recruiting	Drug: interleukin 2 (IL-2) (aldesleukin)| Drug: cyclophosphamide| Biological: KK-LC-1 TCR | Drug: fludarabine
NCT05902520	Adoptive cell therapy using cancer specific $CD8^+$ tumor infiltrating lymphocyte (TIL) in adult patients with solid tumors	Recruiting	Biological: double positive (DP) CD8 TIL | Biological: DP CD8 TIL after programmed death-1 (PD-1) knockdown | Biological: low dose IL-2
NCT05831033	Safety and efficacy of an autologous TIL therapy in patients with advanced solid tumors	Not_yet_recruiting	Biological: BEN101
NCT04842812	Engineered TIL/ cheric antigen receptor (CAR)-TIL to treat advanced solid tumors	Recruiting	Biological: TIL and CAR-TIL targeting human epidermal growth factor receptor 2 (HER2), Mesothelin, prostate stem cell antigen (PSCA), mucin 1, Lewis Y antigen, glypican 3 (GPC3), AXL receptor tyrosine kinase (AXL), epidermal growth factor receptor (EGFR), claudin 18.2 and claudin 6 (Claudin18.2/6), receptor tyrosine kinase-like orphan receptor 1 (ROR1), Ganglioside GD1 (GD1), or B7 homolog 3 protein (B7-H3)
NCT04967833	Study on TIL for the treatment of advanced solid tumors	Recruiting	Biological: TIL

(continued)

Table 1. *(continued)*

NCT number	Study title	Study status	Interventions
NCT06077903	GT101 injection in the treatment of metastatic/ recurrent advanced solid tumors	Recruiting	Biological: GT101
NCT05087745	A clinical study on TIL for the treatment of advanced solid tumors	Recruiting	Biological: tumor infiltrating lymphocytes
NCT03449108	Ln-145 or ln-145-s1 in treating patients with relapsed or refractory ovarian cancer, triple negative breast cancer (TNBC), anaplastic thyroid cancer, osteosarcoma, or other bone and soft tissue sarcomas	Active	Biological: aldesleukin| Biological: autologous tumor infiltrating lymphocytes LN-145| Biological: autologous tumor infiltrating lymphocytes LN-145-S1| Drug: cyclophosphamide| Drug: fludarabine| Biological: Ipilimumab| Biological: nivolumab| Other: quality-of-life assessment| Other: questionnaire administration
NCT06094426	Autologous tumor infiltrating lymphocyte injection for the treatment of advanced solid tumors	Recruiting	Biological: GT316
NCT03935893	Adoptive transfer of tumor infiltrating lymphocytes for advanced solid cancers	Recruiting	Biological: TIL| Drug: fludarabine + cyclophosphamide combination
NCT05397093	ITIL-306 in advanced solid tumors	Active	Biological: ITIL-306
NCT06144671	GT201 Injection for the treatment of advanced solid tumors	Recruiting	Drug: GT201
NCT05499715	A phase I clinical study to evaluate the safety, the tolerability, the pharmacokinetic characteristics and the efficacy of scTIL injection (genetically modified tumor infiltrating lymphocytes) in the treatment of advanced malignant solid tumors	Not_yet_ recruiting	Biological: scTIL injection
NCT05868915	HV-101 for patients with advanced solid tumors	Recruiting	Biological: HV-101
NCT05417750	A phase I study on autologous tumor infiltrating lymphocytes injection (GC101 TIL) for the treatment of advanced malignant solid tumors	Recruiting	Drug: TIL therapy
NCT05539768	Study on the safety and efficacy of autogenous tumor infiltrates lymphocytes for the treatment of advanced solid tumor	Not_yet_ recruiting	Biological: HS-IT101
NCT03610490	Autologous TIL MDA-TIL in treating patients with recurrent or refractory ovarian cancer, colorectal cancer, or pancreatic ductal adenocarcinoma	Active_not_ recruiting	Biological: autologous TIL MDA-TIL| Drug: cyclophosphamide| Drug: fludarabine| Biological: IL-2| Other: quality-of-life assessment
NCT05573035	A study to investigate LYL845 in adults with solid tumors	Recruiting	Biological: LYL845
NCT03991741	Adoptive cell transfer of autologous tumor infiltrating lymphocytes and high-dose IL 2 in select solid tumors	Recruiting	Biological: autologous tumor infiltrating lymphocytes| Biological: high-dose interleukin 2
NCT05971576	A clinical study on TILs for the treatment of advanced solid tumors	Not_yet_ recruiting	Biological: LM103

(continued)

Table 1. *(continued)*

NCT number	Study title	Study status	Interventions
NCT05141474	Assessment of the safety and tolerability of ex vivo next-generation neoantigen-selected TIL therapy in advanced epithelial tumors and immune checkpoint blockade (ICB) resistant solid tumors	Recruiting	Biological: NEXTGEN-TIL| Drug: non-myeloablative lymphodepletion (NMA-LD) regimen| Drug: interleukin-2
NCT06060613	Safety and efficacy of OBX-115 in advanced solid tumors	Recruiting	Biological: OBX-115
NCT02650986	Gene-modified T cells with or without decitabine in treating patients with advanced malignancies expressing New York Esophageal Squamous Cell Carcinoma 1 (NY-ESO-1)	Active_not_ recruiting	Drug: cyclophosphamide| Drug: decitabine| Other: laboratory biomarker analysis| Procedure: leukapheresis| Biological: TGFBDNRII-transduced autologous tumor infiltrating lymphocytes
NCT04571892	A clinical study to observe the safety and efficacy of ScTIL210 in the treatment of malignant solid tumors	Recruiting	Biological: super circulating tumor infiltrating lymphocytes (ScTIL)
NCT03658785	Immunotherapy for the treatment of advanced solid tumor	Recruiting	Biological: TIL| Drug: aldesleukin| Drug: cyclophosphamide| Drug: fludarabine
NCT06088472	TIL injection for the treatment of metastatic or recurrent solid tumors	Recruiting	Biological: TIL injection
NCT05971589	A clinical study on LM103 injection for the treatment of advanced solid tumors	Not_yet_ recruiting	Biological: LM103
NCT05730361	Phase Ib clinical study on the safety, the tolerability, the pharmacokinetics and the efficacy of ScTIL injection (gene modified tumor infiltrating lymphocytes) alone and in combination with B lymphocyte adjuvant in the treatment of digestive system malignant solid tumors	Not_yet_ recruiting	Biological: ScTIL injection| Biological: ScTIL injection and B lymphocytes adjuvant
NCT05724732	Exploratory clinical study of autologous tumor-infiltrating lymphocyte injection (GT201) for advanced gynecologic tumors	Recruiting	Biological: GT201
NCT05576077	A study of tbio-4101 (TIL) and pembrolizumab in patients with advanced solid tumors	Recruiting	Biological: TBio-4101| Drug: pembrolizumab
NCT06107894	TIL therapy for patients with advanced solid tumors	Not_yet_ recruiting	Biological: tumor-infiltrating lymphocytes| Drug: IL-2
NCT05649618	TIL cells for the treatment of the advanced solid tumors patients	Not_yet_ recruiting	Biological: tumor infiltrating lymphocytes| Drug: fludarabine| Drug: cyclophosphamide capsules|drug: IL-2

(continued)

Table 1. *(continued)*

NCT number	Study title	Study status	Interventions
NCT06145802	Clinical study of autologous tumor infiltrating lymphocyte injection (GT316) in the treatment of advanced solid tumors (gynecological tumors)	Recruiting	Biological: GT316
NCT04114136	Anti-programmed death-1 monoclonal antibody (anti-PD-1 mAb) plus metabolic modulator in solid tumor malignancies	Recruiting	Drug: nivolumab or pembrolizumab (dependent upon approved indication)| Drug: metformin| Drug: rosiglitazone
NCT05430373	GT101 injection for the treatment of metastatic or recurrent solid tumors	Recruiting	Biological: GT101
NCT06047977	Tumor infiltrating lymphocyte therapy for pediatric high risk solid tumors	Not_yet_ recruiting	Biological: tumor infiltrating lymphocytes, fludarabine, cyclophosphamide, interleukin-2
NCT05366478	A clinical study of LM103 injection in the treatment of advanced solid tumors	Recruiting	Drug: autologous TILs
NCT03645928	Study of autologous tumor infiltrating lymphocytes in patients with solid tumors	Recruiting	Biological: lifileucel|biological: ln-145| Drug: pembrolizumab| Biological: ln-145-s1| Drug: ipilimumab| Drug: nivolumab
NCT05941936	A clinical study on LM103 for the treatment of advanced solid tumors	Recruiting	Biological: LM103
NCT04643574	NeoTIL in advanced solid tumors	Active_not_ recruiting	Biological: NeoTIL| Drug: cyclophosphamide| Drug: fludarabine| Drug: interleukin-2|Radiation: radiotherapy
NCT06237881	A phase 1/2 Study of KSQ-001EX, autologous tumor infiltrating lymphocytes engineered to inactivate the suppressor of cytokine signaling 1 (SOCS1) gene, in patients with select advanced solid tumors	Not_yet_ recruiting	Drug: KSQ-001EX| Drug: IL-2| Drug: cyclophosphamide| Drug: fludarabine
NCT05729399	Clinical study of autologous tumor-infiltrating lymphocyte injection (GT201) for advanced solid tumors	Recruiting	Biological: GT201

pretation of data (LP, ZS), drafting of the manuscript (ZS), critical revision of the manuscript for important intellectual content (XZ, SJ), administrative, technical, or material support and study supervision (SJ). All authors have made a significant contribution to this study and have approved the final manuscript.

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