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Gastric Signet Ring Cell Carcinoma: Tumor Microenvironment Reprogramming and Novel Therapeutic Targets With Emphasis on GRIN2D

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ABSTRACT

Gastric Signet Ring Cell Carcinoma (GSRCC) is an increasingly recognized subtype of gastric cancer, particularly prevalent in South Asian populations and regions within India. This carcinoma is distinguished by its abundant cytoplasmic mucinous cells and aggressive clinical behavior, often affecting younger individuals and leading to a poor prognosis due to its advanced-stage presentation and resistance to standard treatments. A critical factor in its progression is the tumor's uniquely immunosuppressive and stromal-rich microenvironment, characterized by dysfunctional immune infiltrates, activation of cancer-associated fibroblasts, extracellular matrix remodeling, and complement cascade dysfunction. Recent research has highlighted the significance of key biomarkers, including MSMB, AGR2, CLDN18.2, and notably GRIN2D, which play roles in tumor angiogenesis, immune evasion, and metabolic reprogramming. The interaction of these elements contributes to therapeutic resistance and immune escape, thereby reducing the effectiveness of chemotherapy and checkpoint inhibitor immunotherapies. Innovative strategies that integrate stromal-targeting agents, complement modulators, anti-CLDN18.2 antibodies, and novel GRIN2D-targeted therapies, along with precision molecular profiling, offer potential for enhancing patient outcomes. Tailored approaches that incorporate early detection and dynamic biomarker monitoring may ultimately transform GSRCC management toward personalized, evidence-based therapies and prevention.

1 | Introduction

Gastric cancer remains one of the most significant global health concerns, ranking as the fifth most prevalent malignancy worldwide, accounting for 4.9% of all cancer cases and representing the

fifth leading cause of cancer-related mortality, with a rate of 6.8% [1]. The global standardized incidence and mortality rates were 11.1 and 8.2 per 100,000 persons respectively [2]. Geographical disparities in gastric cancer burden are particularly striking. More than 60% of total cases are concentrated in Eastern and

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South-Eastern Asia, with Eastern Asia alone accounting for half of the global burden [3]. Despite favorable declining trends in mortality worldwide, significant regional variations persist with the highest mortality observed in Eastern Asia (15.9 per 100,000 persons) and the lowest in Northern America (1.8 per 100,000 persons) [2–4]. The etiology of gastric cancer is multifactorial, involving a combination of factors such as high salt consumption, processed food intake, smoking, alcohol use, obesity, and infections including *Helicobacter pylori* (*H. pylori*) and Epstein-Barr virus (EBV). Genetic predisposition accounts for a small proportion of cases, such as hereditary diffuse gastric cancer [5].

Gastric cancer is a highly heterogeneous disease with distinct subtypes on the basis of histological and molecular characteristics. The Lauren classification divides gastric cancer into intestinal and diffuse type adenocarcinomas, which differ significantly in epidemiology, pathogenesis, differentiation and prognosis. The intestinal type is characterized by cohesive tumor cells forming glandular structures with tubular or papillary histology, resembling the intestinal epithelium. It is associated mainly with *H. pylori* infection, chronic atrophic gastritis, and intestinal metaplasia. The diffuse type features diffusive tumor cells that infiltrate the gastric wall without forming distinct glandular structures. The two main diffuse type subtypes are Gastric Signet Ring Cell Carcinoma (GSRCC) and poorly cohesive carcinoma-not otherwise specified (PCC-NOS) [6].

Gastric cancer remains a significant health concern in India, with increasing rates despite a global decline. The prevalence is 5.8 per 1,00,000 population, ranking sixth most common overall and fifth among men. It affects men more than women (ratio 2.3:1), with diagnosis typically occurring between 58 and 60 years of age. Most cases present with locoregionally advanced or metastatic diseases contributing to a five-year survival rate below 20% [7]. Although many parts of the world have experienced a decline in the incidence of gastric cancer, India is experiencing a persistent or even increasing trend in select high-risk regions. Environmental and lifestyle factors drive regional differences [8]. In India, approximately 10.3% of all gastric cancers account for GSRCC, with its relative proportion of which has been rising over recent decades [9]. This trend is particularly evident in high-risk areas such as the Northeast and certain urban regions, highlighting the importance of considering the distinct clinicopathological characteristics and molecular mechanisms of GSRCC when developing research priorities and treatment strategies.

The tumor microenvironment (TME) in GSRCC represents a complex ecosystem of cellular and molecular interactions that fundamentally influence disease progression, therapeutic resistance and clinical outcomes [10]. Recent single-cell RNA sequencing (sc-RNA sequencing) studies have revealed that GSRCC harbors a uniquely immunosuppressive TME characterized by adaptive immune responsiveness. This immunosuppressive landscape manifests as quiescent CD4⁺ and CD8⁺ T cell populations that are difficult to mobilize, subsequently impairing proper B cell functions [10, 11]. Understanding the TME is crucial for developing effective therapeutic strategies, as conventional treatments including chemotherapy, and immune checkpoint blockade therapy have demonstrated limited efficacy in advanced GSRCC [10]. The identification of specific molecular

mechanisms underlying immune evasion, stromal remodeling and therapeutic resistance provides opportunities for targeted intervention and personalized approaches. This review aims to synthesize current knowledge on the distinct TME reprogramming in GSRCC, highlight key mechanisms of immune evasion and therapeutic resistance and explore emerging biomarkers and targeted strategies that hold promise for improving patient management through personalized approaches.

2 | Methodology

This review article conducted a systematic literature search utilizing PubMed and Google Scholar. Keywords such as Gastric signet ring cell carcinoma, Tumor microenvironment, Immune evasion and therapy resistance and GRIN2D were used to find relevant studies. The articles included were original research, review, and meta-analyses written in English. Case reports, editor letters and unrelated studies were excluded. This review focused on TME reprogramming in GSRCC.

3 | Pathological and Clinical Characteristics of GSRCC

3.1 | Histopathological Definition and Classification

GSRCC is histologically defined by the presence of signet ring cells characterized by large cytoplasmic mucin vacuoles that displace the nucleus to the cell periphery, creating a classic signet ring appearance [12]. The WHO classification system requires that signet ring cells compromise more than 90% of the tumor volume for GSRCC diagnosis distinguishing it from poorly cohesive carcinoma not otherwise specified (PCC-NOS); notably GSRCC is considered a Grade 3 tumor according to the histological grading standard [13].

Recent histomorphology studies have identified the developmental origins of GSRCC demonstrating that early lesions arise from proliferative zones in the fundus of gastric foveolae and the neck of gastric glands [14]. This signet ring heterocyst undergoes redifferentiation and repopulation, extending horizontally along the gastric foveolae before infiltrating the lamina propria and submucosa. Differentiation patterns can result from the developmental processes, such as fundus gland adenocarcinoma with signet ring cell differentiation, mucinous adenocarcinoma with signet ring cell differentiation, and undifferentiated adenocarcinoma with signet ring cell differentiation [15].

3.2 | Epidemiological Trends and Demographic Associations

GSRCC exhibits unique clinical features that distinguish it from the other gastric adenocarcinomas. Demographically, GSRCC demonstrates distinct patterns with female predominance constituting approximately 50% of all gastric cancer cases, which is significantly higher than the 30% observed in non-GSRCC cases and presents at a younger age with an average diagnosis at 62 years versus 69 years for non-GSRCC [16]. Additionally, it

was observed that young women with GSRCC exhibit high estrogen receptor expression suggesting a hormonal influence in disease development, resulting in a more aggressive, metastatic tumor phenotype [17, 18]. The association of *H. pylori* infection has been documented with early GSRCC development linked to massive cell proliferation and transformation in deep gastric foveolae following bacterial infection [15].

3.3 | Prognosis in Early vs. Advanced and Treatment

The prognostic implications of GSRCC demonstrate a stage-dependent pattern. Compared with other gastric cancer types, early-stage GSRCC generally has a favorable prognosis; whereas, advanced GSRCC is associated with significantly worse outcomes [19]. The median overall survival (OS) for stage 3 GSRCC has been reported to range between 15 and 24 months, while for resectable gastric cancers the median OS ranges from 28 to 51 months [20].

On the basis of endoscopic ultrasound manifestations, GSRCC can be classified into two distinct types. Type 1, which is more prevalent among older males, is characterized by diffuse gastric wall thickening with loss of stratification, larger tumor size, extensive serosal and lymphatic involvement, and significant weight loss. In contrast, type 2 lesions more common in younger females, retain layer stratification and exhibit localized wall thickening. This tends to be smaller with limited spread and milder symptoms and may appear deceptively intact on imaging despite deeper invasion. Type 1 tumors more frequently involve the gastric fundus and gastric angles, with significantly higher rates of serosal invasion [21, 22]. These findings correlate with more aggressive clinical behavior and poorer prognosis observed in advanced GSRCC cases.

For early GSRCC, tumors <2cm in size without ulceration or lymphatic involvement can be treated with endoscopic resection, whereas lesions with a higher risk of nodal spread require radical gastrectomy with D2 lymphadenectomy. Although, the perioperative FLOT (Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel) regimen has shown improved survival outcomes in advanced GSRCC, the overall chemosensitivity remains suboptimal. In selected patients with limited peritoneal metastasis and a low peritoneal carcinomatosis index, perioperative FLOT along with cytoreductive surgery has been associated with improved overall and recurrence-free survival [23].

4 | Tumor Microenvironment

The TME is a complex and ever-changing ecosystem that supports cancer cells. It's made up of various components like cancer-associated fibroblasts (CAFs), immune cells, endothelial cells, extracellular matrix (ECM) elements, and a wide array of signaling molecules [24]. Together, these elements actively drive cancer progression. This intricate network is crucial for helping tumors grow, survive, and spread, often by suppressing the immune system, promoting new blood vessel formation, and altering cell metabolism [25]. In GSRCC, the TME presents as a highly intricate ecosystem where cellular compartments

undergo significant changes as the disease advances. For instance, sc-RNA sequencing analysis has revealed unique cellular compositions marked by their immunosuppressive characteristics. The immune compartments demonstrate reduced infiltration of cytotoxic T lymphocytes, altered B cell populations, and increased regulatory T cell (Tregs) presence (Figure 1). As GSRCC progresses, the TME undergoes significant reprogramming. Cellular makeup shifts with immune cells becoming less effective and stromal components, such as CAFs and ECM playing a dominant role. Thus, this reprogramming is a key driver of the aggressive behavior and therapy resistance observed in GSRCC [10].

The stromal fibroblasts are dominated by CAFs that undergo activation through Transforming Growth Factor- β (TGF- β) signaling pathways [26]. These activated fibroblasts contribute to desmoplastic reactions and extracellular matrix remodeling that facilitate tumor invasion and metastasis [26, 27]. The vascular compartment shows altered angiogenic patterns influenced by Vascular Endothelial Growth Factor/receptor (VEGF/VEGFR) signaling, while the extracellular matrix undergoes extensive remodeling mediated by matrix metalloproteinases [27, 28].

4.1 | Stromal Reprogramming and Cancer Associated Fibroblasts Heterogeneity

Within TME, CAFs are known to represent one of the most heterogeneous and functionally diverse cell populations [29]. Certain CAFs populations known as inflammatory CAFs (iCAFs) secrete inflammatory cytokines and chemokines, recruiting immune cells paradoxically while maintaining an immunosuppressive environment [30, 31]. Others like myofibroblast CAFs (myCAFs) and matrix CAFs (mCAFs) are primarily involved in depositing and remodeling ECM, especially near tumor cells; thereby, contributing to the physical and biochemical barriers that protect the tumor. Another subset, antigen presenting CAFs (apCAFs) presents antigens and is found near Tertiary Lymphoid Structures (TLS), whereas, another distinct subset of CAFs arises from endothelial cells and contributes to vascular changes within the TME. Therapeutic resistance in GSRCC is closely related to the biology of CAFs. They secrete factors such as PDGFC that activate multiple signaling pathways in tumor cells, including JNK, AKT, PRAS40, c-Jun, and STAT3 [32]. The activation of these pathways promotes tumor cell survival, proliferation, and invasion while also making cancer more resistant to both chemotherapy and immunotherapy [33].

4.2 | TGF- β Signaling and Stromal Activation

The TGF- β signaling pathway plays a central role in stromal reprogramming in GSRCC. Both the tumor cells and CAFs produce high levels of TGF- β 1, which establishes a positive feedback loop that sustains stromal activation and resistance to therapy. TGF- β signaling drives the conversion of normal gastric fibroblasts into cancer-associated phenotypes with extensive changes in gene expression. They also induce Epithelial-Mesenchymal Transition (EMT), resulting in cancer cells being more plastic and invasive, thus enhancing immune suppression by increasing Tregs infiltration and functioning. Furthermore,

Immune Cell Dysfunction In GSRCC

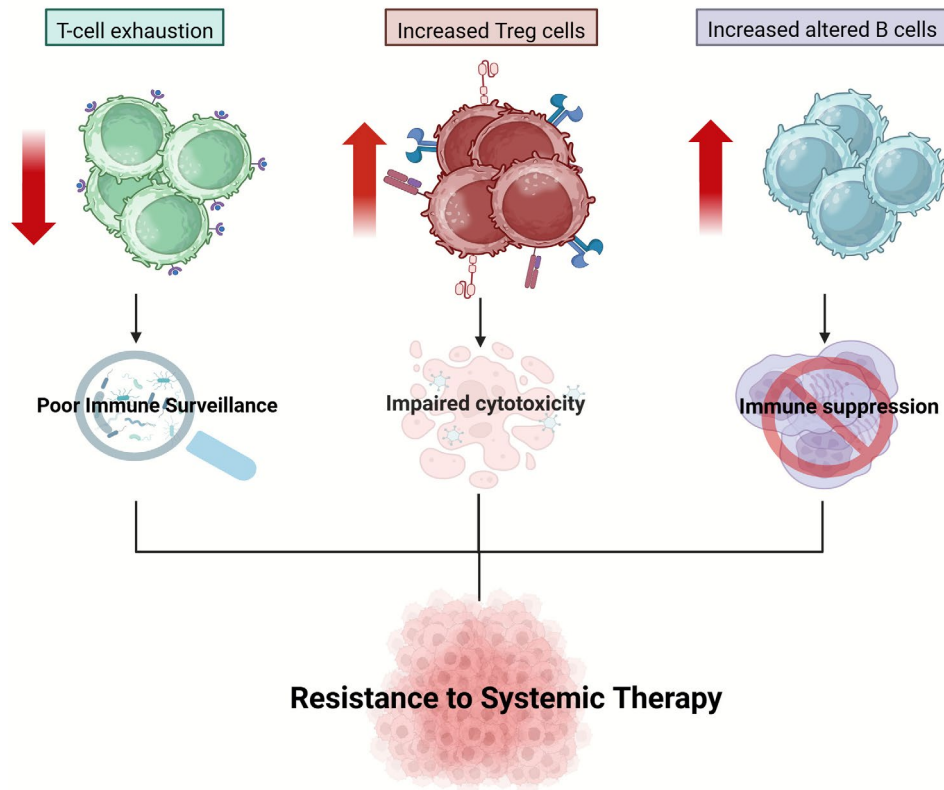


FIGURE 1 | Immune cell dysfunction in Gastric Signet Ring Cell Carcinoma. Principle mechanisms of immune cell dysfunction in GSRCC that underlie resistance to systemic therapies. Exhaustion of cytotoxic T cells, expansion of regulatory T cells, and the presence of altered B cell subsets result in impaired immune surveillance, reduced cytotoxicity and heightened immune suppression. The convergence of these processes establishes an immunosuppressive microenvironment, ultimately reducing the effectiveness of systemic based therapies in GSRCC.

TGF- β upregulates matrix metalloproteinases (MMPs) and collagen deposition that contribute to ECM remodeling. Clinically, the impact of TGF- β is profound. EMT induced by TGF- β is strongly linked to resistance to chemotherapy and immunotherapy. These cancer cells undergo EMT and acquire mesenchymal traits, resulting in lesser sensitivity to treatment and better evasion of the immune system. Inhibiting TGF- β signaling, the transformation of normal fibroblasts into cancer-associated fibroblasts is prevented, thereby disrupting the tumor-promoting microenvironment. Additionally, TGF- β inhibitors have the potential to reverse EMT, which may restore sensitivity to chemotherapy [34, 35].

4.3 | Desmoplasia and ECM Remodeling

Desmoplasia, or the proliferation of myfibroblasts and increased ECM deposition, is a hallmark of GSRCC progression. It is observed in most cases and is associated with more aggressive disease, including higher rates of lymphovascular invasion and venous infiltration. The ECM in GSRCC is dynamically remodeled by MMPs particularly MMP9 and MMP2 which degrade structural components such as type 4 collagen in basement membranes [27]. This degradation facilitates tumor cell migration and invasion along with the secretion of growth factors that promote angiogenesis and further tumor progression [36].

The extent of desmoplasia is clinically significant as patients with stroma-rich tumors generally have a poorer prognosis than those with stroma-poor tumors [37]. Targeting specific MMPs or their regulatory pathways selectively can decrease tumor invasiveness and metastatic potential, though it is crucial to avoid disrupting beneficial MMP functions [38, 39].

4.4 | The CXCL12/CXCR4 Signaling Axis

The CXCL12/CXCR4 signaling axis plays a vital role in TME reprogramming in GSRCC. The loss of E-cadherin in tumor cells leads to increased expression and altered localization of CXCR4 [40, 41]. CAFs, the main source of CXCL12, create a chemokine gradient that supports immune suppression and stromal activation [42]. This helps sustain E-cadherin deficient tumor cells by activating NF- κ B signaling and upregulation of anti-apoptotic genes, while also recruiting immunosuppressive myeloid cells into TME [43].

4.5 | Tumor Stroma Cross Talks and Intertumoral Heterogeneity

The bi-directional communication between tumor cells and stromal compartments creates a dynamic microenvironment

that promotes GSRCC progression. TGF- β 1 secreted by both tumor cells and CAFs enhances the transition from normal gastric fibroblasts to CAFs, establishing a positive feedback loop that amplifies stromal activation. This process results in increased expression of CAF-mediated genes, including CCL2, RAB3B, and TNC along with enhanced production of fibroblast growth factors [26, 44].

5 | Immune Landscape and Immune Evasion Mechanism

The immune compartment of the GSRCC TME is profoundly dysfunctional. Studies have revealed a marked reduction in Tumor Infiltrated Lymphocytes (TILs), especially cytotoxic T cells [11]. The remaining T cells are often naive and show limited clonal expansion indicating a reduced ability to recognize and attack tumor cells [10, 11, 45]. The impaired sharing of T cell receptors (TCRs) among different T cell subsets and altered differentiation patterns, result in reduced cytotoxicity capacity. Along with this, lower expressions of immune checkpoint molecules such as PD-1 and PD-L1, correlate with a poor response to immune checkpoint blockade therapies. These mechanisms, including low TILs, T cell exhaustion, expansion of Tregs and shifts in B cell compartments collectively result in diminished immune surveillance, impaired cytotoxicity, immune suppression and altered antigen presentation, ultimately driving immune evasion in GSRCC (Figure 2) [10, 46].

B cell dysfunction in GSRCC leads to poor antibody production and a shift toward less effective follicular B cells, undermining anti-tumor immunity [10]. Elevated Tregs cells, driven by TGF- β , further suppress cytotoxic responses and promote immune evasion [47, 48]. Additionally, GSRCC resists immune checkpoint therapies through genetic alterations, increased immunosuppressive factors, and predominance of suppressive B cell populations, resulting in the development of difficult therapies [10]. Efforts to counter immune escape in GSRCC continue, with combination therapies targeting both immune checkpoints and other immunosuppressive pathways within the tumor microenvironment [49].

6 | Complement Cascade and Immune Modulation

Proteomic studies have shown that the complement cascade especially the classical and lectin pathways, is distinctly activated in GSRCC [16]. This activation is marked by increased levels of complement proteins such as C1q, C4, C3, C5, and C9 and is accompanied by increased antigen presentation and immunoglobulin production. The classical pathway is often initiated by immunoglobulins binding to C1 complexes, whereas the lectin pathway is activated by mucins produced by the tumor [16, 33, 50]. The complement system plays a dual role in tumor immunity. Activation of the complement cascade can lead to the formation of Macrophage Activated Complex (MAC), that induces tumor cell apoptosis and enhances adaptive immunity, whereas complement activation can promote tumor progression by recruiting Myeloid Derived Suppressor Cells (MDSC) and

Tumor Associated Macrophages (TAMs), which create an immunosuppressive microenvironment [33]. Anaphylatoxins generated during complement activation can also stimulate tumor cell proliferation and survival [16]. Tumor cells in GSRCC often overexpress complement mediated lysis by enhancing the decay of complement convertases and preventing MAC formation [16]. Thus, overexpression is a hallmark of GSRCC and contributes to immune evasion and therapeutic resistance by further dampening the anti-tumor response.

The TME in GSRCC is reprogrammed at multiple levels such as stromal, immune and molecular levels, creating a highly supportive niche for tumor growth and spread while simultaneously undermining the body's ability to defend against and resist therapy. Thus, understanding these complex interactions is crucial in developing effective, targeted treatments for aggressive tumors like GSRCC. By modulating the complement system, particularly through targeting complement regulatory proteins, complement-mediated tumor immunity may be restored. This strategy seeks to enhance anti-tumor activity while preventing excessive complement activation which could lead to tumor progression or tissue damage [51].

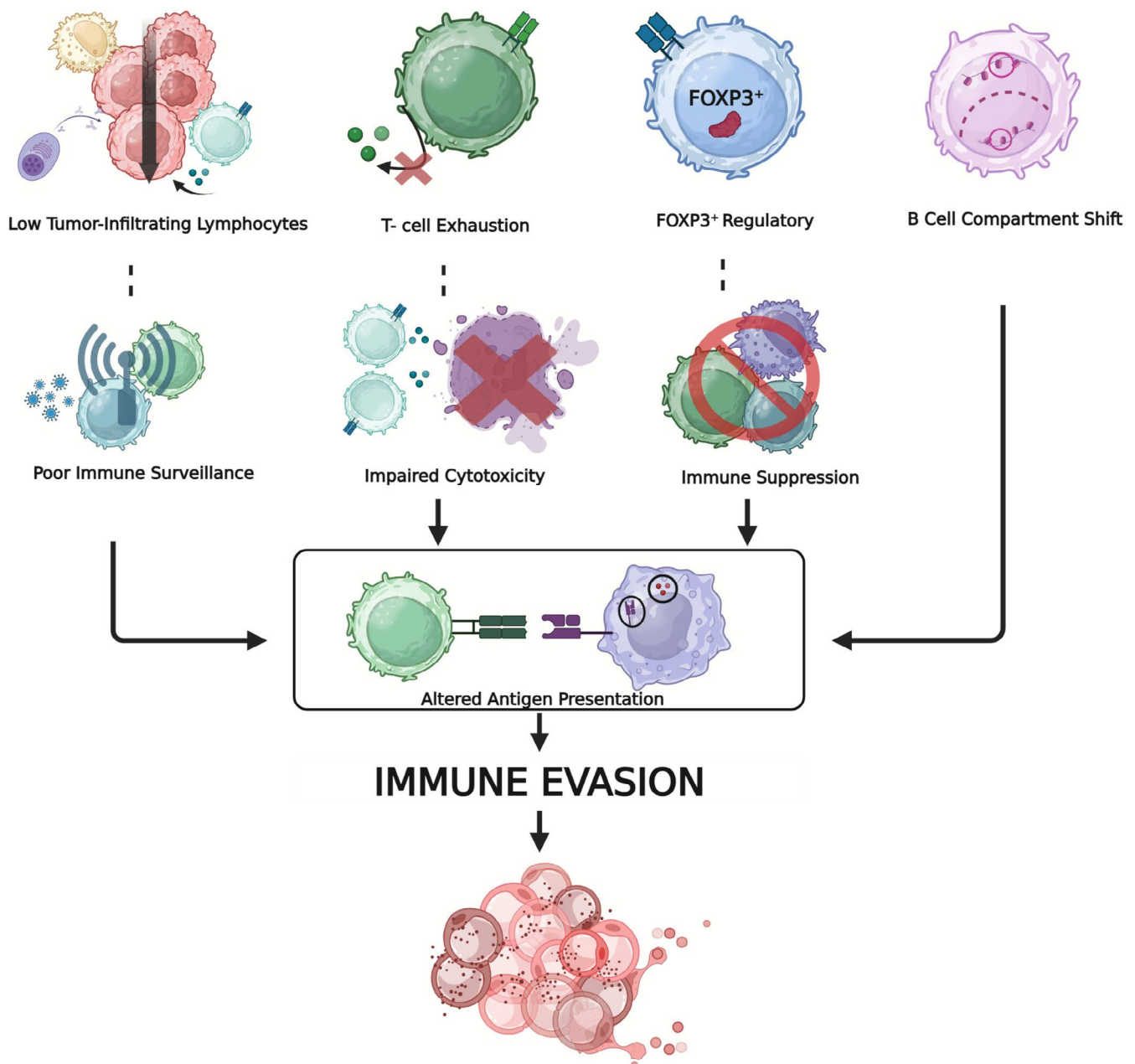
7 | Potential Biomarkers in GSRCC: MSMB, AGR2, and CLDN18.2

7.1 | Microsemino Protein β (MSMB) (Gene ID 4477)

The Microsemino Protein β (MSMB) was identified through scRNA sequencing can differentiate between poorly differentiated adenocarcinomas including signet ring cell carcinoma and moderately differentiated adenocarcinoma (Table 1). This can help identify the cellular differentiation states and tumor heterogeneity present within these tumors and identify GSRCC [52].

7.2 | Anterior Gradient 2 (AGR2) (Gene ID 10551)

Anterior Gradient 2 (AGR2) is a protein disulfide isomerase that is known to be overexpressed in various cancers including GSRCC. It is located primarily in the endoplasmic reticulum where it exerts its role in assisting protein folding and helps cancer cells to overcome endoplasmic reticulum stress that is commonly observed in the rapidly changing TME [53, 54]. It is also noted that AGR2 can be secreted by signet ring cell carcinoma cells and is subsequently taken up by fibroblasts where it activates these cells and promotes tumor progression. This activation leads to the migration, invasion, and secretion of various growth factors by fibroblasts which fuels tumor growth. Clinically it is observed that AGR2 expression is elevated in more than half of gastric cancer patients and is closely associated with larger tumor size, deeper invasion, advanced TNM stage and lymphatic metastasis. It is observed that high AGR2 expression is correlated with shorter survival rates indicating its role as an independent prognostic factor for disease progression in GSRCC [55]. Agr2 can serve as a biomarker by modulating the TME through fibroblast activation and immune suppression. Its overexpression can be correlated with poor T cell infiltration,



GSRCC -- PROGRESSION AND METASTASIS

FIGURE 2 | Immune dysfunction within the tumor microenvironment enables GSRCC to evade immune detection and destruction. Key features included reduced infiltration of protective lymphocytes, T cell exhaustion, increased regulatory T cell-FOXP3+ and altered B cell compartments. These changes collectively lead to immune escape and promote tumor progression and metastasis.

therapy resistance and aggressive tumor behavior. It can easily be detected in body fluids offering non-invasive diagnostic potential. It can also be a potential therapeutic target as it is a Tumor-Associated Antigen and is not expressed in normal cells [56].

7.3 | Claudin 18.2 (Gene ID 51208)

Claudin 18.2 (CLDN18.2) has recently emerged as a highly selective and actionable biomarker in gastric cancer, including GSRCC. Abnormally expressed on the cell surface in roughly one-third of

gastric cancers, CLDN18.2 is especially prevalent in diffuse-type tumors and in younger patients [57, 58]. Interestingly, a significant proportion of CLDN18.2-positive cases do not overlap with other common biomarkers such as Human Epidermic Growth Factor (HER2) or EBV, suggesting that CLDN18.2 defines a distinct molecular subtype within gastric cancers [59]. This unique expression pattern has paved the way for targeted therapies, most notably zolbetuximab, an anti-CLDN18.2 monoclonal antibody. Zolbetuximab has demonstrated significant clinical benefit, with FDA approval for use in CLDN18.2-positive advanced gastric cancer, particularly when combined with chemotherapy [60]. Patients treated with this regimen have shown marked improvements in

both progression-free survival (PFS) and OS, underscoring the therapeutic potential of targeting CLDN18.2 in GSRCC. The meta-analysis of three randomized controlled trials demonstrated that zolbetuximab plus chemotherapy significantly improved PFS (HR 0.64, 95% CI 0.49–0.84) with median PFS across the trials ranging from 7.5 to 10.61 months versus 5.3 to 8.67 months with chemotherapy alone. OS was significantly prolonged with the combination of zolbetuximab along with chemotherapy (HR 0.72, 95% CI 0.62–0.83) with median OS improvements from 13.0 versus 8.3 months in the FAST trial, 14.39 versus 12.16 months in the GLOW trial, and 18.23 versus 15.54 months in the SPOTLIGHT trial. Recent studies have revealed that CLDN18.2 mediates critical interactions between gastric cancer cells and cancer-associated fibroblasts within the TME, facilitating adhesion that leads to clustering into emboli and enhanced metastatic progression. This can also correlate with heightened infiltration of CAFs providing insights into potential therapeutic avenues through combined CAF inhibition strategies [61–63].

7.4 | GRIN2D (Gene ID 2906) as an Emerging Biomarker and Therapeutic Target

We performed comprehensive in silico analysis utilizing the UALCAN database and identified GRIN2D (glutamate ionotropic receptor NMDA type subunit 2D) as a potential promising biomarker that is uniquely overexpressed in GSRCC compared with other gastric cancer subtypes (Figure 3) [64, 65].

GRIN2D encodes a subunit of the NMDA-type glutamate receptor, which is best known for its role in mediating calcium influx in response to glutamate signaling [66]. While these receptors are well studied in the nervous system, their function within the TME is only beginning to be understood. In the context of GSRCC, GRIN2D appears to play a significant role in regulating endothelial function and promoting angiogenesis a key process that supports tumor growth and the development of new blood vessels within the tumor vasculature.

TABLE 1 | Biological Functions and therapeutic implications of key biomarkers in GSRCC.

Biomarker	Biological function	Therapeutic implications
MSMB	Regulate immune response, modulate cell proliferation	Target for immune-modulating therapies
AGR2	Disulfide isomerase involved in mucin production, ER homeostasis and cell migration	Target for disrupting tumor growth and inhibit metastasis in GSRCC
CLDN18.2	Tight junction protein-epithelial barrier integrity	Targeted by monoclonal antibodies (Ex: Zolbetuximab along with standard chemotherapy regimen)
GRIN2D	NMDA receptor subunit, regulates calcium influx	Target for disrupting tumor metabolic reprogramming and preventing angiogenesis in GSRCC

Expression of GRIN2D in STAD based on histological subtypes

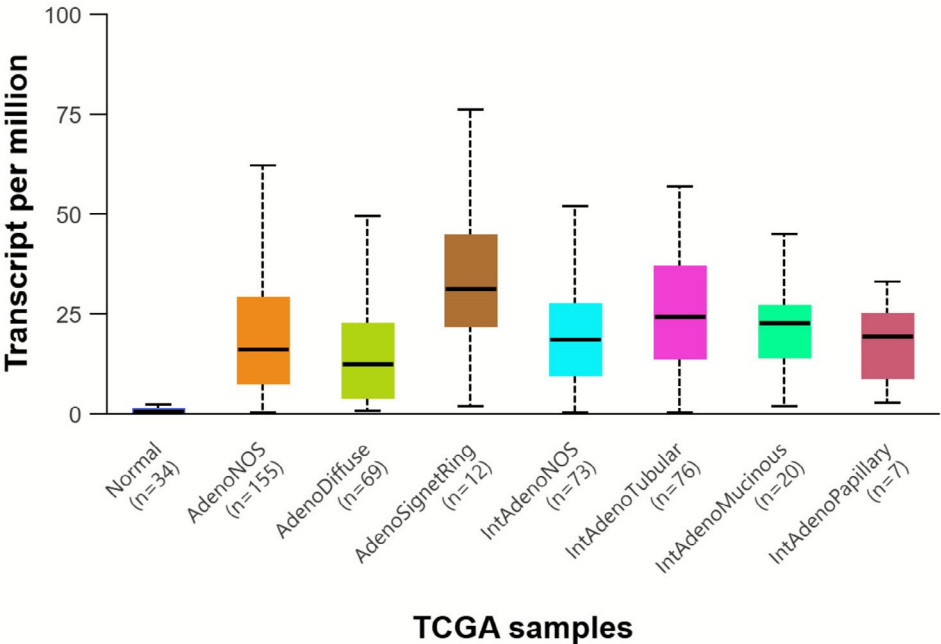


FIGURE 3 | Expression of GRIN2D among histological subtypes of gastric cancer from UALCAN.

Beyond its vascular effects, GRIN2D also shapes the immune landscape of the tumor. Studies in hepatocellular carcinoma have demonstrated that high GRIN2D expression is associated with increased infiltration of Tregs and CD4⁺ T cells, both of which can contribute to an immunosuppressive microenvironment. Conversely, GRIN2D expression is negatively correlated with the presence of natural killer (NK) cells, naive B cells, and monocytes—cell types that are typically involved in anti-tumor immunity [67]. These findings indicate the role of GRIN2D in evading immune surveillance in tumors.

GRIN2D is also known to be involved in the expression of immune checkpoint genes, which can pose as a potential biomarker for predicting immunotherapy response. Through Tumor Immune Dysfunction Exclusion (TIDE) analysis, it was observed that high GRIN2D expression was associated with poor immune response, underscoring its potential utility in stratifying patients who might possibly benefit from immune checkpoint inhibitors or immunotherapy approaches [67].

Recent studies have identified the involvement of GRIN2D in complex regulatory networks within gastric cells. The CircBIRC6-miR-488-GRIN2D axis has been shown to promote the expression of CAV1 that reduces autophagy in gastric cells further supporting tumor growth and survival [68].

7.4.1 | GRIN2D Targeting

GRIN2D emerges as a multifaceted player in GSRCC pathogenesis, with demonstrated involvement in metabolic reprogramming, tumor angiogenesis, immune evasion and cellular survival mechanisms. Its marked overexpression in GSRCC compared to other adenocarcinoma subtypes positions it as both a promising prognostic marker and a novel therapeutic target. Inhibiting GRIN2D or its transcriptional regulator BHLHE40 could disrupt critical metabolic pathways and impede tumor growth [69, 70]. The current evidence supporting GRIN2D's role in GSRCC progression is substantial. Multiple studies have documented its involvement in tumor metabolism and growth regulation, establishing a compelling preclinical foundation for therapeutic intervention. However clinical validation remains limited. To establish GRIN2D as a reliable prognostic and therapeutic tool in GSRCC management, comprehensive validation across large clinical cohorts is essential. Such validation studies should integrate GRIN2D expression data with established diagnostic and prognostic markers to fully elucidate its independent predictive value and therapeutic potential.

8 | Therapeutic Resistance and Emerging Strategies in GSRCC

8.1 | Limitations of Current Chemotherapy and Immunotherapy

Advanced GSRCC is known to be non-responsive to conventional therapeutic approaches that raise significant challenges for clinicians. The standard chemotherapy regimens often yield limited benefit as GSRCC tumors exhibit intrinsic resistance to cytotoxic agents. Therapeutic resistance can be driven by

various mechanisms such as drug metabolism, enhanced DNA repair capabilities and the activation of survival pathways to protect tumors from chemotherapy-induced apoptosis.

Immunotherapy, particularly immune checkpoint blockade, has transformed the management of several cancer types. However, GSRCC patients have derived less benefit from these advances. For example, the overall response rate to pembrolizumab monotherapy in advanced gastric and gastroesophageal junction cancers is only 11.6%, with better responses in PD-L1-positive patients. GSRCC, however, tends to have lower rates of PD-L1 expression, further diminishing the efficacy of checkpoint inhibitors [49]. The immunosuppressive tumor microenvironment characterized by T cell exhaustion, regulatory T cell infiltration, and altered antigen presentation contributes to poor immunotherapy responses. Both CD4⁺ and CD8⁺ T cells in GSRCC often exist in a quiescent state, making them difficult to reactivate even with checkpoint inhibition. Additionally, the loss of certain exhausted T cell populations and reduced clonal crosstalk further compromise the effectiveness of immunotherapy.

8.2 | Potential for Combination Therapy and Personalized Approaches

The complex and multifaceted resistance mechanisms in GSRCC underscore the need for combination therapeutic strategies. Approaches that simultaneously target the immunosuppressive microenvironment, stromal activation, metabolic dependencies, and complement dysregulation are likely to be more effective than single-agent therapies [71]. Ongoing clinical trials are investigating various combination regimens, with early results suggesting improved efficacy. Personalized medicine, guided by molecular profiling and single-cell analysis, is poised to transform GSRCC management. Factors such as somatic mutation (ARID1A, CDH1, ERBB2, and TP53) status, complement activation patterns, and immune cell composition can inform treatment selection and predict therapeutic response. Patients with CDH1 mutations may benefit from Poly (ADP-ribose) polymerase (PARP) or Wee1 inhibitors for better outcomes [72]. Integrating blood-based biomarkers with molecular profiling allows real-time monitoring of treatment response and detects therapy resistance at the earliest to enable different alternative treatment strategies. With advancements in research, future therapeutic strategies for GSRCC.

9 | Conclusion

GSRCC exemplifies evolving challenges in gastric cancer through increasing incidence, younger patient onset, and advanced-stage presentation. Its immunosuppressive, stromal-rich TME impedes treatment effectiveness. In India's diverse population, GSRCC significantly impacts mortality, necessitating targeted public health approaches. Single-cell RNA sequencing and molecular profiling have revealed GSRCC vulnerabilities, including TGF- β -driven CAF activation, complement cascade dysregulation, CXCL12/CXCR4-mediated immune exclusion, and GRIN2D's role in angiogenesis and immune checkpoint expression. These findings enable precision interventions that combine stromal-targeting agents with

complement modulators, anti-CLDN18.2 antibodies, and immune microenvironment remodels. Integration of anti-GRIN2D strategies with FLOT chemotherapy and biomarker monitoring shows promise. Personalized treatments based on CDH1 mutation status, CAF profiling, and complement patterns can transform GSRCC management. Early detection through targeted screening and biomarker assays remains crucial. These mechanistically informed strategies aim to convert GSRCC from a fatal diagnosis to a manageable condition.

Author Contributions

D.R., N.A.N.K., S.P., designed the research; D.R., A.M., S.N.S.S., performed the research; D.R., R.R.D., S.C., P.S.S., M.R., N.A.N.K., analyzed the data; D.R., N.A.N.K., S.P., wrote the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

References

1. H. Sung, J. Ferlay, R. L. Siegel, et al., "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries," *CA: A Cancer Journal for Clinicians* 71, no. 3 (2021): 209–249, <https://doi.org/10.3322/CAAC.21660>.
2. A. P. Thrift and H. B. El-Serag, "Burden of Gastric Cancer," *Clinical Gastroenterology and Hepatology* 18, no. 3 (2019): 534, <https://doi.org/10.1016/J.CGH.2019.07.045>.
3. A. Etemadi, S. Safiri, S. G. Sepanlou, et al., "The Global, Regional, and National Burden of Stomach Cancer in 195 Countries, 1990–2017: A Systematic Analysis for the Global Burden of Disease Study 2017," *Lancet Gastroenterology & Hepatology* 5, no. 1 (2020): 42–54, [https://doi.org/10.1016/S2468-1253\(19\)30328-0](https://doi.org/10.1016/S2468-1253(19)30328-0).
4. S. E. Mousavi, M. Ilaghi, I. Elahi Vahed, and S. A. Nejadghaderi, "Epidemiology and Socioeconomic Correlates of Gastric Cancer in Asia: Results From the GLOBOCAN 2020 Data and Projections From 2020 to 2040," *Scientific Reports* 15, no. 1 (2025): 6529, <https://doi.org/10.1038/S41598-025-90064-6>.
5. T. Grantham, R. Ramachandran, S. Parvataneni, D. Budh, S. Gollapalli, and V. Gaduputi, "Epidemiology of Gastric Cancer: Global Trends, Risk Factors and Premalignant Conditions," *Journal of Community Hospital Internal Medicine Perspectives* 13, no. 6 (2023): 100–106, <https://doi.org/10.55729/2000-9666.1252>.
6. F. Berth, E. Bollschweiler, U. Drebber, A. H. Hoelscher, and S. Moenig, "Pathohistological Classification Systems in Gastric Cancer: Diagnostic Relevance and Prognostic Value," *World Journal of Gastroenterology* 20, no. 19 (2014): 5679–5684, <https://doi.org/10.3748/WJG.V20.I19.5679>.
7. R. P. Dikshit, G. Mathur, S. Mhatre, and B. B. Yeole, "Epidemiological Review of Gastric Cancer in India," *Indian Journal of Medical and Paediatric Oncology* 32, no. 1 (2011): 3–11, <https://doi.org/10.4103/0971-5851.81883>.
8. K. Sathishkumar, M. Chaturvedi, P. Das, S. Stephen, and P. Mathur, "Cancer Incidence Estimates for 2022 & Projection for 2025: Result

From National Cancer Registry Programme, India," *Indian Journal of Medical Research* 156, no. 4–5 (2023): 598, https://doi.org/10.4103/IJMR.IJMR_1821_22.

9. T. S. Shakuntala, S. K. Krishnan, P. Das, et al., "Descriptive Epidemiology of Gastrointestinal Cancers: Results From National Cancer Registry Programme, India," *Asian Pacific Journal of Cancer Prevention* 23, no. 2 (2022): 408, <https://doi.org/10.31557/APJCP.2022.23.2.409>.
10. Y. Q. Xie, C. C. Li, M. R. Yu, and J. Cao, "Immunosuppressive Tumor Microenvironment in Gastric Signet-Ring Cell Carcinoma," *World Journal of Clinical Oncology* 15, no. 9 (2024): 1126–1131, <https://doi.org/10.5306/WJCO.V15.I9.1126>.
11. J. Chen, K. Liu, Y. Luo, et al., "Single-Cell Profiling of Tumor Immune Microenvironment Reveals Immune Irresponsiveness in Gastric Signet-Ring Cell Carcinoma," *Gastroenterology* 165, no. 1 (2023): 88–103, <https://doi.org/10.1053/J.GASTRO.2023.03.008>.
12. J. Machlowska, M. Puculek, M. Sitarz, P. Terlecki, R. Maciejewski, and R. Sitarz, "State of the Art for Gastric Signet Ring Cell Carcinoma: From Classification, Prognosis, and Genomic Characteristics to Specified Treatments," *Cancer Management and Research* 11 (2019): 2151–2161, <https://doi.org/10.2147/CMAR.S188622>.
13. I. D. Nagtegaal, R. D. Odze, D. Klimstra, et al., "The 2019 WHO Classification of Tumours of the Digestive System," *Histopathology* 76, no. 2 (2020): 182–188, <https://doi.org/10.1111/HIS.13975>.
14. Z. S. Zhang, W. Y. Deng, S. L. Huang, et al., "Clinicopathological Characteristics of Signet-Ring Cell Carcinoma Derived From Gastric Foveolar Epithelium," *Journal of Digestive Diseases* 23, no. 7 (2022): 396–403, <https://doi.org/10.1111/1751-2980.13120>.
15. Y. Wang, Y. Li, B. Wang, et al., "Early Onset, Development and Histological Features of Gastric Signet-Ring Cell Carcinoma," *Frontiers in Oncology* 13 (2023): 1166549, <https://doi.org/10.3389/FONC.2023.1166549>.
16. Y. Fan, B. Bai, Y. Liang, et al., "Proteomic Profiling of Gastric Signet Ring Cell Carcinoma Tissues Reveals Characteristic Changes of the Complement Cascade Pathway," *Molecular & Cellular Proteomics* 20 (2021): 100068, <https://doi.org/10.1016/J.MCPRO.2021.100068>.
17. M. Matsui, O. Kojima, S. Kawakami, Y. Uehara, and T. Takahashi, "The Prognosis of Patients With Gastric Cancer Possessing Sex Hormone Receptors," *Surgery Today* 22, no. 5 (1992): 421–425, <https://doi.org/10.1007/BF00308791>.
18. Y. Choi, N. Kim, J. H. Park, C. H. Song, and H. J. Oh, "Expression Rates of Sex Hormone Receptors With Their Clinical Correlates in Gastric Cancer Patients and Normal Controls," *World Journal of Men's Health* 43 (2025): 980–991, <https://doi.org/10.5534/WJMH.240272>.
19. E. Ursu, "Gastric Signet Ring Cell Carcinoma: An Overview," *Journal of Medical and Radiation Oncology* II, no. 1 (2022): 9–17, <https://doi.org/10.53011/JMRO.2022.01.02>.
20. R. Giampieri, M. G. Baleani, A. Bittoni, et al., "Impact of Signet-Ring Cell Histology in the Management of Patients With Non-Metastatic Gastric Cancer: Results From a Retrospective Multicenter Analysis Comparing FLOT Perioperative Chemotherapy vs. Surgery Followed by Adjuvant Chemotherapy," *Cancers (Basel)* 15, no. 13 (2023): 3342, <https://doi.org/10.3390/CANCERS15133342/S1>.
21. J. Xu, J. Zhu, L. Lin, et al., "Endoscopic and Clinicopathologic Features of Early Gastric Signet Ring Cell Carcinoma ≤ 20 mm: A Retrospective Observational Study," *Scandinavian Journal of Gastroenterology* 58, no. 1 (2023): 38–44, <https://doi.org/10.1080/00365521.2022.2100227>.
22. S. Liu, C. Han, Q. He, et al., "The Comparison of Clinicopathological Characteristics of Two Distinct Manifestations of Gastric Signet Ring Cell Carcinoma Under EUS," *Endoscopic Ultrasound* 13, no. 5 (2024): 293–299, <https://doi.org/10.1097/EUS.0000000000000085>.

23. N. A. N. Kumar, A. Jose, N. Usman, et al., "Signet Ring Cell Cancer of Stomach and Gastro-Esophageal Junction: Molecular Alterations, Stage-Stratified Treatment Approaches, and Future Challenges," *Lan- genbeck's Archives of Surgery* 407, no. 1 (2022): 87–98, <https://doi.org/10.1007/S00423-021-02314-6>.
24. N. M. Anderson and M. C. Simon, "Tumor Microenvironment," *Current Biology* 30, no. 16 (2020): R921, <https://doi.org/10.1016/J.CUB.2020.06.081>.
25. Q. Wang, X. Shao, Y. Zhang, et al., "Role of Tumor Microenvi- ronment in Cancer Progression and Therapeutic Strategy," *Cancer Medicine* 12, no. 10 (2023): 11149–11165, <https://doi.org/10.1002/CAM4.5698>.
26. H. Yoon, C. M. Tang, S. Banerjee, et al., "TGF- β 1-Mediated Transi- tion of Resident Fibroblasts to Cancer-Associated Fibroblasts Promotes Cancer Metastasis in Gastrointestinal Stromal Tumor," *Oncogene* 10, no. 2 (2021): 13, <https://doi.org/10.1038/S41389-021-00302-5>.
27. K. Chen, M. Xu, F. Lu, and Y. He, "Development of Matrix Metalloproteinases-Mediated Extracellular Matrix Remodeling in Re- generative Medicine: A Mini Review," *Tissue Engineering and Regener- ative Medicine* 20, no. 5 (2023): 661–670, <https://doi.org/10.1007/S13770-023-00536-X>.
28. D. Luo, Y. Liu, Z. Lu, and L. Huang, "Targeted Therapy and Im- munotherapy for Gastric Cancer: Rational Strategies, Novel Advance- ments, Challenges, and Future Perspectives," *Molecular Medicine* 31, no. 1 (2025): 52, <https://doi.org/10.1186/S10020-025-01075-Y>.
29. H. Sun, X. Wang, X. Wang, M. Xu, and W. Sheng, "The Role of Cancer-Associated Fibroblasts in Tumorigenesis of Gastric Cancer," *Cell Death & Disease* 13, no. 10 (2022): 874, <https://doi.org/10.1038/s41419-022-05320-8>.
30. J. Zhang, S. Li, Y. Zhao, et al., "Cancer-Associated Fibroblasts Pro- mote the Migration and Invasion of Gastric Cancer Cells via Activating IL-17a/JAK2/STAT3 Signaling," *Annals of Translational Medicine* 8, no. 14 (2020): 877, <https://doi.org/10.21037/ATM-20-4843>.
31. E. Ozmen, T. D. Demir, and G. Ozcan, "Cancer-Associated Fibro- blasts: Protagonists of the Tumor Microenvironment in Gastric Can- cer," *Frontiers in Molecular Biosciences* 11 (2024): 1340124, <https://doi.org/10.3389/FMOLB.2024.1340124>.
32. Z. Fang, Q. Meng, J. Xu, et al., "Signaling Pathways in Cancer- Associated Fibroblasts: Recent Advances and Future Perspectives," *Cancer Communications* 43, no. 1 (2022): 3, <https://doi.org/10.1002/CAC2.12392>.
33. M. M. Olcina, R. K. Kim, S. Melemenidis, E. E. Graves, and A. J. Giaccia, "The Tumour Microenvironment Links Complement System Dysregulation and Hypoxic Signalling," *British Journal of Radiology* 92, no. 1093 (2018): 20180069, <https://doi.org/10.1259/BJR.20180069>.
34. Y. Y. Sheen, M. J. Kim, S. A. Park, S. Y. Park, and J. S. Nam, "Target- ing the Transforming Growth Factor- β Signaling in Cancer Therapy," *Biomolecules & Therapeutics* 21, no. 5 (2013): 323–331, <https://doi.org/10.4062/BIOMOLTHER.2013.072>.
35. X. Lv and G. Xu, "Regulatory Role of the Transforming Growth Factor- β Signaling Pathway in the Drug Resistance of Gastrointestinal Cancers," *World Journal of Gastrointestinal Oncology* 13, no. 11 (2021): 1648–1667, <https://doi.org/10.4251/WJGO.V13.I11.1648>.
36. B. Wolf, L. Weydandt, N. Dornhöfer, et al., "Desmoplasia in Cervi- cal Cancer Is Associated With a More Aggressive Tumor Phenotype," *Scientific Reports* 13, no. 1 (2023): 1–9, <https://doi.org/10.1038/s41598-023-46340-4>.
37. N. Kemi, M. Eskuri, A. Herva, et al., "Tumour-Stroma Ratio and Prognosis in Gastric Adenocarcinoma," *British Journal of Cancer* 119, no. 4 (2018): 435–439, <https://doi.org/10.1038/S41416-018-0202-Y>.
38. S. Verma, K. Kesh, N. Ganguly, S. Jana, and S. Swarnakar, "Matrix Metalloproteinases and Gastrointestinal Cancers: Impacts of Dietary Antioxidants," *World Journal of Biological Chemistry* 5, no. 3 (2014): 355–376, <https://doi.org/10.4331/WJBC.V5.I3.355>.
39. C. L. Sampieri, K. León-Córdoba, and J. M. Remes-Troche, "Matrix Metalloproteinases and Their Tissue Inhibitors in Gastric Cancer as Molecular Markers," *Journal of Cancer Research and Therapeutics* 9, no. 3 (2013): 356–363, <https://doi.org/10.4103/0973-1482.119302>.
40. K. Yamaguchi, T. Yoshihiro, H. Ariyama, et al., "Potential Thera- peutic Targets Discovery by Transcriptome Analysis of an In Vitro Human Gastric Signet Ring Carcinoma Model," *Gastric Cancer* 25, no. 5 (2022): 862–878, <https://doi.org/10.1007/S10120-022-01307-8>.
41. M. K. Yeo, S. H. Kang, K. B. Jeong, et al., "Comparison of Gene Ex- pression Profiles of Signet Ring Cell Carcinoma and Poorly Cohesive Carcinoma in Early Gastric Cancer," *Clinical Medicine Insights: Oncol- ogy* 16 (2022): 11795549221097941, <https://doi.org/10.1177/11795549221097941>.
42. C. Rubie, A. Kauffels, K. Kölsch, M. Glanemann, and C. Justinger, "CXCL12/CXCR4 Display an Inverse mRNA Expression Profile in Gas- tric Carcinoma That Correlates With Tumor Progression," *Oncology Letters* 11, no. 1 (2016): 360–364, <https://doi.org/10.3892/OL.2015.3850>.
43. S. K. Daniel, Y. D. Seo, and V. G. Pillarisetty, "The CXCL12-CXCR4/ CXCR7 Axis as a Mechanism of Immune Resistance in Gastrointestinal Malignancies," *Seminars in Cancer Biology* 65 (2020): 176–188, <https://doi.org/10.1016/J.SEMCANCER.2019.12.007>.
44. G. J. Yoshida, "Regulation of Heterogeneous Cancer-Associated Fi- broblasts: The Molecular Pathology of Activated Signaling Pathways," *Journal of Experimental & Clinical Cancer Research* 39, no. 1 (2020): 112, <https://doi.org/10.1186/S13046-020-01611-0>.
45. H. H. Workel, J. M. Lubbers, R. Arnold, et al., "A Transcriptionally Distinct CXCL13pCD103pCD8 β T-Cell Population Is Associated With B-Cell Recruitment and Neoantigen Load in Human Cancer," *Cancer Immunology Research* 7, no. 5 (2019): 784–796, <https://doi.org/10.1158/2326-6066.CIR-18-0517>.
46. X. Song, W. Qi, J. Guo, et al., "Immune Checkpoint Inhibitor Com- bination Therapy for Gastric Cancer: Research Progress," *Oncology Let- ters* 20, no. 4 (2020): 46, <https://doi.org/10.3892/OL.2020.11905>.
47. X. Liu, Z. Zhang, and G. Zhao, "Recent Advances in the Study of Reg- ulatory T Cells in Gastric Cancer," *International Immunopharmacology* 73 (2019): 560–567, <https://doi.org/10.1016/J.INTIMP.2019.05.009>.
48. M. Yoshii, H. Tanaka, M. Ohira, et al., "Expression of Forkhead Box P3 in Tumour Cells Causes Immunoregulatory Function of Signet Ring Cell Carcinoma of the Stomach," *British Journal of Cancer* 106, no. 10 (2012): 1668–1674, <https://doi.org/10.1038/bjc.2012.141>.
49. I. A. Voutsadakis, "A Systematic Review and Meta-Analysis of PD-1 and PD-L1 Inhibitors Monotherapy in Metastatic Gastric and Gastro- esophageal Junction Adenocarcinoma," *Euroasian Journal of Hepato Gastroenterology* 10, no. 2 (2020): 56–63, <https://doi.org/10.5005/JP-JOURNALS-10018-1321>.
50. V. Afshar-Kharghan, "The Role of the Complement System in Can- cer," *Journal of Clinical Investigation* 127, no. 3 (2017): 780–789, <https://doi.org/10.1172/JCI90962>.
51. P. Nesargikar, B. Spiller, and R. Chavez, "The Complement System: History, Pathways, Cascade and Inhibitors," *European Journal of Mi- crobiology and Immunology* 2, no. 2 (2012): 103–111, <https://doi.org/10.1556/EUJMI.2.2012.2.2>.
52. W. Zhao, Y. Jia, G. Sun, et al., "Single-Cell Analysis of Gastric Signet Ring Cell Carcinoma Reveals Cytological and Immune Microenviron- ment Features," *Nature Communications* 14 (2023): 1–15, <https://doi.org/10.1038/s41467-023-38426-4>.
53. S. Zhang, Q. Liu, Y. Wei, et al., "Anterior Gradient-2 Regulates Cell Communication by Coordinating Cytokine–Chemokine Signaling and Immune Infiltration in Breast Cancer," *Cancer Science* 114, no. 6 (2023): 2238–2253, <https://doi.org/10.1111/CAS.15775>.

54. P. Bouchalova, L. Sommerova, D. Potesil, et al., "Characterization of the AGR2 Interactome Uncovers New Players of Protein Disulfide Isomerase Network in Cancer Cells," *Molecular & Cellular Proteomics* 21, no. 2 (2022): 100188, <https://doi.org/10.1016/J.MCPRO.2021.100188>.
55. T. Tsuji, R. Satoyoshi, N. Aiba, et al., "Agr2 Mediates Paracrine Effects on Stromal Fibroblasts That Promote Invasion by Gastric Signet-Ring Carcinoma Cells," *Cancer Research* 75, no. 2 (2015): 356–366, <https://doi.org/10.1158/0008-5472.CAN-14-1693>.
56. A. Y. Liu, A. D. Kanan, T. P. Radon, et al., "AGR2, a Unique Tumor-Associated Antigen, Is a Promising Candidate for Antibody Targeting," *Oncotarget* 10, no. 42 (2019): 4276–4289, <https://doi.org/10.18632/ONCOTARGET.26945>.
57. W. Zhang, Y. Shu, W. Zhang, et al., "Prognostic Significance of Frequent CLDN18-ARHGAP26/6 Fusion in Gastric Signet-Ring Cell Cancer," *Nature Communications* 9, no. 1 (2018): 1–11, <https://doi.org/10.1038/s41467-018-04907-0>.
58. F. Zhang, V. Sahu, K. Peng, et al., "Recurrent RhoGAP Gene Fusion CLDN18-ARHGAP26 Promotes RHOA Activation and Focal Adhesion Kinase and YAP-TEAD Signalling in Diffuse Gastric Cancer," *Gut* 73, no. 8 (2024): 1280–1291, <https://doi.org/10.1136/GUTJNL-2023-329686>.
59. K. Jia, Y. Chen, Y. Sun, et al., "Multiplex Immunohistochemistry Defines the Tumor Immune Microenvironment and Immunotherapeutic Outcome in CLDN18.2-Positive Gastric Cancer," *BMC Medicine* 20, no. 1 (2022): 1–15, <https://doi.org/10.1186/S12916-022-02421-1>.
60. FDA, "FDA Approves Zolbetuximab-Clzb With Chemotherapy for Gastric or Gastroesophageal Junction Adenocarcinoma," accessed July 5, 2025, <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-zolbetuximab-clzb-chemotherapy-gastric-or-gastroesophageal-junction-adenocarcinoma>.
61. S. Liu, Z. Zhang, L. Jiang, M. Zhang, C. Zhang, and L. Shen, "Claudin-18.2 Mediated Interaction of Gastric Cancer Cells and Cancer-Associated Fibroblasts Drives Tumor Progression," *Cell Communication and Signaling* 22, no. 1 (2024): 27, <https://doi.org/10.1186/S12964-023-01406-8>.
62. A. Tojjari, Y. A. Idrissi, and A. Saeed, "Emerging Targets in Gastric and Pancreatic Cancer: Focus on Claudin 18.2," *Cancer Letters* 611 (2025): 217362, <https://doi.org/10.1016/J.CANLET.2024.217362>.
63. K. Zampouka, C. Tsiantas, M. A. Stavropoulou, et al., "Correlation of CLDN18.2 and Tumor Microenvironment in Gastric Cancer: A Systematic Review," *Cancers (Basel)* 17, no. 13 (2025): 2120, <https://doi.org/10.3390/CANCERS17132120>.
64. D. S. Chandrashekar, S. K. Karthikeyan, P. K. Korla, et al., "UALCAN: An Update to the Integrated Cancer Data Analysis Platform," *Neoplasia (United States)* 25 (2022): 18–27, <https://doi.org/10.1016/j.neo.2022.01.001>.
65. D. S. Chandrashekar, B. Bashel, S. A. H. Balasubramanya, et al., "UALCAN: A Portal for Facilitating Tumor Subgroup Gene Expression and Survival Analyses," *Neoplasia* 19, no. 8 (2017): 649–658, <https://doi.org/10.1016/J.NEO.2017.05.002>.
66. Z. Chen, Y. Song, P. Li, and W. Gao, "GRIN2D Knockdown Suppresses the Progression of Lung Adenocarcinoma by Regulating the E2F Signalling Pathway," *Cellular Signalling* 107 (2023): 110685, <https://doi.org/10.1016/J.CELLSIG.2023.110685>.
67. Y. G. Zhang, M. Z. Jin, X. R. Zhu, and W. L. Jin, "Reclassification of Hepatocellular Cancer With Neural-Related Genes," *Frontiers in Oncology* 12 (2022): 877657, <https://doi.org/10.3389/FONC.2022.877657>.
68. Z. Tang, J. Li, B. Lu, et al., "CircBIRC6 Facilitates the Malignant Progression via miR-488/GRIN2D-Mediated CAV1-Autophagy Signal Axis in Gastric Cancer," *Pharmacological Research* 202 (2024): 107127, <https://doi.org/10.1016/j.phrs.2024.107127>.
69. J. Wang, C. H. Wong, Y. Zhu, et al., "Identification of GRIN2D as a Novel Therapeutic Target in Pancreatic Ductal Adenocarcinoma," *Biomarker Research* 11, no. 1 (2023): 1–13, <https://doi.org/10.1186/S40364-023-00514-4>.
70. B. Liu, Y. Sun, W. Wang, J. Ren, and D. Wang, "BHLHE40-Mediated Transcriptional Activation of GRIN2D in Gastric Cancer Is Involved in Metabolic Reprogramming," *Functional & Integrative Genomics* 24, no. 6 (2024): 214, <https://doi.org/10.1007/S10142-024-01495-9>.
71. S. Giordano and A. Petrelli, "From Single- to Multi-Target Drugs in Cancer Therapy: When Aspecificity Becomes an Advantage," *Current Medicinal Chemistry* 15, no. 5 (2008): 422–432, <https://doi.org/10.2174/092986708783503212>.
72. J. Wang, J. Xiu, F. Battaglin, et al., "Large-Scale Analysis of CDH1 Mutations Defines a Distinctive Molecular Subset With Treatment Implications in Gastric Cancer," *NPJ Precision Oncology* 8, no. 1 (2024): 1–10, <https://doi.org/10.1038/s41698-024-00694-8>.