Research advances in the role of gastric cancer-derived mesenchymal stem cells in tumor progression (Review)

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Abstract. Gastric cancer (GC) is one of the most common malignancies and the second leading cause of cancer-associated death in the world. The carcinogenesis and development of GC involves complicated steps and various factors, in which the tumor microenvironment serves a vital role. Mesenchymal stem cells (MSCs), also known as mesenchymal stromal cells, are multipotent stromal cells, and have gained increasing attention due to their wound-healing ability, as well as their tumor-promoting potential. MSCs are essential components of the tumor microenvironment and serve important roles in tumor initiation, progression and metastasis. The present review focuses on GC and discusses recent advances in understanding the effect of GC-derived MSC-like cells (GC-MSCs) on tumor progression, chemoresistance and immune escape. Additionally, the mechanism underlying the tumor tropism of bone marrow-derived MSCs and the malignant transition of these cells to GC-MSCs are addressed. The potential of GC-MSCs in the treatment of GC, such as for predicting prognosis and as therapeutic targets, is also discussed in association with their critical role in tumor progression. The information on the characteristics and functions of GC-MSCs provided in the present review may promote the development of novel therapeutic strategies against GC.

Contents

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1. Introduction

According to global cancer statistics, gastric cancer (GC) ranked fifth in incidence (5.7% of the total cases) and third in mortality (8.2% of the total cancer deaths) among malignancies worldwide in 2018 (1). When detected early, GC is usually curable and has a 5-year survival rate of >90%; however, the prognosis of patients with advanced GC remains poor (2). The lack of early clinical symptoms often delays the diagnosis of GC, resulting in the development of an incurable disease in a number of patients (3). Another reason for the high mortality is that surgical resection is the only curative treatment for GC (4). Despite the availability of a number of novel therapies, including targeted therapy and immunotherapy (3,5), the treatment of GC remains unsatisfactory. Therefore, elucidating the underlying mechanisms underlying tumor progression may help develop more effective treatments.

The tumor microenvironment (TME) is a complex and dynamic cellular community composed of cancer cells, endothelial cells, fibroblasts, immune cells, and mesenchymal stem cells (MSCs) (6). The TME is formed via the recruitment of tumor-supporting MSCs and extensive remodeling of adjacent tissues; thus, the TME differs from normal tissues in numerous aspects, including the extracellular matrix, blood vessels and phenotypes of cells (7). The interaction between tumor cells and the TME serves an important role in tumor initiation, progression, chemoresistance and immune escape, and certain molecules present in the TME are prognosis predictors in various types of cancer, such as pancreatic cancer, GC and urothelial carcinoma (8-11). MSCs, which are important components of the TME and serve critical roles in tumor progression, have been extensively studied.

MSCs, also known as mesenchymal stromal cells, are multipotent stromal cells with the ability to differentiate into osteoblasts, adipocytes, chondrocytes and other types of cells under different conditions (12). Despite extensive research efforts, the multi-differentiation potential of MSCs has only been demonstrated *in vitro*, and there are few studies

describing their characteristics *in vivo* (13,14). MSCs can accelerate wound healing by regulating inflammation (15). Additionally, MSCs can suppress the function of both innate and adaptive immune cells, including macrophages and lymphocytes (15). In cases of weak inflammatory responses, MSCs can act as antigen-presenting cells and increase the immune response (15). In cancer, MSCs are critical components of the TME and promote the progression of several types of tumor, such as hepatocarcinoma and colorectal cancer (16,17). Tumors are considered to be 'wounds that never heal', and MSCs can migrate to injured tissues, supporting the tumor tropism of MSCs and their ability to sense wound-associated signals (18). Upon recruitment to tumors, MSCs are converted into tumor-associated MSCs (TA-MSCs), which can promote tumor progression more potently (19). TA-MSCs interact with tumor cells and are involved in the remodeling of the TME in response to signals from tumor cells and other stromal cells (19,20). The crosstalk between TA-MSCs and tumor cells can be mediated by several mechanisms, including paracrine signals, exosomes and direct contact (21,22). Furthermore, TA-MSCs can differentiate into cancer-associated fibroblasts, which promote tumor progression (23).

In the present review, the effect of GC-derived MSC-like cells (GC-MSCs) on GC progression, metastasis, chemoresistance and immune escape are described. Additionally, the mechanisms by which GC cells, immune cells and other stromal cells educate MSCs and skew MSCs towards the GC-MSC fate are discussed. Finally, the therapeutic potential of GC-MSCs as both targets and biomarkers are summarized.

2. Biological characteristics of GC-MSCs

Friedenstein *et al* (24) discovered the presence of mouse bone marrow (BM)-derived fibroblast-like cells in the early 1970s, which are currently known as MSCs. MSCs are present in numerous tissues, including the stomach (25). GC-MSCs have been successfully isolated and characterized from patients with GC (26,27). Similarly to other stem cells, GC-MSCs have the potential to differentiate into adipocytes and osteocytes (28). Since no specific surface markers of GC-MSCs have been identified, they can only be characterized by *in vitro* experiments; GC-MSCs express high levels of CD29, CD90 and CD105 and barely detectable levels of CD34, CD45 and CD19 (28). Although BM-MSCs and GC-adjacent non-cancerous tissue-derived MSCs (GCN-MSCs) can transform into GC-MSCs in the TME, these three types of cells exhibit both similarities and differences (23). The three types of cells have similar morphology when isolated from patients (Fig. 1A), as well as surface markers and differentiation potential. They are all slender and look like a shuttle under the microscope. The three types of cells are positive for CD29, CD44 and CD105, and negative for CD14 and CD34 (26). BM-MSCs and GCN-MSCs express CD13, whereas GC-MSCs do not (26). They all have a pluripotent differentiation potential and can differentiate into osteocytes and adipocytes (26). However, GC-MSCs can proliferate twice as fast as GCN-MSCs and BM-MSCs (26). GC-MSCs differ from BM-MSCs in the number of cytoplasmic organelles, tumor-promoting capacity and secretion levels of numerous inflammatory cytokines, such as IL-6, monocyte chemoattractant protein 1 and VEGF (26,29). GC-MSCs can improve the proliferative, migratory and pro-angiogenic abilities of GC cells more potently than GCN-MSCs and BM-MSCs, partly by secreting IL-8 (30). These findings suggest that GC-MSCs maintain the mesenchymal lineage and stem cell capabilities, and differ from MSCs from non-GC tissues in several aspects, especially their tumor-promoting capabilities.

3. Formation of GC-MSCs

MSCs migrate to the tumor. Studies have revealed that BM-MSCs have tropism to several types of tumor, such as glioma and breast cancer, by intravenous or intraperitoneal injection (31,32). CXC-chemokine ligand 16 (CXCL16) secreted by breast cancer cells binds to its receptor CXC-chemokine receptor 6 (CXCR6) on BM-MSCs, which in turn produce CXCL10, thereby promoting the recruitment of BM-MSCs to cancer cells (33). The combination of CXCL12 and CXCR6 facilitates the recruitment of BM-MSCs to prostate tumors (34). Other chemokines and growth factors also participate in the migration of MSCs from non-cancer to cancer tissues, such as transforming growth factor-β (TGF-β), platelet-derived growth factor, monocyte chemoattractant protein-1 and stromal cell-derived factor-1 (35-37). Hypoxia in the TME induces BM-MSCs tropism to breast cancer (33). Thus, there are various mechanisms involved in the migration of MSCs from non-cancer to tumor tissues. In GC, Berger *et al* (38) performed a 'plug assay', in which GC and lung carcinoma cell-derived microvesicles (MVs) were collected and used as a Matrigel plug, which was implanted into teratoma tissues; 6-10 days after the injection, the plug was harvested and subjected to histological analysis or dissociated into a single cell suspension. The results revealed that MSCs were present in the plug containing GC cell-derived MVs, whereas the control group did not exhibit MSCs, suggesting that GC cell-derived MVs are responsible for the migration of MSCs, although the underlying mechanism remains unknown (38). To the best of our knowledge, there are no studies investigating the tropism of MSCs from non-GC to GC tissues, and additional studies are required to understand this migration and to identify key cytokines or chemokines.

MSCs transform into GC-MSCs. After their recruitment to the tumor site, MSCs from non-cancer tissues are converted into TA-MSCs under the influence of tumor cells, immune cells, local TA-MSCs and other stromal cells (34). In GC, tumor cells are involved in the malignant transition of MSCs through several mechanisms (Table I). For example, Shamai *et al* (39) revealed that GC cells have the capacity to increase R-spondin expression in GC-MSCs, and GC-MSCs can in turn upregulate Lgr5 expression in GC cells. Therefore, tumor cells can alter gene expression in GC-MSCs and GC-MSCs can induce tumor cell stemness. Exosomes from GC cells regulate the immunomodulatory properties of adipose-derived MSCs by activating the NF-κB signaling pathway (40). GC-MSCs exposed to GC cell-derived exosomes can activate both macrophages and T lymphocytes, thus maintaining the inflammatory TME and promoting tumor progressio (40). MicroRNAs (miRNAs/miRs) are involved in the malignant transition of MSCs from non-GC tissues.

Table I. Mechanisms of the malignant transition of MSCs to GC-MSCs.

First author, year	Regulation mechanism	Effect on malignant transition	(Refs.)
Shamai *et al*, 2019	GC cells increased R-spondin expression in GC-MSCs	Promote	(39)
Shen *et al*, 2019	GC cells secreted exosomes to activate NF-κB signaling pathway	Promote	(40)
Zhu *et al*, 2016	miR-155-5p inhibited NF-κB signaling pathway	Inhibit	(41)
Ji *et al*, 2017; Sun *et al*, 2018	miR-374 activated Wnt5a/β-catenin signaling pathway	Promote	(42,43)
Yang *et al*, 2014	Macrophages activated NF-κB signaling pathway	Promote	(44)
Xu *et al*, 2018	$CD4^+$ T cells upregulated PD-L1 expression in GC-MSCs through phosphorylated-STAT3	Enhance GC-MSCs tumor-promoting effect	(45)
Zhang *et al*, 2016	*Helicobacter pylori* infection activated NF-κB signaling pathway	Promote	(46)

miR, microRNA; GC-MSCs, gastric cancer-derived MSC-like cells; PD-L1, programmed cell death-ligand 1.

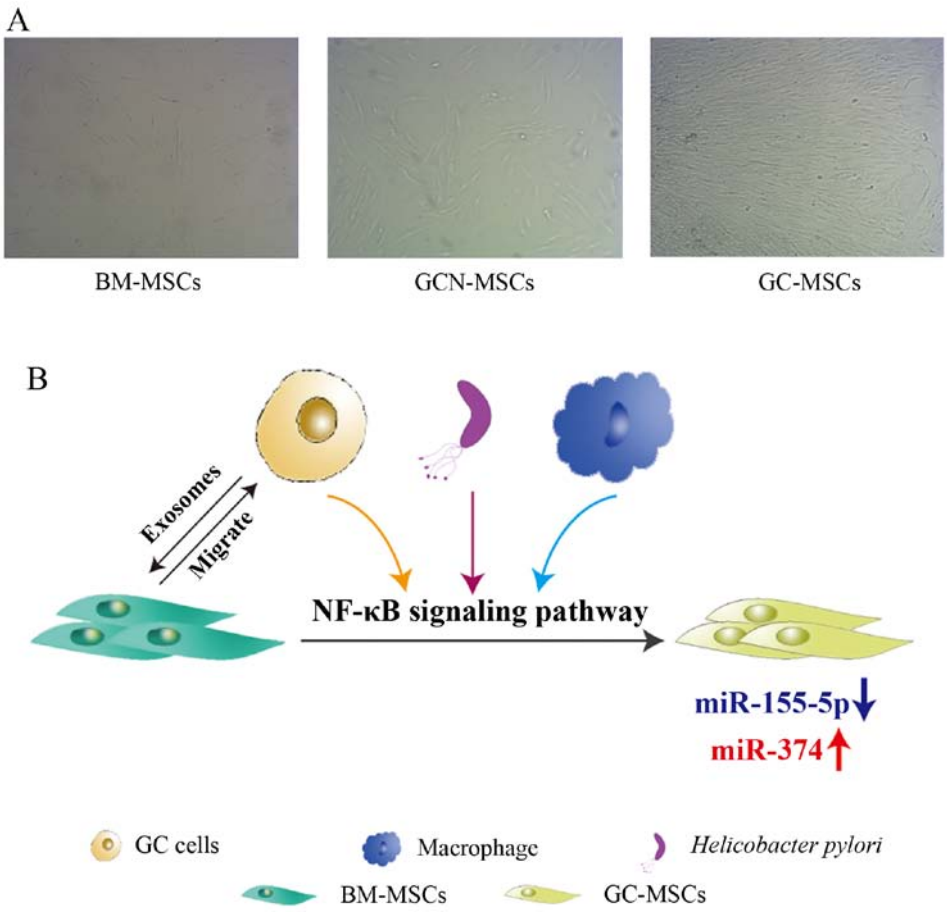

Figure 1. (A) Morphology of GC-MSCs, GCN-MSCs and BM-MSCs (magnification, x400). Cells in the images were isolated as part of a previous study (28) and the current images were taken for the present study. (B) Malignant transition of MSCs and underlying mechanisms. MSCs, mesenchymal stem cells; BM-MSCs, bone marrow-derived MSCs; GC-MSCs, gastric cancer-derived MSC-like cells; GCN-MSCs, GC-adjacent non-cancerous tissues-derived MSCs; miR, microRNA.

The downregulation of miR-155-5p expression caused by the activation of NF-κB signaling in GC-MSCs promotes this process, as demonstrated by the effect of miR-155-5p inhibition on conferring BM-MSCs a GC-MSC-like phenotype and function (41). Unlike miR-155-5p, miR-374 expression is upregulated in GC-MSCs, and overexpression of miR-374 promotes the proliferation and migration of MSCs from normal gastric tissues by regulating the Wnt5a/β-catenin signaling pathway (42,43). Additionally, immune cells can participate in the malignant transition of MSCs. Macrophages activate umbilical cord-derived MSCs and confer these MSCs a pro-inflammatory phenotype, which can promote

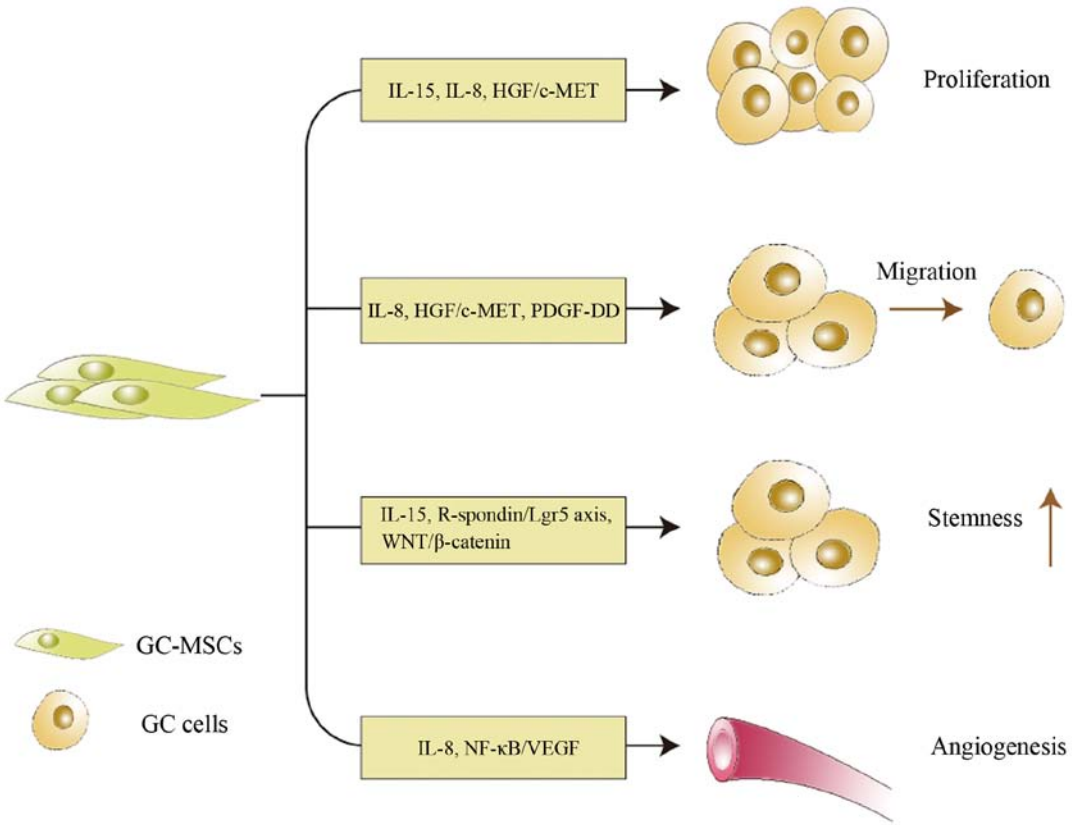

Figure 2. GC-MSCs promote tumor progression. GC-MSCs can promote proliferation and migration of GC cells and induce stemness and tumor angiogenesis by secreting cytokines and activating signaling pathways. GC-MSCs, gastric cancer-derived mesenchymal stem cell-like cells; HGF, hepatocyte growth factor; PDGF, platelet-derived growth factor.

GC progression partly through the NF-κB signaling pathway, as demonstrated by *in vitro* and *in vivo* experiments (44). $CD4^+$ T lymphocytes may also be involved in this process; although the effect of $CD4^+$ T cells on the malignant transition of MSCs has not been investigated, these cells upregulate the expression levels of PD-L1 in GC-MSCs through the p-STAT3 signaling pathway, and GC-MSCs with positive PDL1 expression protect tumor cells from immune cells (45). Patients with GC infected with *Helicobacter pylori* have a high mortality rate because this bacterium confers MSCs a pro-inflammatory phenotype through the activation of the NF-κB signaling pathway (46). Overall, these findings suggest that GC cells, as well as immune cells and bacteria, can convert BM-MSCs into GC-MSCs (Fig. 1B).

4. Effects of GC-MSCs on tumor progression and the tumor microenvironment

GC-MSCs promote tumor progression. TA-MSCs promote tumor progression by secreting cytokines, which act directly on tumor cells or other stromal cells in the TME (47-49). GC-MSCs can promote GC progression through various mechanisms (Fig. 2). For example, IL-15 secreted by GC-MSCs induces GC cell epithelial-mesenchymal transition and promotes GC cell migration, which are associated with tumor growth and metastasis, respectively (28). Consistently, IL-15 levels are higher in patients with GC than in healthy donors in both serum and tissues in association with lymph node metastasis (28). In addition, GC-MSCs produce high levels of IL-8, which serves a role in tumor cell proliferation and migration, and in angiogenesis (30). However, the tumor-promoting ability of IL-8 has only been demonstrated *in vitro* and the underlying mechanisms remain unknown. In addition to cytokines, other molecules serve roles in the tumor-promoting effect of GC-MSCs. The interaction between GC cells and GC-MSCs maintains GC cell stemness through the activation of the R-spondin/Lgr5 axis and WNT/β-catenin signaling pathway (39). Hepatocyte growth factor (HGF) exclusively secreted by GC-MSCs promotes the proliferation and migration of GC cells through the activation of the HGF/c-MET signaling pathway (38). Furthermore, platelet-derived growth factor-DD (PDGF-DD) secreted by GC-MSCs increases the phosphorylation of PDGF receptor-β in GC cells, thus promoting GC cell proliferation and migration; recombinant PDGF-DD can mimic the tumor-promoting effect of GC-MSCs conditioned medium (CM) on GC cell proliferation and migration (50). GC-MSCs induce VEGF expression in GC cells *in vitro* and *in vivo*, and contribute to GC-MSC-mediated angiogenesis by activating the NF-κB/VEGF signaling pathway (51). Since tumor neovascularization is indispensable for continuous tumor growth, this pathway may be a potential target to inhibit tumor growth. Notably, lung carcinoma cell proliferation is independent of lung carcinoma MSCs, whereas GC cell proliferation is critically dependent on the presence of their counterparts GC-MSCs (38). This phenomenon suggests that tumor growth does not always depend on the counterpart

TA-MSCs. The interaction between tumor cells and TA-MSCs is specific not only for the requirements of the tumor cells, but also their capacity to recruit MSCs and educate them to further promote tumor progression (38). Overall, these results demonstrate that GC-MSCs serve essential roles in GC progression.

GC-MSCs induce tumor chemoresistance. Chemotherapy is the first-line treatment for patients with advanced GC; pre- or post-operative chemotherapy with 5-fluorouracil (5-FU) and cisplatin has improved the survival rates of patients with GC (52-54). However, the response rate for this therapy is limited by the development of chemoresistance (55,56). Therefore, it is urgent to investigate the mechanisms underlying GC cell chemoresistance. The TME can protect tumors from chemotherapy through physical barriers and metabolites, exosomes and other substances secreted by tumor stromal cells (57). One of the key components of the TME, TA-MSCs, induces tumor cell chemoresistance through various mechanism, such as elevating tumor cell stemness and secreting certain molecules, such as interleukins and chemokines (58-60). Cancer stem cells (CSCs), also known as cancer initiation cells, were identified based on the observation of histological heterogeneity in tumors and on the fact that a single mouse tumor cell can form a new tumor (61). Although the definition of CSC is contentious, these cells have self-renewal and differentiation capacities and sustain the growth of tumors (62,63), which is associated with tumor cell chemoresistance. In GC, He *et al* (64) suggested that MSCs promote GC cell stemness and chemoresistance through fatty acid oxidation (FAO) based on *in vitro* and *in vivo* experiments. Mechanistically, TGF-β1 secreted by MSCs activates SMAD2/3 through TGF-β receptors, which then induces lncRNA MACC1-AS1 expression in GC cells and promotes FAO-dependent stemness and chemoresistance by antagonizing miR-145-5p (64). GC-MSCs express high levels of the ATP-binding cassette subfamily B member 1 transporter, which results in decreased drug accumulation in chemoresistant cells (39). Exosomes secreted by GC-MSCs induce GC cell resistance to 5-FU by activating calcium/calmodulin-dependent protein kinases and the Raf/MEK/ERK kinase cascade, thus upregulating the expression levels of multi-drug resistance-associated proteins (65). The aforementioned studies indicate that GC-MSCs can induce GC cell chemoresistance by secreting cytokines and exosomes, although there may be other undiscovered mechanisms that may help develop strategies to overcome chemoresistance.

GC-MSCs suppress antitumor immunity. The number and types of inflammatory factors in the TME can alter the immune responses to tumors, although the underlying mechanisms remain obscure. MSCs modulate immune cells and can suppress the immune response; however, they can also promote immune responses when inflammatory conditions are not enough (66). Additionally, GC-MSCs can modulate antitumor immunity by interacting with immune cells, such as macrophages, neutrophils and T lymphocytes. Macrophages are associated with a poor prognosis of GC and are used as prognostic indicators (67). Li *et al* (68) suggested that GC-MSCs may trigger the polarization and generation of M2-like macrophages by activating the JAK2/STAT3 signaling pathway via high secretion of IL-6/IL-8. M2-like macrophages can facilitate the metastasis and progression of GC by enhancing epithelial-mesenchymal transition in GC cells (68). Exosomes extracted from the GC AGS cell line can induce macrophage phagocytosis and promote the secretion of pro-inflammatory factors, thereby activating CD69 and CD25 on the surface of T cells through the NF-κB signaling pathway in MSCs (40). Regarding neutrophils, there is a reciprocal interaction between GC-MSCs and neutrophils. GC-MSCs can induce chemotaxis and neutrophil activation, as well as suppress neutrophil spontaneous apoptosis through the activation of the STAT3 and ERK1/2 signaling pathways (29). Neutrophils incubated with GC-MSCs or GC-MSCs-CM can promote the migration of tumor cells and induce the formation of tube-like structures in endothelial cells (29). Furthermore, GC-MSC-treated neutrophils can in turn convert normal MSCs into tumor-associated fibroblasts (30). GC-MSCs-CM pretreatment reverses the inhibitory effect of peripheral blood mononuclear cells and promotes GC liver metastases by disrupting the balance of regulatory T cells and T helper 17 cells (69). Both innate and adaptive immune cells can be affected by GC-MSCs, and they can gain tumor-promoting abilities or be inhibited.

GC-MSCs upregulate PD-L1 expression in GC cells. In past years, immune checkpoints, including programmed cell death protein 1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4 and T-cell immunoglobulin domain and mucin domain-3, have attracted increasing attention for their ability to weaken the function of T lymphocytes and induce tumor immune escape. Blocking the interaction between PD1 and PD-L1 has exhibited promising results in the treatment of several types of cancer, including breast cancer and squamous cell carcinoma of the head and neck (70,71). In GC, pembrolizumab, a PD-1 inhibitor, has shown good results in phase I/II trials, with objective response rates of 11.6-25.8% and low toxicity (72,73), and the combination of nivolumab and regorafenib, which respectively inhibit PD-1 or VEFGR tyrosine kinase, also exhibits antitumor activity (74). However, the response to this therapy cannot be predicted due to a lack of effective biomarkers (72). GC-MSCs upregulate PD-L1 expression in GC cells by secreting IL-8, which can regulate the STAT3 and mTOR signaling pathways (75). The role of GC-MSCs in regulating PD-L1 in GC cells has not been investigated extensively. Further investigation of the involvement of GC-MSCs in the regulation of PD-L1 expression and elucidation of the underlying mechanism may help the development of anti-PD-L1 therapy and may provide novel biomarkers.

5. Therapeutic opportunities for GC-MSCs

Since MSCs can be isolated from bone marrow and adipose tissues, they have been used in numerous studies in past years (76,77). MSCs from non-cancer tissues can suppress immune responses and have immune evasion properties; they are therefore stable in an allogeneic environment and display promise for cell therapy (78). For instance, exosomes from MSCs from non-GC tissues and MSCs themselves can serve as vehicles to transport miRNAs or drugs and cytokines to tumors, thus suppressing tumor progression, according to laboratory tests and clinic trials (79-81).

Unlike MSCs from non-GC tissues, GC-MSCs cannot be used as drug carriers due to their critical role in tumor progression. Instead, they should be specifically targeted to eliminate their effect on tumor cell proliferation, drug-resistance and migration. However, GC-MSCs have no specific surface markers, and therefore they cannot be targeted without affecting other cells. Only the substances released by GC-MSCs can serve as targets to suppress their tumor-promoting capability. For example, GC-MSCs can induce chemoresistance in tumor cells through FAO, and inhibition of FAO attenuates this phenomenon, suggesting that FAO may be a potential target to reduce chemoresistance in GC (64). Similarly, GC-MSCs-CM treatment can promote tumor cell proliferation and migration and increase pro-angiogenic abilities through the secretion of IL-8; therefore, the use of an IL-8 neutralizing antibody may suppress the effects of GC-MSCs (30). In addition, IL-8 produced by GC-MSCs upregulates PD-L1 expression in tumor cells and can thus induce tumor cell resistance to $CD8^+$ T cells, and inhibition of IL-8 can eliminate resistance (75). The aforementioned studies indicate that target key modulators in the tumor-promoting process of GC-MSCs can suppress tumor progression and chemoresistance. Furthermore, this strategy may be effective in combination with other therapies, such as chemotherapy and anti-PD-L1 therapy.

Furthermore, miRNAs and cytokines secreted by GC-MSCs can predict prognosis. For instance, GC-MSCs have higher expression levels of miR-214, miR-221 and miR-222 than GCN-MSCs, and high expression levels of miR-221 and miR-222, or miR-214 and miR-222 in the tissues of patients with GC are positively associated with lymph node metastasis and serosal invasion, respectively (82). IL-15 in the GC microenvironment is mostly derived from GC-MSCs and is associated with lymph node metastasis (28). GC-MSCs can secrete high levels of IL-8, which predicts a poor prognosis in patients with GC (30). In summary, GC-MSCs can potentially be developed into novel therapies and prognostic biomarkers.

6. Conclusions

In past years, the interaction between MSCs and tumors has gained increasing attention. The present review focused on the transformation of MSCs from non-GC tissues into GC-MSCs and the role of GC-MSCs in tumor progression, chemoresistance and immune escape. In addition to GC cells, immune cells and bacteria can be involved in the malignant transformation of MSCs into GC-MSCs. GC-MSCs can in turn promote tumor progression, induce chemoresistance and confer immune cells a tumor-promoting phenotype. Regarding their therapeutic potential, the upstream or downstream modulators of GC-MSCs can serve as targets to weaken their effect on tumor progression. However, the interaction between other stromal cells and GC-MSCs, and the underlying mechanisms require further investigation, including the roles of natural killer cells and endothelial cells. In addition, specific surface markers of GC-MSCs remain to be identified, which may facilitate the specific targeting of GC-MSCs without affecting other cells. The association between GC-MSCs and PD-L1 should be investigated further, as it may provide new insight into PD-L1 co-therapy. Despite numerous advances in the understanding of the effect of GC-MSCs on tumor progression, elucidating the function and underlying mechanisms of GC-MSCs may provide valuable information to improve the treatment of GC.

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Availability of data and materials

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Authors' contributions

JS and WZ reviewed the literature on the role of GC-MSCs in tumor progression and the tumor microenvironment, and wrote most of the review. WZ discussed the role of GC-MSCs in GC treatment. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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