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EDITORIAL

Immunosuppressive tumor microenvironment in gastric signet-ring cell carcinoma

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Abstract

Gastric signet-ring cell carcinoma (GSRCC) is a subtype of gastric cancer with distinct phenotype and high risk of peritoneal metastasis. Studies have shown that early GSRCC has a good prognosis, while advanced GSRCC is insensitive to radiotherapy, chemotherapy or immune checkpoint blockade therapy. With technological advancement of single-cell RNA sequencing analysis and cytometry by time of flight mass cytometry, more detailed atlas of tumor microenvironment (TME) in GSRCC and its association with prognosis could be investigated extensively. Recently, two single-cell RNA sequencing studies revealed that GSRCC harbored a unique TME, manifested as highly immunosuppressive, leading to high immune escape. The TME of advanced GSRCC was enriched for immunosuppressive factors, including the loss of *CXCL13*$^{+}$-cluster of differentiation 8^{+}-Tex cells and declined clonal crosstalk among populations of T and B cells. In addition, GSRCC was mainly infiltrated by follicular B cells. The increased proportion of SRCC was accompanied by a decrease in mucosa-associated lymphoid tissue-derived B cells and a significant increase in follicular B cells, which may be one of the reasons for the poor prognosis of GSRCC. By understanding the relationship between immunosuppressive TME and poor prognosis in GSRCC and the underlying mechanism, more effective immunotherapy strategies and improved treatment outcomes of GSRCC can be anticipated.

Key Words: Gastric signet-ring cell carcinoma; Single-cell RNA sequencing; Immunosuppressive tumor microenvironment; Immune checkpoint blockade therapy; Prognosis

Core Tip: Two single-cell RNA sequencing studies in 2023 revealed an immunosuppressive tumor microenvironment in gastric signet-ring cell carcinoma (GSRCC). Advanced GSRCC was enriched for immunosuppressive factors, including the loss of *CXCL13*$^+$-cluster of differentiation 8$^+$-Tex cells and declined clonal crosstalk among populations of T and B cells. In addition, GSRCC was mainly infiltrated by follicular B cells. Distinct molecular characteristics and more effective immunotherapy strategies should be investigated to improve the clinical outcomes of GSRCC.

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INTRODUCTION

Gastric cancer (GC) is the fifth most frequently diagnosed malignancy and the fourth leading cause of cancer-associated mortality worldwide. With the widespread application of gastroscopy screening and tissue biopsy, the incidence of distal, intestinal-type GC has decreased, whereas the proportion of tumors with Lauren diffuse or World Health Organization poorly cohesive, including gastric signet-ring cell carcinoma (GSRCC) histology has increased in recent years[1]. GSRCC is characterized by a distinct set of epidemiological, histological features and clinical outcomes associated with a younger age at diagnosis and more female sex distribution[2]. It has been suggested that the prognosis of GSRCC largely depends on the tumor stage. Early stage is a favorable factor, whereas advanced GSRCC is often associated with more aggressive metastasis ability and higher recurrence rate than other types of GC[3]. Advanced GSRCC is associated with a shorter overall survival (OS) and disease-free survival (DFS), the median OS of stage III GSRCC was reported to be only 20.4 months[4]. The clinical management strategies for advanced GSRCC are limited and compromised. Radical surgery is the only effective method to treat GC at early stage, but patients with GSRCC usually experience tumor recurrence after radical surgery. GSRCC is also resistant to conventional chemotherapy, radiotherapy and targeted therapy. Although immune checkpoint blockade (ICB) therapy offers promising clinical benefits among multiple tumor types, it shows a low response rate and limited survival outcomes in GSRCC[5,6]. Therefore, it is necessary to understand the specific tumor microenvironment (TME) characteristic of such a defined "cold" tumor.

Single-cell RNA sequencing has been used to analyze the TME of GC recently, but due to the high complexity of GC, previous investigations have not revealed the specific characteristics of GSRCC yet. In 2023, two articles were published by using single-cell RNA sequencing analysis, which consistently revealed immunosuppressive TME in GSRCC[7,8]. The TME of advanced GSRCC was enriched for immunosuppressive factors, including the loss of *CXCL13*$^+$-cluster of differentiation (CD) 8$^+$-Tex cells and declined clonal crosstalk among populations of T and B cells. In addition, GSRCC was mainly infiltrated by follicular B cells, which harbored relatively weak immune responses. The increased proportion of signet ring carcinoma cells was accompanied by a decrease of mucosa-associated lymphoid tissue-derived B (MALT-B) cells and a significant increase of follicular B cells.

To better understand the differences between non-GSRCC and GSRCC, more multi-dimensional research is needed to investigate the molecular characteristics and TME that may contribute to tumorigenesis, metastasis, and resistance to therapeutics.

T CELL RESPONSIVENESS IS GREATLY IMPAIRED IN GSRCC

T cells are critical in mediating antigen-specific and long-term immunity against viral infections and cancers. T-cell receptor (TCR) is a complex of integral membrane proteins that participates in the activation of T cells. Under normal conditions, T cells responded well to antigen-specific stimulation. However, most T cells remained naive in GSRCC. Expanded CD4$^+$ and CD8$^+$ clonotypes markedly decreased. TCR sharing was almost extinguished among CD4$^+$ subsets and dramatically attenuated among CD8$^+$ subsets. Impaired T cell response in GSRCC may result from proliferation or differentiation blockade. CD4$^+$-Th1 amplification was impaired, CD4$^+$-Tfh showed a delayed augmentation, whereas CD4$^+$-Th17 was characterized by transiently pronounced augmentation at the middle stage of the trajectory in GSRCC[7].

The infiltration characteristics of T cells in GSRCC also differed from those in non-GSRCC. The infiltration rate of CD4$^+$-Treg-*FOXP3* cells was significantly higher in GSRCC than moderately/poorly differentiated adenocarcinoma (M/PDA). Meanwhile, GSRCC had fewer tumor-infiltrating CD8$^+$-Teff cells than M/PDA, mainly manifesting as an immunosuppressive microenvironment[8]. However, another research revealed a significantly lower ratio of regulatory CD4$^+$-Treg-*FOXP3* and exhausted CD8$^+$-Tex cells in GSRCC than in non-GSRCC[7]. It seems to conflict with the anticipation that enrichment of these cell types would contribute to a worse prognosis of GSRCC. This reflects the complexity of the TME, and more detailed sub-types of these cells and other factors should be analyzed systematically.

B CELL-MEDIATED IMMUNE RESPONSE IS DAMPENED IN GSRCC

Memory B cells can differentiate into antibody-secreting plasma cells (PCs) upon antigen stimulation. B-cell receptor (BCR)-sequencing results showed that expanded B-cell clonotypes were mainly PCs, preferred to be IgG-PC in non-GSRCC. However, many memory B cells failed to develop into IgG-PC or IgA-PC in GSRCC, manifesting a poorly responsive landscape. B cells with somatic hypermutation were fewer in GSRCC than non-GSRCC, implying attenuated antigen-specific priming of B cells. IgG-PC in GSRCC was premature, with more early-stage markers (*TCL1A*, *CD22*, *MS4A1*, *CXCR5*) and lowered activation markers (*EGR1*, *EGR3*, *GNLY*, *IGHG1* secreted). There was a remarkable BCR overlap between IgM$^+$ memory B cells and IgG-PC in GSRCC, reflecting the abnormal IgG origin that led to GSRCC malfunction[7].

The cytokine and chemokine-producing effect of CD4$^+$-Tfh, CD4$^+$-Th17, and CD8$^+$-Tex was also impaired in GSRCC, especially for *CXCL13*. It was recognized as a typical marker of tertiary lymphoid structures (TLSs) and participated throughout TLS organizations. The *CXCL13*$^+$-CD8$^+$-Tex is proposed to recruit other immunocytes, thereby facilitating the initiation of TLS formation in individuals with tumors. By staining with nine specific marker panels, the results showed widespread well-organized TLSs with abundant *CXCL13*$^+$-CD4$^+$ and *CXCL13*$^+$-CD8$^+$ cells in non-GSRCC. In contrast, the TLSs were barely visible in GSRCC. Thus, the down-regulation of this *CXCL13*-mediated regulatory effect in CD8$^+$-Tex would contribute to poor outcomes in GSRCC patients. For GSRCC patients, improving the *CXCL13*-producing ability of CD8$^+$-Tex cells may be crucial to reverse the low immune response rate of ICB[7].

MALT-B cells mainly express IgA-related genes, which play an important role in immune response, B cell activation and complement activation. However, follicular B cells have relatively weak immune responses in immune system development and B cell regulation. It was reported that MALT-B and memory B cells were the main infiltrating cells in M/PDA tissue, while follicular B and memory B cells were the main infiltrating cells in poorly differentiated adenocarcinoma with SRCC and GSRCC. The increased proportion of signet ring carcinoma cells was accompanied by a decreased proportion of MALT-B cells and a significant increase of follicular B cells, this could also be one of the reasons for the poor prognosis of GSRCC[8].

MORE EXTENSIVE MECHANISM STUDIES ARE NEEDED TO REVEAL IMMUNO-SUPPRESSIVE TME CHANGE IN GSRCC

The two studies mentioned above consistently revealed immunosuppressive TME in advanced GSRCC through single-cell RNA sequencing or cytometry by time of flight mass cytometry, but more extensive mechanism studies are needed. For example, the molecular mechanism for regulating the expression of *CXCL13* in CD4$^+$-Tfh, CD4$^+$-Th17, CD8$^+$-Tex; the crosstalk between *CXCR5*-*CXCL13* signaling and ICB targeting genes, especially in CD8$^+$-Tex and CD4$^+$-Treg-*FOXP3* cells; the critical obstacle factors which block T cell proliferation and differentiation in GSRCC.

Stage or gender-based TME analysis in GSRCC

GSRCC is a subtype of GC with distinct epidemiological characteristics, and it is important to clarify cytological characteristics and immune microenvironment by stage or gender. One limitation of the present studies is that due to the limited samples, no stage or gender-based analysis was performed.

The prognosis of GSRCC at the early stage is better than that of other types of GC, while at the advanced stage is relatively poorer. The potential for immune system to shape the early development of GSRCC has been elucidated. By using laser capture micro-dissection to separate GSRCC tissue in Stage IA germline pathogenic *CDH*1 variants and hereditary diffuse GC syndrome, whole-exome bulk RNA sequencing (RNA-seq) showed an elevation in CD4$^+$ T cells and influx of Treg cells in GSRCC, which supported a hypothesis of immune-mediated control of early-stage tumor growth and a potential initiating step in immune evasion[9].

Clinical statistics also showed that patients with GSRCC tend to be female and young[10,11]. The role of sex-associated factors, such as estrogen receptor (ER) β, which was dominantly expressed in gastric tissue, has been studied in GSRCC. Results showed ERβ may prevent GSRCC progression in young patients by inhibiting pseudopodia formation *via* the *mTOR-ARPC1B/EVL* signaling pathway. GSRCC Patients with low ERβ expression were at risk of poor prognosis and higher T stage[12]. The TME status of GSRCC in young female or ER-positive samples has not been elucidated. We questioned whether specific ER subtype expression or higher serum estrogen concentration would provoke a more suppressive TME.

Different genetic alterations-based TME analysis in GSRCC

According to the cancer genome atlas database, GC can be divided into four subtypes: Epstein-Barr virus-positive tumors, microsatellite unstable tumors, genomically stable tumors, and tumors with chromosomal instability. In early stage, GSRCC was associated with genetic alterations similar to non-GSRCC, while in advanced stage, GSRCC was associated with a higher frequency of mutations in *TP53*, *ARID1A*, *CDH1*, *BAP1*, and *ERBB2*[13,14]; prevalence of *CLDN18-ARHGAP26/6* fusion; More *PIK3CA* amplifications; Fewer microsatellite instability-high (MSI-H) when compared to non-GSRCC[15]. Although GSRCC was more frequently diagnosed in female and young groups, genetic predispositions, such as *ESR1* gene mutation or amplification, have not been established yet. Epigenetic modification may play an important role in the regulation of ER. Germline *CDH1* mutation, generally due to frameshift, single nucleotide variants or splice site mutations, remained a major risk of GSRCC. GSRCC Patient with *CLDN18-ARHGAP26/6* fusion was related to worse

survival outcomes and got no benefit from oxaliplatin/fluoropyrimidines-based chemotherapy[16]. Due to the important role of TME in regulating ICB therapy efficacy, it would be helpful to distinguish TME status with different genetic alterations to find optimized ICB combination schemes.

POTENTIAL STRATEGIES TO IMPROVE IMMUNOTHERAPEUTIC EFFICACY

ICB therapy offers encouraging hopes for tumor patients, but unfortunately, only a small portion of patients with GC respond well to programmed death receptor 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors, and even worse in GSRCC. In an anti-PD-1 therapy cohort, the response rate, median progression-free survival, OS were 22%, 2.3 months, and 9.0 months in advanced-GC patients without liver metastases[17]. Although single-cell RNA sequencing research revealed immunosuppressive TME in GSRCC, more complicated mechanisms remain unknown. In addition to conventional attempts to combine ICB with chemotherapy, more efforts are encouraged in delineating tumor progression mechanisms and exploring more precise combination regimens to improve the clinical outcomes of GSRCC. Some potential strategies can be considered to improve ICB efficacy in GSRCC.

Remodeling immunosuppressive TME

It is hypothesized that the immunosuppressive TME can block immune cell infiltration and drug delivery, which results in immune evasion and cancer progression. Attempt to remodel TME is an ideal choice to enhance the efficacy of ICB therapy, such as by remodeling TLS development or regulating the crosstalk between tumor-infiltrating lymphocytes and cancer-associated fibroblasts (CAFs).

CXCL13 is recognized as a crucial chemokine that acts *via* its receptor *CXCR5* to promote B lymphocyte recruitment during TLS formation[18]. It was reported that the expression level of *CXCL13* was decreased in $CD8^+$-Tex cells, along with a decline of *CXCL13*$^+$$CD8^+$-Tex cell numbers within TLSs in GSRCC. *CXCL13*$^+$$CD103^+$$CD8^+$-Trm clusters in the TLS-high group responded favorably to anti-PD-1 therapy. Activated B cells induce the secretion of *CXCL13* and granzyme B in *CXCL13*$^+$$CD103^+$$CD8^+$-Trm cells through the lymphotoxin-α (LT-α)/tumor necrosis factor receptor 2 (TNFR2) axis. Up-regulation of the LT-α/TNFR2 axis by LT-α or TNFR2 agonist is a potential strategy to enhance *CXCL13* expression[19]. Promoting *CXCL13* production by transforming growth factor-β also represents a newly immune-regulatory mechanism to shape the immune infiltrate of the TME[20]. Recently, a prospective clinical trial in unresectable stage IV melanoma patients with bone metastases reported that a combination use of receptor activator of nuclear factor k-B ligand inhibitor denosumab and dual checkpoint inhibition (nivolumab, ipilimumab) could increase *CXCL13* serum concentration and improve immunological effects[21].

Meanwhile, the upregulation of chemokine *CXCL5* by anti-PD-1 therapy in GC could lead to an immunosuppressive TME by recruiting tumor-associated neutrophils through the *CXCL5*-*CXCR2* axis. Apatinib, a vascular endothelial growth factor receptor 2 tyrosine kinase inhibitor, can block the *CXCL5*-*CXCR2* axis to enhance anti-PD-1 immunotherapy[22]. Platelet-derived growth factor (PDGF)-PDGF receptors (PDGFR) signaling plays a vital role in the recruitment of polymorphonuclear myeloid-derived suppressor cells and resistance to anti-PD-1 therapy in diffuse-GC. The expression of *CXCL1*, *CXCL3*, *CXCL5*, and *CXCL8* was upregulated in CAFs stimulated with PDGFs. Combination treatment with dual PDGFR α/β inhibitor regorafenib and anti-PD-1 antibody can reprogram the CAFs-associated TME and restore the efficacy of ICB in diffuse-GC synergistically[23].

Matrix metalloproteinases are a family of proteolytic enzymes that degrade multiple extracellular matrix components. Matrix metalloproteinase 3 (MMP-3) was specifically abundant in *CDH1*-aberrant GSRCC[24]. Extracellular *AGR2*, which acts as a chaperon-like enhancer to vascular endothelial growth factor (VEGF) and *FGF2*, can activate stromal fibroblasts and promote fibroblast-associated cancer invasion by exerting paracrine effects on fibroblasts in the TME of GSRCC[25,26]. Therefore, inhibitors for MMP-3 or monoclonal antibody targeting *AGR2* may also represent a promising choice to enhance the efficiency of ICB by remodeling immunosuppressive TME in GSRCC.

Proteomic profiling of GSRCC tissue revealed that the complement cascade pathway is activated more than in non-GSRCC. Therapies targeting the complement cascade have already experimented against immune system-related diseases. Targeting the complemental regulation protein (C4b-binding protein, decay-accelerating factor and carboxypeptidases N) might be a practical approach to optimize the effects of ICB therapy[27].

Application of mutation-derived neoantigen

PD-L1 combined positive score, tumor mutation burden (TMB) and MSI are important predictive biomarkers for evaluating the efficacy of immunotherapy in GC. Results showed that PD-L1 was overexpressed in 45% of GSRCC, and only 1.8% TMB-high and 3.5% MSI-H were identified[28,29], which was consistent with the low response rate of ICB therapy in GSRCC. It is suggested ICB therapy may not be the best choice for GSRCC treatment.

Mutation-derived neoantigen peptides are crucial elements in neoantigen-reactive T cells (NRTs) immunotherapy. Ding *et al*[30] have explored the safety and efficacy of NRTs by targeting mutant *KARS*, *CDH1*, *TP53*, *BRAF*, and *ERBB2* in 20 patients with stage III GSRCC after postoperative chemotherapy. The results demonstrated a prolonged DFS and OS compared to previous studies, which exhibited a potential application of NRTs immunotherapy in the treatment of advanced GSRCC.

CONCLUSION

In addition to the canonical awareness of the high invasion ability caused by pathogenic germline *CDH1* variants, single-cell RNA sequencing analysis also revealed an immunosuppressive TME in GSRCC, consistent with its low response rate to ICB therapy and poor prognosis. Investigation into carcinogenesis and TME remodeling will provide us better understandings of the pathogenesis of GSRCC, and new clues for the development of innovative therapeutic strategies in the future as well.

FOOTNOTES

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