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Review Article

Role of lysine-specific demethylase 1 in immunotherapy of gastric cancer: An update

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Abstract

Gastric cancer (GC) ranks 3rd in incidence rate and mortality rate among malignant tumors in China, and the age-standardized five-year net survival rate of patients with GC was 35.9% from 2010 to 2014. The tumor immune microenvironment (TIME), which includes T cells, macrophages, natural killer (NK) cells and B cells, significantly affects tumor progression, immunosuppression and drug resistance in patients with GC. In recent years, immunotherapy has become the first-line or second-line treatment for GC. Lysine-specific demethylase 1 (LSD1, also known as KDM1A) was the first identified human histone demethylase, and high expression of LSD1 in GC is closely related to the dysfunction of the above types of immune cells. Therefore, LSD1 inhibitors could regulate the cytotoxic effects of immune cells against tumor cells through a variety of mechanisms to control tumor progression. In this review, we discuss the effects of LSD1 inhibitors on immune cells in GC and propose LSD1 as a new potential target for immunotherapy in GC.

Keywords: LSD1; immune cells; gastric cancer; immunotherapy

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Introduction

Gastric cancer (GC) is a major public health problem in China. In a recent annual report, there were 478,508 new GC cases and 373,789 related deaths; it has a 3rd highest incidence rate and 3rd highest mortality rate among malignant tumors in China (1,2). According to CONCORD-3 (3), from 2010 to 2014, the age-standardized five-year net survival of patients with GC in China reached 35.9%, which was a great improvement from the rates for 2005–2009 (33.2%) and 2000–2004 (30.2%). In recent years, many exploratory clinical studies have been conducted on immunotherapy as a new therapeutic approach for the first-line treatment of patients with advanced GC, and many studies continue to show promising results (4,5).

Lysine-specific demethylase 1 (LSD1, also known as KDM1A) was the first identified human histone demethylase (6). LSD1 specifically demethylates mono- and dimethylated H3 lysine 4 through flavin adenine

dinucleotide (FAD)-dependent amine oxidase activity; it represses gene expression by removing active histone marks (H3K4me2 modifications) from gene promoter regions (6). However, LSD1 functions as a transcriptional coactivator when bound to the androgen receptor (AR); when it demethylates repressive histone marks at H3K9, it derepresses the expression of AR target genes (7). LSD1 is highly expressed in various cancer types, and this phenotype is correlated with poor overall survival in patients, including those with breast, prostate, oesophageal, bladder and lung cancer, neuroblastoma, and acute myeloid leukaemia (AML) (8). LSD1 promotes cancer progression through hypoxia, epithelial-to-mesenchymal transition (EMT), cancer stemness, differentiation, and antitumor immunity. Kim *et al*. reported that LSD1 promotes cancer progression by regulating gene expression in cancer cells to promote adaptation to the tumor microenvironment (TME) (9). Therefore, LSD1 has become an attractive target in the search for specific inhibitors as potential anti-GC agents (10). In this review, we summarize the role of LSD1 in the immune microenvironment of GC and the potential value of LSD1 inhibitors in GC immunotherapy.

Structural skeleton and featured functions of LSD1

LSD1 structure

The process of methylating histones was long thought to be irreversible until the first demethylase, LSD1, was discovered in 2004 (6). The structure of LSD1 is highly conserved, and there are three structural domains in LSD1, namely, the C-terminal amino oxidase-like (AOL) domain, the SWI3/RSC8/MOIRA (SWIRM) domain, and the flexible N-terminal region (*Figure 1*). The catalytic region of LSD1 resides on the AOL domain, which is divided into two lobes by the tower structural field (11). The first lobe contains the follistatin domain (FSD)-binding site carrying oxidation, and the second lobe contains the site for substrate recognition (11). The space between these 2 submodules forms an open cavity where demethylation takes place (12). The AOL domain also contains a Tower domain accompanied by alpha helices, which interacts with the repressor element 1 (RE1) silencing transcription factor (REST) corepressor (CoREST) complex and is critical for the H3K4 demethylase activity of LSD1. Extranucleosomal DNA can bind to the AOL domain along with the CoREST complex (6). The SWIRM domain of LSD1 is incapable of binding to DNA but is useful as a docking site for interacting with other proteins and maintaining LSD1 protein stability (13).

Function of LSD1

LSD1 acts as an eraser of histone lysine methylation by removing mono- and dimethyl groups from histone 3 lysine 4 (H3K4), thereby suppressing the transcription of target genes and playing the role of an oncogene in tumorigenesis. In addition to its effects on histones, LSD1 has also been confirmed to demethylate non-histone substrates, such as the E2F transcription factor 1 (E2F1), DNA methyltransferase 1 (DNMT1), tumor suppressor protein p53, signal transducer and activator of transcription

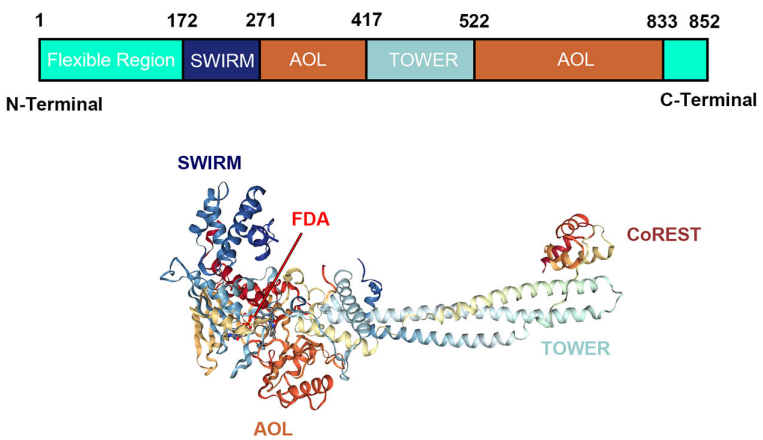

Figure 1 Structure and function of LSD1. LSD1 crystal structure (PDB code: 2V1D). LSD1 consists of the SWIRM, TOWER, and AOL domains. CoREST is an interaction site with the TOWER domain and is critical for H3K4 demethylase activity. LSD1, lysine-specific demethylase 1; SWIRM, SWI3/RSC8/MOIRA; AOL, amine oxidase-like; FAD, flavin adenine dinucleotide; CoREST, repressor element 1 (RE1) silencing transcription factor (REST) corepressor. Completed by Figdraw (www.figdraw.com).

3 (STAT3), and hypoxia-inducible factor 1-alpha (HIF-1α) (14). Recently, several proteins associated with tumor progression have been discovered to interact with LSD1, extending beyond its function as a demethylase and leading to diverse biological effects. For instance, F-box and WD-40 domain-containing protein 7 (FBXW7), estrogen-related receptor alpha (ERRα), sequestosome 1 (SQSTM1, also known as p62), and zinc finger protein 217 (ZNF217) have been identified as interaction partners of LSD1 (15).

Dysregulation of LSD1 expression has been observed in a variety of malignant tumors and is closely associated with numerous biological effects. It promotes the adaptability and survival of tumor cells by regulating the expression of genes related to tumor growth. In prostate cancer, the AR or AR in collaboration with Jumonji domain containing 2C (JMJD2C), works with LSD1 to promote AR-dependent gene expression through its histone demethylase activity, thereby contributing to the progression of prostate cancer (PCa) (16). LSD1 is involved in the regulation of the epithelial-mesenchymal transition (EMT) process, which is associated with increased invasiveness and metastatic potential of tumors. It has been reported that LSD1-mediated stabilization of septin 6 (SEPT6) activates the transforming growth factor (TGF)-β1 pathway and regulates the metastasis of non-small cell lung cancer (NSCLC) (17). The activity regulation of LSD1 also impacts drug resistance in tumors (18,19). For instance, in invasive MDA-MB-468 breast cancer cells that have developed drug resistance, pretreatment with GSK-LSD1 significantly enhances the inhibitory effect of doxorubicin on cell proliferation. This suggests that reducing LSD1 expression may increase the sensitivity of drug-resistant tumor cells to chemotherapeutic agents (20).

LSD1 plays a role in tumor immune evasion by influencing the function of immune cells in the tumor microenvironment, particularly T cells and macrophages. Studies have shown that in activated CD8 T cells, the absence of LSD1 leads to an increase in programmed cell death 1 (PD-1) mRNA levels and its expression on the cell surface (21). We will focus on elucidating the role of LSD1 in the GC immune microenvironment in the following content.

Overview of GC immune microenvironment

Immune microenvironment of GC

The TME, which comprises various immune cells, stromal cells, and extracellular components, profoundly affects tumorigenesis, progression, immune escape and therapeutic resistance (22). The stomach has a strongly acidic environment and a unique endocrine system, which also results in differences in the TME between GC and other tumor types (23).

The components of tumor immune microenvironment (TIME), including T cells, macrophages, B cells and natural killer cells, are being increasingly studied in the field of immunotherapy (24,25). These tumor immune cells are heterogeneous in terms of features, show functional and phenotypic plasticity and may exert both protumorigenic and antitumorigenic effects (26) (*Figure 2*).

T cells

T cells exert antiviral or antitumor immune effects by directly or indirectly killing target cells. Patients with GC with high levels of tumor-infiltrating lymphocytes had a better prognosis than those with low levels of these cells, and T-cell adaptive immunity plays a key role in tumor lymphocyte infiltration in the GC immune microenvironment. In the TME, CD8+ T cells kill tumor cells, and regulatory T cells (Tregs) are the most representative CD4+ immunosuppressive cells. This different feature of T cells allows them to play completely different roles in tumors.

A decrease in the number of CD8+ T cells and dysfunction of these cells is the reason for GC immune tolerance. When the proportion of infiltrated CD8+ T cells was less than 2.2%, the risk of disease progression after cancer surgery increased 4-fold [hazard ratio (HR)=3.84, P<0.01] (27). Patients with high chromatin accessibility at specific genomic positions in their circulating CD8+ T cells demonstrate significantly better survival times than those with closed chromatin, which explains why GC patients with high chromatin accessibility in circulating CD8+ T cells respond better to pembrolizumab than those with low chromatin accessibility (28).

Sequencing revealed that compared to normal tissues, gastric tumor tissues were significantly enriched in Tregs and presented increased expression of immune suppression-related genes, which suggested a more immunosuppressive microenvironment (29). Tregs are enriched in early intestinal-type GC and can promote the growth of spheroids by inducing interleukin-2Rα (IL-2Rα) expression and activating the mitogen-activated protein kinase (MAPK) signalling pathway in tumor cells (30). Therefore, Tregs play an important role in the progression of GC by inducing immune tolerance.

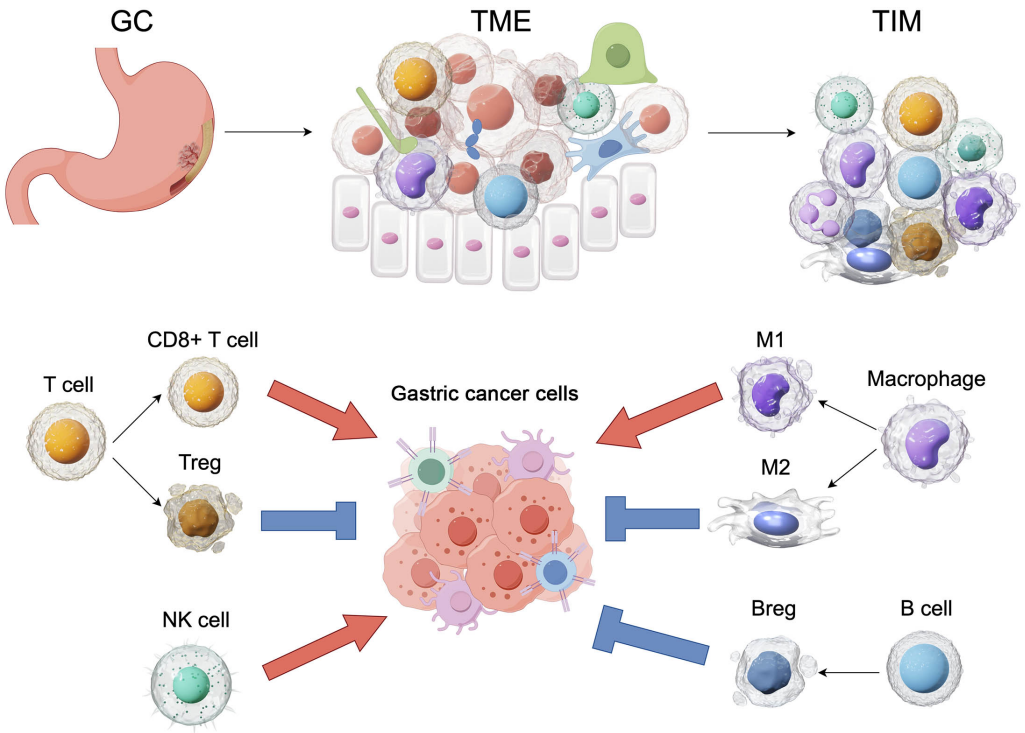

Figure 2 Immune microenvironment of GC. TME of GC includes various tumor cells, immune cells, normal gastric epithelial cells, fibroblasts and extracellular components. TIME, which includes T cells, macrophages, B cells and natural killer cells, shows functional and phenotypic plasticity and has different effects on tumor cells. GC, gastric cancer; TME, tumor microenvironment; TIME, tumor immune microenvironment.

Macrophages

Macrophages phagocytose products from the TME to mediate tumor immunity. Tumor-associated macrophages (TAMs) infiltrate the TME and have two polarization states that indicate their activation state and function: classical M1 macrophages have a tumor-suppressive function, while alternatively activated M2 macrophages have a tumor-promoting function (31). Studies have indicated that TAMs predominantly exhibit an M2-like phenotype, which manifests as an immunosuppressive state and promotes tumor progression (32). A meta-analysis of 12 studies concluded that the number of M2 macrophages might be an adverse prognostic factor in GC patients (33). Notably, M1 and M2 polarization are not irreversible processes, and macrophages can switch between these two states; thus, these states can be used as potential targets for GC immunotherapy (34).

In addition, TAMs trigger the infiltration of Tregs through the secretion of chemokines, inhibiting the antitumor response of T cells, disrupting the interaction of immune cells and eventually leading to immune evasion by GC cells (35).

Natural killer (NK) cells

Compared with T cells, NK cells have greater cytotoxicity, lower immunogenicity and a faster response to tumors (36). GC patients with a high percentage of NK cells survived longer than those with a low percentage of NK cells (37). In a study, cytokines such as IL-2, IL-12, IL-15 and IL-18 were shown to enhance NK cell activity, increase the cytotoxicity of DTCR-NK92 cells to SGC-7901 cells, and exert strong antitumor effects on a mouse model of GC (38). Recent studies have shown that the levels of NK cells, similar to those of CD8+ T cells and macrophages, are negatively correlated with the expression of PD-1/programmed cell death ligand 1 (PD-L1) immune checkpoints (39). On the other hand, a phase I clinical trial confirmed that NK-cell therapy in combination with trastuzumab was well tolerated, with target engagement and preliminary antitumor activity in patients with human epidermal growth factor receptor 2 (HER2)-positive cancers (40). This provides a new idea for clinical immunotherapy for GC, especially for trastuzumab-resistant HER2-positive GC.

B cells

Qin *et al*. first demonstrated that the low immunogenicity of tumors was caused by B cells, whose presence in the priming phase results in disabled CD4+ T cells that facilitate cytotoxic T-cell-mediated tumor immunity (41). In recent years, the number of regulatory B (Breg) cells in GC tissues has increased significantly, and these subsets of Breg cells inhibit the antitumor response by producing anti-inflammatory cytokines and inhibiting the expression of inhibitory molecules. By coculturing B cells *in vitro*, one group found that T follicular helper differentiation and CXCL13 expression were promoted, which resulted in an increase in the proportions of T follicular helper and Breg cells, and these changes are involved in immune suppression in GC (42).

In addition, high numbers of CD20+ follicular B cells are associated with improved relapse-free survival according to transcriptomic data from an independent cohort of 365 patients with localized GC (43). However, a study showed that the percentage of CD20+ B cells was not a prognostic factor in an unadjusted analysis of time to recurrence (TTR) in GC patients (44).

Above all, additional studies are needed to clarify the significance of B cells in GC.

Immune checkpoint inhibitors (ICIs) in cancer treatment

In the last decade, there have been unprecedented advances in cancer immunotherapy; by far, the most widely used ICIs are blocking antibodies targeting immune inhibitory receptors such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4), PD-1 and PD-L1 (45).

CTLA-4 is an inhibitory receptor expressed primarily by T cells that functions to dampen T-cell activity and is upregulated upon T-cell activation (46). The first report that inhibiting CTLA-4 activity can induce *in vivo* antitumor effects was published in 1996. In the present study, mice engrafted with colon carcinoma or fibrosarcoma cells either were cured of their tumors or exhibited a drastically reduced tumor burden when injected with anti-CTLA-4 antibodies (47). In 2010, a phase III clinical trial in patients with metastatic melanoma demonstrated that the anti-CTLA-4 antibody ipilimumab extended the median overall survival of patients by more than 3 months (48). Thus, the FDA approved this antibody for treating late-stage melanoma patients in 2011.

Like that of CTLA-4, the binding of PD-1 to its ligands (PD-L1 and PD-L2) leads to the suppression of T-cell-mediated immune responses (49). Although PD-1 is expressed on the surface of most activated immune cells, such as macrophages, dendritic cells (DCs), Langerhans cells, B cells, and T cells, its expression is most highly upregulated on exhausted T cells (50). Monoclonal antibodies blocking PD-1/PD-L1 have shown remarkable clinical efficacy in patients with a variety of cancers, including melanoma, colorectal cancer, NSCLC, and Hodgkin's lymphoma (51-53). The anti-PD-1 antibodies nivolumab, nivolumab and pembrolizumab have been approved for the treatment of many cancer types, including both solid and liquid tumors. In 2020, two clinical studies based on KEYNOTE-059 and ATTRACTION-02 established the use of pembrolizumab and nivolumab as third-line treatments for advanced GC (54,55). With the progress of clinical research, PD-1 monoclonal antibody immunotherapy has entered the first treatment stage for GC.

LSD1 in immune microenvironment of GC

T cells and LSD1

Stamos *et al*. reported that LSD1 regulates multiple repressive gene programs during T-cell development (56). In addition, targeting nuclear LSD1 to reprogram cancer cells could reinvigorate exhausted T cells via the novel LSD1-EOMES switch, leading to enhanced CD8+ T-cell cytotoxicity (57). LSD1 deficiency in CD8+ T cells enhances the cytotoxicity of CD8+ T cells, as indicated by elevated cytokine secretion and CD8+ T-cell infiltration, thus slowing tumor proliferation and decreasing tumor burden; moreover, LSD1 inhibitors may increase the response to ICIs (58-60). As a new epigenetic repressor of T cells, LSD1 may also regulate other T-cell functions, such as differentiation, development, maturation, and immunoregulation.

Notably, LSD1 can affect the expression of PD-1 and PD-L1 in various mechanisms and may affect the efficacy of tumor therapy. The ablation of LSD1 in multiple tumor cells induces TGF-β expression, which inhibits T-cell immunity by suppressing the cytotoxicity of intratumoral CD8+ T cells and consequently decreases the antitumor effect of LSD1 ablation-induced T-cell infiltration, providing a theoretical basis for the combination of LSD1 inhibition with dual PD-1/TGF-β blockade in treating certain poorly immunogenic tumors (61). Similarly, combining LSD1 inhibitors with an anti-PD-1 antibody

significantly suppressed breast tumor growth and pulmonary metastasis by reducing Ki-67 levels and augmenting CD8+ T-cell infiltration (62). In a study of infection with lymphocytic choriomeningitis virus, LSD1 was found to be recruited to the pdcd1 locus by Blimp-1, which downregulated PD-1 expression by removing histone H3 lysine 4 methylation marks (21). In the immune microenvironment of GC, LSD1 deletion decreased exosomal PD-L1 levels and restored the T-cell response (63). The inhibition of LSD1 could decrease the expression of PD-L1 in BGC-823 and MFC cells, leading to the inhibition of stemness and migration in GC cells (64).

Above all, the theory of the effect of LSD1 on the function of T cells in the TME provides a new idea for clinical tumor immunotherapy, specifically, immunotherapy with anti-PD-1 antibodies.

Macrophages and LSD1

In mouse bone marrow-derived macrophages (BMDMs), LSD1 mediates the demethylation of the p65 promoter region, which can increase the stability of p65 and maintain the inflammatory response (65). Similarly, Tokarz *et al*. demonstrated that LSD1 removes the transcription-promoting methylation modification on H3K4 and leads to the displacement of p65, leading to the termination of mRNA synthesis at a later stage of macrophage polarization (66). On the other hand, by enhancing FAD/LSD1 signalling to regulate the histone demethylation of Bcl2l11 and Dusp2, γ-amino butyric acid (GABA) treatment inhibits IL-1β production by inflammatory macrophages (67). In addition, the inhibitory effect of LSD1 on macrophages occurs mainly at the binding sites of CoREST and FAD, which can reduce the transcription of proinflammatory cytokines and surface markers related to M1 macrophages (68). Phenelzine, an LSD1 inhibitor that targets the binding domain of FAD and CoREST, promotes the transcription and expression of M1-related genes (13).

Recent studies show that LSD1 inhibitors can induce M1 polarization of macrophages, which is expected to provide new ideas for immunotherapy.

NK cells and LSD1

However, studies on the effect of LSD1 on NK cells are rare. LSD1 inhibition can restore the expression of ULBPs via induction of CEBPA expression in AML cells, leading to increased sensitivity to NK-induced lysis (69). Pretreatment of diffuse intrinsic pontine glioma (DIPG) with catalytic LSD1 inhibitors (not scaffolding LSD1 inhibitors) could increase NK cell cytotoxicity and induce tumor regression, which is related to the expression of immune response genes (70). However, other researchers have shown that scaffolding LSD1 inhibitors impair NK cell metabolism and cytotoxic function through depletion of glutathione (71). Some scholars believe that the opposite effects of different LSD1 inhibitors on NK cytotoxicity occur because it is challenging for NK cells to be modified genetically and because it is difficult to expand primary NK cells *in vitro* (72). More mechanistic studies on the function of LSD1 in controlling NK cell function could be helpful for clinical tumor treatment.

B cells and LSD1

The LSD1-BCL6 complex is a critical factor among a vast array of genetic and epigenetic molecules that regulate B-cell behavior during immune responses (73). BCL6 directly binds LSD1 and recruits it primarily to intergenic and intronic enhancers, inducing germinal centre B-cell maturation (74). Studies have shown that LSD1 is necessary for the proliferation and differentiation of mouse naive B cells into plasmablasts (75). Additionally, LSD1 was found to interact with the noncanonical NF-κB transcription factor p52, which is a step essential for the development of marginal zone B cells (75). LSD1 is a key molecule in B-cell development and may play an important role in the treatment of haematological tumors.

LSD1 inhibitors and GC

Mechanisms of LSD1 inhibitors in GC

Based on the known role of LSD1 in disease, research and development regarding its inhibitors are becoming increasingly extensive. Currently, nine of these compounds have entered clinical trials; these compounds include eight irreversible inhibitors, TCP (76), GSK-2879552, IMG-7289, ORY-1001 (77), INCB059872, ORY-2001, TAK-418, and LH-1802; two reversible inhibitors, CC-90011 and SP-2577; a novel LSD1 inhibitor, SYHA1807 (structure unpublished); and two dual LSD1/HDAC inhibitors, 4SC-202 and JBI-802 (72,78,79). There are few clinical studies on LSD1 inhibitors in GC, but some basic studies have provided theoretical support for the clinical treatment of GC.

First, LSD1 plays an important role in the proliferation

and metastasis of GC cells. LSD1 regulates E-cadherin expression by demethylating H3K4me2, thereby promoting the proliferation, migration and invasion of GC cells (80). Fang *et al*. reported that LSD1-mediated epigenetic silencing of KLF2 was involved in the proliferation, migration and invasion of GC cells (81). By interacting with LincRNAFEZF1-AS1 (82), LncRNA HOXA11-AS (83), Linc01503 (84) and LincRNA01446 (85), LSD1 regulates multiple oncogenes to promote GC proliferation. Furthermore, LSD1 deletion was found to suppress GC migration by decreasing intracellular miR-142-5p levels (86).

Second, by decreasing LSD1 activity, LSD1 inhibitors modulate multiple processes involved in gastric carcinogenesis. Upon treatment with compound 5ac, a novel acridine-based LSD1 inhibitor, BGC-823 cells became more sensitive to T-cell-mediated killing and presented decreased expression of PD-L1 (87). Compound 383 induced the degradation of LSD1 and inhibited MGC-803 cell proliferation, migration and invasion through increasing H3K4 methylation at the E-cadherin promotor (88). Arborinine, a potential LSD1 inhibitor, suppressed the EMT of SGC-7901 and adriamycin-resistant SGC-7901/ADR cells (10). Another study confirmed that capsaicin could bind and inhibit LSD1 in BGC-823 cells and further inhibit cell invasion and migration by reversing EMT (89). Compound 12u increased the level of H3K4 and H3K9 mono- and dimethylation, inducing apoptosis and differentiation in GC cells and inhibiting cell migration and cell stemness (90). Compound I-25 (MY-943) dose-dependently induced the accumulation of H3K4me1/2 and H3K9me2 to induce G2/M phase arrest and cell apoptosis and suppressed the migration of MGC-803 and SGC-7901 cells (91).

Notably, treatment with a novel, bifunctional LSD1/HDAC inhibitor significantly altered the expression of Bcl-2, Bax, vimentin, ZO-1 and E-cadherin; induced apoptosis; and suppressed colony formation and migration in MGC-803 cancer cells (92).

Taken together, these findings suggest that LSD1 inhibitors can interfere with the progression of GC by regulating the EMT process and autophagy, providing new insights into targeted therapeutic agents for GC treatment.

LSD1 inhibitors and immune microenvironment of GC

As mentioned above, LSD1 deletion can decrease exosomal PD-L1 expression and restore the T-cell response in GC (63). Compound 3s (the most potent LSD1 inhibitor among chlorpromazine derivatives), 2-aryl-4-aminoquinazolin-based LSD1 inhibitor, compound 5ac and 6x (a novel acridine-based LSD1 inhibitor) inhibited LSD1 expression at the cellular level and downregulated the expression of PD-L1 in BGC-823 and MFC cells to enhance T-cell cytotoxicity (64,87,93,94) (*Table 1*). LSD1 inhibitor treatment increased the proportion of CD8+ T cells and increased the proportion of differentiated T cells, which could transform into tumor-killing cytotoxic T cells to further promote T-cell mediated cytotoxicity, enabling a durable response to anti-PD-1 therapy (58). In addition, LSD1 inhibitor-treated mesenchymal stromal cells efficiently stimulate CD8+ T-cell activation and elicit antigen-presenting cell-like capabilities to promote the antitumor immune response (95).

In summary, LSD1 inhibitors mainly increase the activity of CD8+ T cells to promote their cytotoxic effects on tumor cells and play a role in the immune microenvironment of GC. Both alone and in combination with other target inhibitors, LSD1 inhibitors have demonstrated good antitumor activity. These findings highlight the great potential of targeting LSD1 in the clinical treatment of GC. However, additional mechanisms by which LSD1 inhibitors affect the GC immune microenvironment need

Table 1 LSD1 inhibitors' effects on immune functions in GC

Name	Category	Immunologic activity	Ref.
Novel acridine-based LSD1 inhibitor compound 5ac	Cellular active LSD1 inhibitor	Suppresses the expression of PD-L1 Promoted T-cell killing response	(87)
Acridine derivative 6x	Cellular active LSD1 inhibitor	Suppresses the expression of PD-L1 Promoted T-cell killing response	(64)
Chlorpromazine derivative compound 3s	Selective and cellular active LSD1 inhibitor	Suppresses the expression of PD-L1 in GC cells Promoted the T-cell killing response of GC cells	(93)
2-aryl-4-aminoquinazolin-based LSD1 inhibitor	Selective and cellular active LSD1 inhibitor	Suppresses the expression of PD-L1 Enhanced the response of GC cell to T-cell killing	(94)

LSD1, lysine-specific demethylase 1; GC, gastric cancer; PD-L1, programmed cell death ligand 1.

to be explored to improve clinical research.

Application prospects of LSD1 inhibitors in immunotherapy of GC

ICIs have become the first-line treatment for a variety of malignant tumors and have been used in combination with surgery, chemotherapy, radiotherapy, and targeted therapy as the backbone of antitumor therapy (96). Two clinical studies based on KEYNOTE-059 (54) and ATTRACTION-02 (55) established the status of pembrolizumab and nivolumab as third-line treatments for advanced GC, initiating the era of immunotherapy for GC. An increasing number of clinical studies of first-line immunotherapy for GC have since been conducted in China and elsewhere. Currently, immunotherapy plus chemotherapy is considered the first-line treatment for advanced GC. Trastuzumab, nivolumab and pembrolizumab have demonstrated consistent and reliable efficacy in patients with HER2-positive and PD-L1-positive tumors, respectively (97).

While these ICIs offer new hope for patients with advanced GC, some cases of drug resistance or immunotherapy failure are inevitable. There are many reasons why GC patients may not respond to immunotherapy, which our team has described in previous studies (98). The exploration of sensitization targets for immunotherapy has become a new therapeutic idea. Shi *et al.* (99) showed that Dickkopf-1 (DKK1) induces macrophages to become immunosuppressive, thereby inhibiting the antitumor responses of CD8+ T cells and NK cells; this group also found that TAM reprogramming via DKK1 blockade augments the efficacy of PD-1 blockade in GC models. MFSD2A potentiates the GC response to anti-PD-1 immunotherapy by reprogramming the TME to activate the T-cell response (100). Additionally, therapeutic strategies targeting urokinase-type plasminogen activator receptor (uPAR) potentiate anti-PD-1 efficacy in diffuse-type GC (101).

Similarly, LSD1 is considered a promising immunotherapeutic target for improving the response to PD-1 blockade therapy in GC. As mentioned before, LSD1 inhibitors potentiate the GC response to anti-PD-1 immunotherapy by increasing the cytotoxicity of T cells, macrophages, and NK cells against tumor cells through a variety of pathways (63,93). Additionally, studies have shown that targeting LSD1 can trigger intracellular double-stranded RNA (dsRNA) stress and interferon activation, thereby promoting antitumor T cell immunity and enhancing the response to PD-1 blockade (18). In addition, several LSD1 inhibitors have been tested in clinical trials, and the results of these studies highlight their potential as potent and selective anticancer agents (*Figure 3*).

Conclusions

According to the 2020 World Cancer Report (1), there were 1.09 million new cases of GC worldwide, accounting for 5.6% of all malignant tumors and 770,000 of related deaths. Exploring new ideas for the treatment of GC has become an important task for researchers worldwide (102). Advancements in immunotherapy have significantly improved the survival rate of GC patients and provided a new perspective for updating treatment regimens.

The present review demonstrated that in the immune microenvironment of GC, T cells, macrophages, NK cells and B cells exhibit great functional heterogeneity. The different effects of different cell subtypes on tumors reveal the complexity of immune regulation. Under these complex regulatory mechanisms, LSD1 promotes tumor progression and immunosuppression by participating in gene methylation. In addition, the combination of an LSD1 inhibitor with other immunotherapy drugs, such as PD-1/PD-L1 inhibitors and CAR-T cells, can increase immunotherapy efficacy and exert important inhibitory effects on tumor growth and metastasis (103). Therefore, LSD1 is expected to become an important target for GC immunotherapy.

While pivotal studies have established the connection between LSD1 and the tumor microenvironment, numerous questions in this field remain unanswered. Although the effects of LSD1 on specific immune cells, such as T cells and macrophages, have been extensively studied, its impact on other immune cells like B cells and neutrophils warrants further in-depth exploration. Additionally, the potential influence of LSD1 inhibition on other immune checkpoints, including lymphocyte-activation gene 3 (LAG3), T cell immunoglobulin and mucin-domain containing-3 (TIM3), and T cell immunoreceptor with Ig and ITIM domains (TIGIT), is a research direction that deserves further investigation.

At present, there is a relative scarcity of LSD1 inhibitors that are effective within GC immune microenvironment. Future research should focus on developing more potent LSD1 inhibitors and advancing these into clinical trials.

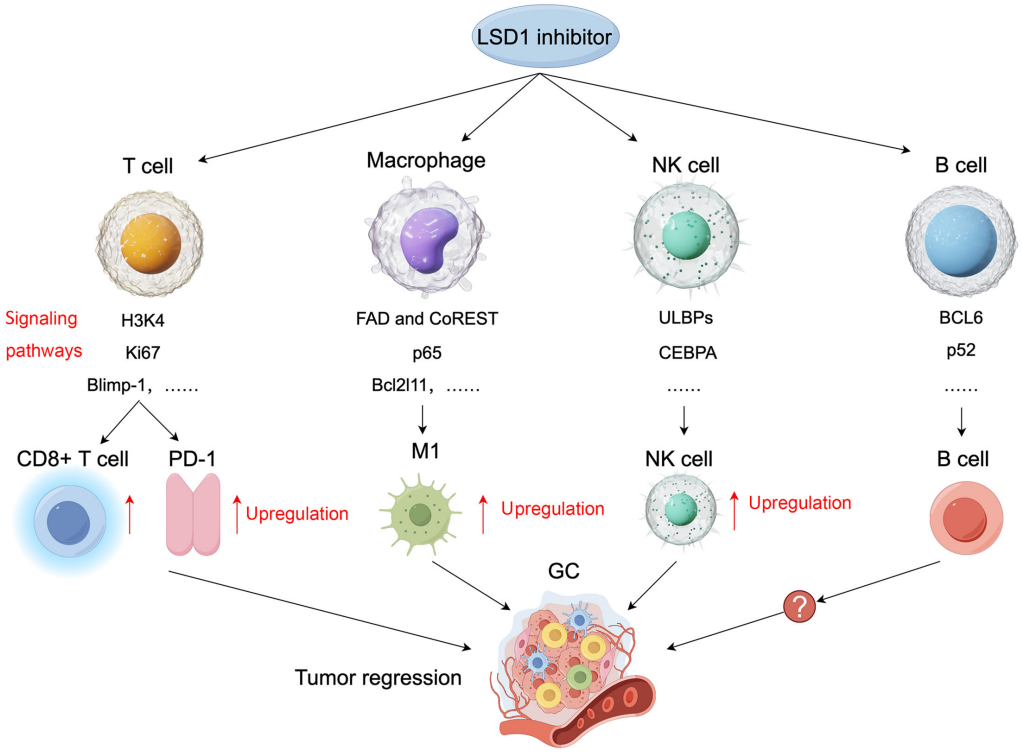

Figure 3 Role of LSD1 inhibitors in GC immunotherapy. LSD1 inhibitors alter CD8+ T-cell infiltration and upregulate PD-1 expression in T cells. By inducing the polarization of M1 macrophages, these cells play a role in tumor suppression. Catalytic LSD1 inhibitors could increase NK cell cytotoxicity and induce tumor regression. LSD1 inhibitors affect the development and maturation of B cells, but the effect on GC is unclear. LSD1, lysine-specific demethylase 1; GC, gastric cancer; NK, natural killer; FAD, flavin adenine dinucleotide; CoREST, repressor element 1 (RE1) silencing transcription factor (REST) corepressor; PD-1, programmed cell death 1. Completed by Figdraw (www.figdraw.com).

We anticipate that LSD1 inhibitors, when used in conjunction with targeted therapies, will play a significant role in the treatment of GC, offering new therapeutic hopes for patients.

As our understanding of LSD1's mechanisms in GC deepens, and with the continuous development of novel LSD1 inhibitors, there is reason to believe that these inhibitors will become an important direction in the field of GC immunotherapy. Future studies will not only enhance our knowledge of LSD1's role in tumor immunity but may also provide more effective treatment options for GC patients.

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Footnote

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