Roles and functions of tumor-infiltrating lymphocytes and tertiary lymphoid structures in gastric cancer progression

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Gastric cancer (GC), a leading cause of cancer mortality, exhibits profound molecular heterogeneity and immunosuppressive tumor microenvironment (TME) features that limit therapeutic efficacy. This review elucidates the dual roles of tertiary lymphoid structures (TLS) and tumor-infiltrating lymphocytes (TILs) in GC progression. TLS, ectopic lymphoid organs formed under chronic inflammation, correlate with improved survival and immunotherapy sensitivity by fostering effector T/B cell interactions and antigen presentation. Conversely, immunosuppressive TME components like regulatory T cells (Tregs) and tumor-associated macrophages (TAMs) drive immune evasion via cytokine-mediated suppression and checkpoint activation (PD-1/PD-L1). CD8$^+$ T cells exert context-dependent effects, with high infiltration reducing recurrence risk but paradoxically inducing exhaustion in PD-L1-rich microenvironments. Th17 and memory T cells further modulate disease through IL-17-driven angiogenesis and CD45RO$^+$ immune memory dynamics. Multi-omics-based TLS scoring and combinatorial therapies emerge as promising strategies to overcome resistance.

KEYWORDS

gastric cancer, tertiary lymphoid structures, tumor-infiltrating lymphocytes, tumor microenvironment, immune checkpoint inhibitors, progression, biomarkers

1 Introduction

Gastric cancer (GC) poses a significant public health challenge due to its substantial disease burden and clinical management complexities [1]. Molecularly and phenotypically heterogeneous feature exhibits distinct clinical intervention strategies [2–4]. The tumor microenvironment (TME) plays a pivotal role in therapeutic resistance [5–9], where emerging evidence highlights tertiary lymphoid structures (TLS) as critical immunological determinants. These ectopic lymphoid organs exhibit distinct morphogenesis and functional specialization compared to embryonically derived secondary lymphoid organs (SLOs). While SLOs develop constitutively during

embryogenesis, TLS form *de novo* in inflamed non-lymphoid tissues via lymphoid neogenesis under chronic inflammatory conditions (10–12). Their molecular assembly is initiated by stromal CXCL13 and IL-7 secretion, recruiting lymphoid tissue inducer (LTi) cells that drive maturation through LTα/β and TNF signaling, ultimately inducing VEGF-C-dependent high endothelial venule (HEV) formation and PNAd-mediated lymphocyte homing (13, 14).

Notably, TLS are associated with prolonged OS and enhanced immunotherapy sensitivity in solid tumors (12, 15), likely through sustaining effector T-cell clonal expansion and promoting B-cell-mediated humoral immunity. This is particularly relevant given the current landscape of immune checkpoint inhibitors (ICIs), which reactivate antitumor immunity by targeting PD-1/PD-L1 signaling and offer survival benefits for heavily pretreated advanced patients (16). However, the objective response rate (ORR) in GC remains markedly lower than in immunogenic cancers such as melanoma (17–19), underscoring the need to better understand TLS biology and its clinical implications. Histological features including TLS maturity, spatial distribution patterns of tumor-infiltrating lymphocytes, and stromal composition are now recognized as critical biomarkers for predicting immunotherapy responsiveness (20–23), positioning TLS as both biological regulators and therapeutic targets in GC management.

2 Immunoregulatory network of TLS in GC

2.1 Spatial interplay between TLS and immune cells

GC-associated TLS exhibit a spatially organized immune cell architecture: B-cell zones are dominated by CD20^{+} B lymphocytes accompanied by CD21^{+} follicular dendritic cells, while T-cell zones primarily comprise CD3^{+} T lymphocytes, including CD8^{+} cytotoxic T lymphocytes (CTLs) and CD4^{+} helper T cells, forming a functionally complementary immune microenvironment (24–26). Notably, tumor-infiltrating B cells in GC predominantly cluster within TLS. These antigen-experienced B cells can differentiate into antigen-presenting cells, promoting CTL clonal expansion and survival by presenting tumor-associated antigens, thus serving as pivotal orchestrators of antitumor immunity (27). Clinico-pathological evidence reveals that TLS-high gastric tumors exhibit significantly elevated infiltration of CD20^{+} B cells, CD8^{+} T cells, and CD3^{+} T cells compared to TLS-low counterparts, with CD20^{+} B/CD8^{+} T cell co-infiltration independently correlated with prolonged overall survival (28, 29). Mechanistically, TLS enhance T-cell-mediated antitumor immunity by supporting CD8^{+} T cell differentiation into effector memory T cells and driving Th1-type cytokine secretion, like IFN-γ, TNF-α, as demonstrated by transcriptional profiling of tumor-infiltrating lymphocytes (30). Hennequin et al. (31) further identified a strong positive correlation between B-cell aggregate density within gastric TLS and Tbet[+] effector T-cell infiltration, a phenotype linked to

improved recurrence-free survival. These findings collectively suggest that TLS orchestrate T/B cell crosstalk to maintain tumor-immune equilibrium. Recent evidence reveals the spatiotemporal co-evolution of TLS and TILs during tumor progression, wherein immature TLS mature into organized FDC networks with HEVs (32, 33), while TILs transition from naïve/effector to memory/exhausted phenotypes, with longitudinal studies showing that TLS germinal center maturation correlates with CD8^{+} T cell proliferation but also eventual exhaustion, underscoring their dynamic interplay in antitumor immunity (34).

2.2 Prognostic significance of TLS and the immunosuppressive microenvironment

TLS development proceeds through distinct stages: (i) stromal cells secrete homeostatic chemokines to attract lymphocytes; (ii) lymphoid tissue inducer (LTi) cells are recruited to the inflammatory site; (iii) LTβR and TNF signaling drive vascular remodeling and lymphocyte retention; (iv) high endothelial venules (HEVs) expressing PNAd emerge, facilitating lymphocyte trafficking; and (v) organized B/T cell zones form with follicular dendritic cell (FDC) networks, establishing functional TLS capable of antigen presentation and immune cell activation (27, 35). The prognostic impact of TLS is critically modulated by TAMs. CD68^{+} TAM infiltration inversely correlates with TLS density in gastric cancer, while elevated TAM levels predict increased risks of tumor progression (36–40). Furthermore, immune checkpoint dysregulation within TLS may counteract their protective functions: high expression of TIGIT in TLS-associated CD20^{+} B cells accelerates CD8^{+} T cell exhaustion, correlating with reduced median OS. Intriguingly, this TIGIT-enriched subset may derive therapeutic benefit from adjuvant chemotherapy (41). In the gastric cancer microenvironment, TAMs polarize into M1-like (pro-inflammatory) or M2-like (immunosuppressive) phenotypes via cytokine/growth factor signals, regulating TLS formation (42). Mature TLS correlate with robust antitumor immunity, CD8^{+}/memory T cell infiltration, and improved survival, supporting immune surveillance (43, 44). Immature TLS lack structured T/B zones/FDC networks, yielding poor responses. Mature TLS predict better immunotherapy efficacy via efficient neoantigen presentation/T cell priming, unlike immature TLS.

2.3 TLS and neoantigen-driven immune responses

Genomic studies have established a positive correlation between TLS formation and tumor neoantigen burden (45). As central hubs for antigen presentation within the TME, TLS facilitate cross-presentation of tumor-derived neoantigens via enriched mDCs, thereby driving T-cell receptor clonal expansion—a process validated in both gastric and other solid tumors (40, 46, 47). Single-cell technologies have unveiled the intricate connections among diverse cells within the complex tumor microenvironment

(48), including novel cell subtypes (49, 50). Single-cell RNA sequencing analyses of GC-associated mTLS reveal mucosal-associated lymphoid tissue-derived IgA$^+$ plasma cells and natural killer T (NKT) cell subsets, with upregulated complement activation-related genes, such as C1QA, C3AR1, suggesting coordinated humoral and innate antitumor mechanisms (51). Furthermore, Zhu et al. (52) demonstrated that TLS-resident naïve T cells undergo clonal selection and activation through direct contact with mDCs in lung cancer models. The homology of this mechanism in GC, however, requires experimental validation to confirm its conservation across malignancies.

2.4 TLS and cancer immunotherapy

TLS serve as pivotal immunotherapeutic hubs, with their biological traits correlating multidimensionally with treatment sensitivity (53, 54). Cottrell et al. (55) demonstrated TLS-plasma cell co-localization in PD-L1-responsive tumors, implicating TLS in enhancing effector T/B cell synergy. Memory B cells within TLS exhibit dual roles: as APCs driving T-cell expansion and as antibody-secreting plasma cells, while shaping pro-inflammatory microenvironments via TNF/IL-6/IFN-γ secretion (56). TLS density correlates with immune-active tumor microenvironments, supporting TLS-induction therapies (57). Genomically, TLS are enriched in EBV-positive, MSI-high, and PI3K-mutant gastric cancers, where TLR/NF-κB activation driven by high neoantigen loads may enhance responses to PD-1 blockade (28, 45, 58). Clinically, TLS scoring systems have emerged as valuable predictors of immunotherapy efficacy, with a 2.1-fold increase in objective response rate (ORR) observed in high-TLS patients, particularly those harboring CD103$^+$ tissue-resident memory T cell niches (59, 60). Besides, current therapeutic approaches involving triggering the formation of TLS are being applied in GC therapy (61). Therapeutic strategies targeting TLS or checkpoint pathways differ in both mechanism and maturity of evidence. PI3K inhibitors (BAY1082439) promote TLS maturation through chemokine induction and HEV formation—findings supported by preclinical models and early-phase clinical data (62). TLR/NF-κB agonists (CpG-ODNs) stimulate *de novo* TLS formation and remain in the experimental phase with robust murine evidence but limited clinical translation (63, 64). Conversely, PD-1/PD-L1 inhibitors (pembrolizumab) primarily reverse T-cell exhaustion, with efficacy validated in phase II/III trials such as KEYNOTE-061 (65). Combination strategies (PI3K+PD-1 blockade) are currently under early-phase investigation and exhibit synergistic immunostimulatory effects in gastric and other solid tumors (66–68).

Notably, despite its promise as a predictive biomarker, the utility of TLS scoring techniques is constrained by several limitations. First, spatial heterogeneity within tumors means TLS density may vary significantly across sampled regions, leading to under- or overestimation depending on biopsy location. Second, sampling bias in endoscopic or surgical specimens may fail to capture peritumoral TLS clusters that critically influence immune responses. Third, TLS undergo dynamic remodeling during disease progression and treatment, including transitions from immature to mature states or regression following chemotherapy, complicating longitudinal assessments.

3 Role of TILs in gastric cancer development

3.1 Dynamics and functions of CD4$^+$ and CD8$^+$ T cells in gastric cancer

CD4$^+$ helper T cell polarization imbalance drives GC immune evasion, with Th1/Th2 disequilibrium being pivotal. Th1 cells enhance cellular immunity via IL-2/IFN-γ/TNF-β, promoting CTL/NK activity, while Th2 cells stimulate humoral immunity through IL-4/IL-6/IL-10-mediated B-cell differentiation (69). Cross-regulation occurs via IFN-γ suppression of Th2 and Th2 cytokine inhibition of Th1 (70–74). *H. pylori* and dietary carcinogens promote Th2 bias, inducing Treg/M2 macrophage-mediated immunosuppressio*n* (75, 76). Th17 cells, regulated by TGF-β/IL-6/STAT3, secrete IL-17 to promote tumor progression primarily through pro-inflammatory and pro-angiogenic effects. IL-17 enhances angiogenesis by stimulating the expression of chemokines, while simultaneously recruiting neutrophils via IL-8/IL-17 feedback loops, thereby facilitating local inflammation and metastasis in gastric cancer (77). In early-stage GC, IL-17A can activate the NF-κB pathway and induce stromal remodeling, leading to enhanced tumor proliferation. Moreover, certain IL-17 cytokines, including IL-17B, IL-17C, and IL-17F, upregulate VEGF and MMP-9, contributing to vascular invasion and extracellular matrix degradation (78, 79).

Conversely, Th17 cells also exhibit immunostimulatory functions. IL-21 produced by Th17 cells recruits CD8+ cytotoxic T lymphocytes through the CXCR3–CXCL10 axis and enhances their cytolytic capacity by upregulating granzyme B expression. Furthermore, RORγt$^+$ IL-17A$^+$ Th17 cells are associated with increased infiltration of mast cells and NK cells, correlating with improved patient survival and suppression of M2 macrophage-mediated immunosuppression (78, 80). The duality of Th17 cell function appears to be context-dependent: promoting tumorigenesis via NF-κB in early-stage cancer while enhancing immunotherapy response in advanced disease (74, 76). Additionally, IL-17D and IL-17E have been shown to stimulate IFN-γ production by CD8+ T cells, contributing to antitumor immunity (78).

CD8$^+$ T cells, as central effectors of cellular immunity, mediate tumor cell lysis via MHC-I-restricted antigen recognition, migrating along chemokine gradients to infiltrate tumor parenchyma and executing cytotoxicity through granzyme-perforin-mediated exocytosis and Fas/FasL death receptor signaling (81). Pan-cancer analyses substantiate the prognostic universality of CD8$^+$ T cell infiltration, with elevated densities correlating significantly with improved outcomes in cervical, colorectal, and breast cancers (82–84). In GC-specific studies, Li

et al. (33) demonstrated that high CD8^{+} T cell infiltration inversely associates with histological grade (G1/G2) and early TNM staging (I/II), confirming their tumor-suppressive role. Furthermore, Wang et al. (85) revealed in multicohort analyses that GC patients with CD8^{+} T cell-rich infiltrates exhibit significantly reduced lymphovascular invasion and perineural infiltration rates, underscoring their metastasis-inhibitory potential. The immunosuppressive TME, however, counteracts these advantages: dysregulated PD-L1 upregulation engages the PD-1/PD-L1 inhibitory pathway, driving CD8^{+} T cells toward functional impairment and clonal depletion, a process strongly associated with aggressive disease manifestations (81). Thus, although the extent of CD8^{+} T cell infiltration provides essential prognostic insights in GC, their cytotoxic potential is continuously shaped by immunoediting processes within the tumor (Figure 1).

3.2 Regulatory T cells in gastric cancer pathogenesis and progression

Regulatory T cells (Tregs) play dual roles in gastric cancer, suppressing immunity via contact-dependent mechanisms and inhibitory IL-10 and TGF-β, while impairing NK cell activity (86–90). Treg subsets include CD4^{+}CD25^{+}, Tr1 (IL-10^{+}), Th3 (TGF-β^{+}), and CD4^{−}CD8^{−} populations, with FOXP3 as the definitive marker for functional CD4^{+}CD25^{+} Tregs (88).

Clinically, FOXP3^{+} Treg infiltration correlates with advanced tumor stage and reduces 5-year survival by 41.3% (91). Notably, aberrant FOXP3 expression in GC cells promotes PBMC differentiation into Tregs via the miR-155/miR-21 axis, while inducing PBMC secretion of IL-35 and TGF-β to establish immune escape circuits (92). Spatial transcriptomic evidence demonstrates that FOXP3^{+} Tregs form immunosuppressive synapses with CD20^{+} B cells in metastatic niches, driving regulatory B cell (Breg) differentiation via LAG-3/MHC-II interactions to synergistically enforce immune tolerance (92–94). Recent studies have also identified a subset of CCR8^{+} tumor-specific Tregs in advanced GC exhibits strong immunosuppression and TLS proximity, impairing antitumor immunity by suppressing T-cell activation (95). Thus, targeting CCR8 may restore immune responses in treatment-resistant cases.

3.3 CD45RO^{+} memory T cells in gastric cancer pathogenesis and progression

CD45RO^{+} T cells, the core subset of memory T cells, play pivotal roles in antitumor immunity through their unique immune memory retention and effector cell activation properties. They express high levels of adhesion molecules like CD44, facilitating rapid inflammatory homing and endothelial adhesion, sustaining long-term memory and swift secondary immune responses.
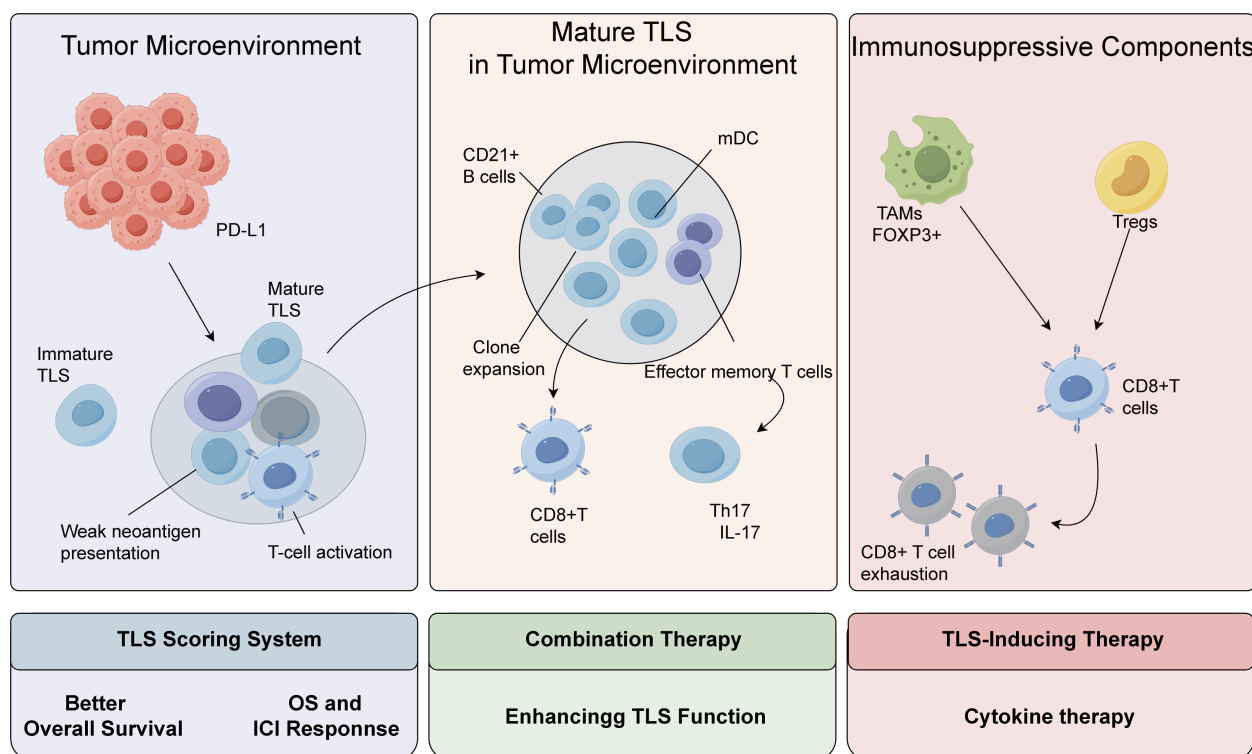

FIGURE 1
The immune interactions between TLS and TILs in gastric cancer and their impact on immunotherapy response.

Clinically, CD45RO$^+$ T cells decline during GC progression: stage III–IV patients show reduced peripheral frequencies versus healthy controls and stage I–II patients, with metastatic tumors exhibiting lower CD45RO$^+$ density than non-invasive lesions. This depletion impairs tumor-specific T cell activation, hindering metastatic cell clearance (96). Mechanistically, CD45RO$^+$ memory T cell decline may stem from chronic tumor-associated antigen exposure-induced clonal exhaustion, compounded by excessive TGF-β secretion in the TME that disrupts memory-to-effector differentiation, ultimately fostering a pro-metastatic immune landscape.

4 Impact of tumor-infiltrating lymphocytes on gastric cancer prognosis

4.1 Prognostic implications of CD4$^+$ T cells in gastric cancer

The dynamic equilibrium of CD4$^+$ T cell subsets, particularly the Th1/Th2 polarization bias, holds critical prognostic significance in GC immunoregulation. Th1 cells orchestrate antitumor immunity through IL-2 and IFN-γ secretion, activating CTLs and enhancing NK cell cytotoxicity, whereas Th2 cells drive humoral responses via IL-4, IL-6, and IL-10 production, with reciprocal regulatory mechanisms maintaining immune homeostasis (97). GC patients exhibit characteristic Th1 suppression. Th2 activation, a disequilibrium that impairs immune surveillance and accelerates disease progression (98). Clinical evidence indicates that Th2-dominant polarization correlates with elevated risks of tumor recurrence and metastasis, mechanistically linked to Treg expansion and M2-polarized TAM infiltration. Consequently, contemporary immunotherapeutic strategies focus on redirecting naïve T cell differentiation toward Th1 polarization to restore Th1/Th2 balance, while monitoring IL-2/IL-4 cytokine profiles in tumor tissues provides molecular insights for personalized treatment optimization and prognostic stratification.

4.2 Impact of regulatory T cells on GC prognosis

Regulatory T cells (Tregs), as pivotal immunosuppressive components within the TME, exert profound clinical significance in GC prognosis through dynamic functional modulation. Inflammatory factors play important roles in disease's progression (99–103). Tregs impair antitumor immunity by secreting inhibitory cytokines and inducing effector T cell dysfunction via direct contact-dependent mechanisms such as CTLA-4/B7-1 interactions, while concurrently promoting vascular endothelial apoptosis to facilitate immune escape (104). Notably, advanced GC patients exhibit characteristic peripheral Treg expansion coupled with B-cell lymphopenia, an immune imbalance partially reversible through neoadjuvant chemotherapy combined with surgical intervention, which restores B-cell-mediated humoral immunity and improves survival outcomes. The prognostic relevance of Tregs has galvanized efforts to develop novel therapeutic strategies targeting the FOXP3 signaling axis, aiming to deplete Tregs or disrupt their immunosuppressive functions to remodel the TME, thereby advancing precision immunotherapy for metastatic GC (105).

4.3 Prognostic impact of CD45RO$^+$ memory T cells in GC

CD45RO$^+$ memory T cells, a critical subset of TILs, exhibit stage-dependent prognostic associations with GC progression. In early-stage GC, CD45RO$^+$ cells confer physiological protection by sustaining immune surveillance, with infiltration density positively correlating with tumor cell clearance efficiency. Conversely, in advanced-stage patients, high CD45RO$^+$ infiltration significantly correlates with improved disease-free survival (DFS) and OS, underscoring its phase-specific prognostic utility (106–108). CD45RO$^+$ T cell infiltration is an independent predictor of survival benefit in advanced solid tumors (106, 107). Notably, while post-operative CD45RO$^+$ infiltration serves as a biomarker for prognostic stratification in advanced GC, its predictive power

TABLE 1 Tumor-infiltrating lymphocyte (TIL) subsets in gastric cancer: functional dichotomy and clinical impact.

TIL Subset	Pro-Tumor Mechanisms	Anti-Tumor Mechanisms	Prognostic Association	Targeted Strategies
CD8+ T cells	PD-L1-induced exhaustion via TIM-3/LAG-3 upregulation	Granzyme B-mediated cytotoxicity; IFN-γ-dependent MHC-I upregulation	High infiltration improves OS (HR=0.54) in PD-L1-low tumors	PD-1 blockade + IL-15 superagonist reverses exhaustion
Th17 cells	IL-17A-driven angiogenesis (VEGF↑, CXCL8↑)	IL-21-mediated CTL recruitment via CXCL10	Dual role: Early-stage IL-17A↑ predicts poor OS; Late-stage correlates with ICI response	Anti-IL-17A mAbs in early GC; IL-17F agonists in advanced
Tregs	FOXP3+CTLA-4+ subset induces CD8+ anergy via TGF-β/IL-35	Tumor-intrinsic FOXP3 suppresses proliferation	≥50 FOXP3+ cells/HPF reduces 5-year OS by 41.3%	Depleting CCR4+ Tregs using mogamulizumab
CD45RO+ Tm	Chronic antigen exposure induces clonal attrition	Immune memory against tumor stem cells via CD103+ TRM	Post-op CD45RO+ density ≥25% predicts 68% 3-year DFS	Personalized vaccines to expand tumor-specific Tm
Bregs	LAG-3+ Bregs secrete IL-10; Promote TAM M2 polarization	TLS-associated B cells enhance PD-1 inhibitor efficacy	Breg/Tfh ratio >2.5 correlates with peritoneal metastasis	CD40 agonists + BTK inhibitors to reprogram B cell fate

lacks statistical significance in early-stage disease, likely attributable to incomplete activation of immunoediting mechanisms during initial tumor evolution (109). Clinical observations reveal markedly reduced peripheral CD45RO$^+$ T cell proportions in recurrent/metastatic patients, though surgical resection combined with adjuvant therapy can partially reverse this immune exhaustion phenotype by restoring effector T cell cytotoxicity. Despite the therapeutic potential of targeting CD45RO$^+$ cell dynamics, the development of specific regulatory strategies and pharmacological interventions necessitates further elucidation through multi-omics.

4.4 Prognostic impact of CD8$^+$ T cells in GC

Immune cells, as core effector components of the TME (110–114), exhibit complex spatial distribution patterns that critically influence cancer outcomes (115–117). High-density CD8$^+$ T cell infiltration reduces recurrence risk and improves OS through granzyme-perforin-mediated cytotoxicity and Fas/FasL death receptor signaling, enabling tumor cell-specific elimination (118). demonstrated via multivariate Cox regression analysis of a 509-patient GC cohort that CD8$^+$ T cell density serves as an independent prognostic factor for OS, showing a strong positive correlation with survival benefit. Paradoxically, Thompson et al. (119) revealed that increased CD8$^+$ T cell infiltration may activate the PD-L1/PD-1 immune checkpoint axis, inducing T cell exhaustion and shortening OS. Notably, recent meta-analyses consolidate evidence supporting the unequivocal protective role of CD8$^+$ T cells in GC prognosis, though their effect magnitude is modulated by tumor molecular subtypes and therapeutic regimens (120). Thus, combining immune modulation strategies to enhance CD8$^+$ T cell infiltration with PD-1/PD-L1 blockade to counteract functional suppression represents a promising therapeutic paradigm for optimizing multimodal GC treatment efficacy (Table 1).

5 Conclusion

The interplay between TLS, TIL subsets, and immunosuppressive networks defines GC progression and therapeutic outcomes. TLS enhance antitumor immunity via lymphoid neogenesis and neoantigen presentation, yet their efficacy is counterbalanced by Treg/TAM-mediated suppression and checkpoint dysregulation. CD8$^+$ T cells and Th17 subsets exhibit dual roles, influenced by molecular subtypes and TME spatial architecture. Memory T cell attrition and Th1/Th2 imbalance further impair immune surveillance, highlighting the need for stage-specific therapeutic approaches. Single-cell profiling of TIL exhaustion states and spatial-temporal TLS maturation analysis can refine prognostic and therapeutic strategies (121–123). Key TLS biomarkers such as CXCL13/CCL21 levels and Tfh/B cell clonality may improve patient stratification for combination immunotherapies. Future research should focus on TLS induction, T cell rejuvenation, and biomarker-driven combinations. Cross-omics validation and standardized TLS quantification are essential for clinical translation. Targeted delivery systems could enhance TLS-localized immunomodulation, minimizing systemic toxicity. These advances promise to bridge TLS biology with precision oncology, optimizing GC immunotherapy.

Conflict of interest

The authors declare that no competing financial interests or commercial relationships have influenced the research presented herein.

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