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TOPIC HIGHLIGHT

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Gastric cancer stem cells in gastric carcinogenesis, progression, prevention and treatment

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Abstract

In recent decades, the study of the mechanism of tumorigenesis has brought much progress to cancer treatment. However, cancer stem cell (CSC) theory has changed previous views of tumors, and has provided a new method for treatment of cancer. The discovery of CSCs and their characteristics have contributed to understanding the molecular mechanism of tumor genesis and development, resulting in a new effective strategy for cancer treatment. Gastric CSCs (GCSCs) are the basis for the onset of gastric cancer. They may be derived from gastric stem cells in gastric tissues, or bone marrow mesenchymal stem cells. As with other stem cells, GCSCs highly express drug-resistance genes such as aldehyde dehydrogenase and multidrug resistance, which are resistant to chemotherapy and thus form the basis of drug resistance. Many specific molecular markers such as CD44 and CD133 have been used for identification and isolation of GCSCs, diagnosis and grading of gastric cancer, and research on GCSC-targeted therapy for gastric cancer. Therefore, discussion of the recent development and advancements in GCSCs will be helpful for providing novel insight into gastric cancer treatment.

Key words: Cancer stem cells; Gastric cancer; Drug resistance; Cancer treatment; Molecular mechanism

Core tip: Gastric cancer stem cells (GCSCs) play an important role in the occurrence and development of gastric cancer. They are the basis for tolerance to chemotherapy, as well as the rapid growth and metastasis of tumors. GCSC markers are closely associated with the degree of malignancy of gastric cancer, therefore, marker-targeted therapy is one of the potential directions for the treatment of gastric cancer.

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INTRODUCTION

Cancer stem cells

Stem cells are pluripotent cells with the function of self-renewal and multidirectional differentiation, which differentiate into precursor cells with single-directional differentiation, followed by differentiation into nondifferentiated adult cells involved in the generation and regeneration of tissues and organs. These cells are also considered to exist in tumor cells, where they are involved in the generation and regeneration of tumor tissue, as a basis of tumor formation and development. The cancer stem cells (CSCs) hypothesis believes that few cells in cancer tissues function as CSCs. They can self-regenerate, pro-

liferate and have multiple differentiation potentials. They produce different phenotypes of non tumorigenic tumor cells, constantly enlarging the tumor mass, and thus play a decisive role in the onset and development of the tumors. Furthermore, they become drug resistant during radio- and chemotherapy, and migrate and metastasize rapidly into novel tumors[1-3]. CSCs are considered to be the only cells with metastatic ability in the tumor cell subset. In appropriate tumor microenvironments, CSCs can migrate and proliferate and form new tumors. In 2006, the American Cancer Research Association reached a consensus that some cells in tumor tissues are capable of self-renewal, with relatively static, multidrug resistance and pluripotency, as compared with other tumor cell lines. These cells show greater tumorigenicity and mobility when transplanted *in vivo*, therefore, we confirmed that such cells were CSCs[4].

CSCs and tumors

CSCs were first found in patients with acute myeloid leukemia. Bonnet and Dick isolated one type of hematopoietic stem cells similar to $CD34^+CD38^+$ cells from tumor tissues. It was found that these cells could self-regenerate and become xenografts in nude mice[5]. Breast cancer is one of the earliest tumors discovered to have CSCs. In 2003, in eight of nine patients with breast cancer, Al-Hajj *et al*[6] isolated a $CD44^+/CD24^{-/low}$ cell line, which can survive and grow into tumors in nude mice. In subsequent studies, it was revealed that $CD44^+$ combines with many tumor biomarkers that are used as predictive biomarkers of breast cancer. Combined with Ezrin protein, it can be used as a marker of development and drug resistance in breast cancer. The rate of malignant tumors positive for both $CD44^+$ and Ezrin reaches as high as 81.54%[7]. Ignatova *et al*[8] first isolated $CD133^+$ CSCs in human brain tumors, and found that a single injection of 100 $CD133^+$ tumor cells can differentiate and proliferate into brain tumor. However, even with injection of up to 50000-100000 $CD133^-$ cancer cells, there was no tumor development in mice. This provided strong evidence of the existence of CSCs. Thereafter, researchers proved the existence of CSCs in many solid tumors, including glioma, multiple myeloma, malignant melanoma, colon cancer, pancreatic cancer, prostate cancer, head and neck squamous cell carcinoma, liver cancer, and ovarian cancer. Furthermore, xenograft formation in nude mice was regarded as the gold standard of CSCs in cancer tissues[9-17]. Like the normal stem cells that maintain tissue function, CSCs are the basis of tumor formation. The expression of cancer-suppressing genes within CSCs is inhibited, and that of Shh, Notch, Wnt/β-catenin, Hox and Hedgehog is activated[18-21]. All these findings are helpful for understanding tumors more comprehensively and developing more targeted cancer therapy.

CSCs and gastric cancer

Gastric cancer is a life-threatening malignant tumor in humans, and has the fourth highest incidence among all malignant tumors. Nearly 1 million people are diagnosed with gastric cancer every year worldwide, among which, 70% are in developing countries and more than half in East Asia, especially China[22,23]. In China, the incidence of gastric cancer ranks second among all types of malignant tumors. There are over 400000 newly diagnosed patients with gastric cancer and up to 300000 deaths annually, accounting for > 40% of the overall mortality due to gastric cancer worldwide. Gastric cancer is the second leading cause of cancer mortality after lung cancer[24]. In recent years, with the application of endoscopy, the early detection rate of gastric cancer has continued to rise. The clinical outcome of therapy has improved dramatically, but the 5-year survival rate is still < 40% for gastric cancer. Tumor regeneration and metastasis impose great difficulty for the prevention and treatment of gastric cancer[25]. CSCs are a newly proposed theory for tumor development, and form the basis for tumor proliferation and metastasis. CSCs maintain cancer cell regeneration and are capable of unlimited proliferation[26-28]. The development of gastric cancer is closely associated with gastric CSCs (GCSCs). Cancer cells with $CD44^+$ removed do not have the characteristics of cancer cells, and thus are unable to grow into tumors in nude mice[29,30]. Clinicopathological analysis has demonstrated that the expression of stem cell markers is highly associated with the degree of malignancy and tumor grading[31,32].

In this review, we address the relationship of CSCs and cancer, the role of GCSCs in the development of gastric cancer, and the potential sources and biomarkers of GCSCs (including activation of related signaling pathways), in the hope of exploring the existence of GCSCs and their role in the development of gastric cancer. Furthermore, we review advances in research on GCSCs and the sensitivity of gastric cancer to chemotherapy, as well as GCSC-targeted therapy, with the expectation of providing theoretical support for such therapy in the clinic.

GCSCs AND GASTRIC CANCER CARCINOGENESIS AND PROGRESSION

Origin of GCSCs

Like other stem cells, CSCs are a group of heterogeneous cells that can self-regenerate and have the potential for multiple differentiation, migration, metastasis, and drug resistance[33]. The sources of GCSCs may be closely associated with those of gastric stem cells. Gastric epithelial cells constantly replace the injured or dead cells to maintain their self hemostasis. Under normal physiological conditions, gastric epithelial cells renew once every 2-7 d. When there is injury, this type of epithelial cell renews faster. During this process, stem cells play a vital role[34]. Labeling stem cells by chemical method for mutation detection and tracking their offspring cells, there are multiple potential stem cells in the gastric epithelium of adult mice. Furthermore, it was revealed that the major cell lines within the gastric epithelium (wall, chief, endocrine and mucous cells) are all derived from a single common

stem cell. This suggests that there are gastric stem cells in gastric tissues[35]. When gastric cancer develops, the gastric epithelial cells rapidly proliferate, completing the transformation from normal gastric mucosa to atrophic gastritis, intestinal metaplasia, atypical hyperplasia, and gastric cancer. During this process, the cells complete mutation and become tumor cells. Gastric stem cells are the only vital cells completing the genetic changes needed for accumulated tumor transformation. Tatematsu *et al*[36] confirmed that gastric stem cells differentiate into gastric and intestinal cells during the process of intestinal metaplasia. Gastric cancer cells are classified as cells with gastric and intestinal phenotypes. Both intestinal metaplasia of gastric mucous cells and gastric cancer cells are homeotic. This demonstrates that gastric cancer itself is a disease of stem cells. It is the canceration of the stem cells that causes the development of gastric cancer. GCSCs are derived from gastric stem cells.

Additionally, there is another hypothesis. It is believed that GCSCs are derived from bone-marrow-derived mesenchymal stem cells (BM-MSCs)[37]. BM-MSCs are a type of adult stem cells, with the same genetic basis as the cells in other organs and tissues. They can migrate, regenerate and have the potential for multiple differentiation. On the one hand, hematopoietic stem cells produced *via* hyperplasia and differentiation supplement and maintain the homeostasis of hematopoietic and lymphatic systems[38]. On the other hand, they supplement the need for regenerating other tissues and organs. Like immune cells, these cells move in ameba-like form *via* the capillary walls and enter the solid tissues, and differentiate into all types of tissues and cells. When there is injury, the BM-MSCs can mobilize from the bone marrow, participate in and assist with repair of injured tissues[39,40]. When gastric injury is caused by *Helicobacter felis* infection, BM-MSCs migrate to the gastric epithelium and participate in tissue repair, suggesting that BM-MSCs participate in the development of gastric cancer[41]. In model mice infected by *Helicobacter pylori* (*H. pylori*), it is confirmed that under inflammatory stimulation, BM-MSCs with positive markers migrate to the gastric epithelium and differentiate into gastric cancer. Furthermore, the same positive marker can be detected in the cancer tissues. Thus, it is assumed that the development of gastric cancer may be the result of abnormal differentiation of bone marrow stem cells during regeneration and repair of gastric mucosa[42]. Varon *et al*[43] labeled bone-marrow-derived cells with green fluorescent protein (GFP), and observed *H. pylori*-induced chronic gastritis, atrophic gastritis, intestinal metaplasia, atypical hyperplasia and gastric cancer, and found that GFP was seen in 90% of the mice, and 25% of cancerous cells were derived from bone-marrow-derived cells. This further proved that bone-marrow-derived cells participated in the development of gastric cancer[43], and BM-MSCs are the source of gastric cancer cells.

GCSCs as the basis of gastric cancer

GCSCs were first isolated and identified in 2009. Takaishi *et al*[44] isolated $CD44^+$ cells from gastric cancer cell lines by using common markers of CSCs. It was found that these cells were able to form into spherical colonies in culture medium without serum and form tumors in nude mice, while the xenograft of $CD44^-$ was significantly lower. Thereafter, Han *et al*[45] isolated 4.5% epithelial cell adhesion molecule $(EpCAM)^+/CD44^+$ cells from fresh gastric cancer tissues by using EpCAM and CD44. Furthermore, it was confirmed *in vivo* that these cells formed solid tumors in nude mice. *In vitro* experiments proved that these cells form into colonies in culture medium without serum, have the ability for self-regeneration and the potential for multiple differentiation, and strong drug resistance. This suggests that these cells are GCSCs, and isolation and culture of these cells may be a novel model for gastric cancer research[45]. Clinical trials have shown that GCSCs are highly associated with the degree of malignancy, tumor grading and ranking, and drug resistance. In gastric cancer tissues, the expression of stem cell markers CD44, Musashi-1 and CD133 is increased in precancerous lesions, malignantly transforming tissues, and drug-resistant gastric cancer tissues[46]. The high expression of CD44 is positively correlated with malignant transformation, remote metastasis, TNM grading, and relapse of gastric cancer. The high expression of CD133 is also positively correlated with remote metastasis, invasion depth, and TNM grading of gastric cancer. The expression of CD44 and CD133 can be used as independent predictive molecules for gastric cancer. Combined detection of CD44 and CD133 expression can be used as an effective tool for clinical diagnosis of gastric cancer[47]. The subpopulation (SP) of stem cells isolated from gastric cancer cell line SGC-7901 with Hoechst 33342 staining has stronger proliferation, resistance and colonization ability when cultured *in vitro* without serum. Tumorigenicity experiments *in vivo* have confirmed that the SP has the characteristics of cancer cells. Injection of 2×10^3 SP cells can grow into tumors, whereas, injection of 2×10^4 non-SP cells cannot form into xenografts in nude mice[48], suggesting that GCSCs play an important role in tumorigenicity of gastric cancer. Moreover, in many review articles, it has been clearly stated that GCSCs are the major cause of invasion, metastasis and drug resistance of gastric cancer, and GCSCs should be the central therapeutic target[49-51]. This suggests that GCSCs are the basis of gastric cancer development.

GCSCs and drug resistance

GCSCs are a major factor in gastric cancer resistance to radiation and chemotherapy. The CSCs isolated from gastric cancer cell lines using the SP method have stronger drug tolerance for chemotherapy[52]. Aldehyde dehydrogenase (ALDH) is generally highly expressed in stem cells. Its major function is to protect stem cells and develop cell resistance. In gastric cancer, cells with high expression of ALDH have stronger resistance to 5-fluorouracil (FU) and cisplatin[53]. Using $CD44^+$ as the marker, the stem cells isolated from cancer tissues with magnetic beads have resistance to 5-FU *via* high expres-

sion. The stronger the resistance, the higher the expression of ALDH. $CD44^-$ cells have low expression of ALDH. This suggests that GCSCs are the major cause of drug resistance in gastric cancer[30]. The SP stem cells $EpCAM^+/CD44^+$ isolated from cancer tissues have stronger resistance compared with other SPs to chemotherapeutic drugs[44]. Meanwhile, clinicopathological detection has revealed that resistance of early gastric cancer is mainly associated with the presence of GCSCs. Patients with $CD133^+$ have stronger drug resistance, higher relapse rate (28.1% *vs* 65.8%, $P = 0.002$) and lower 5-year survival rate (47.5% *vs* 74.0%, $P = 0.037$), compared with patients with $CD133^-$[54].

GCSCs AND GASTRIC CANCER TREATMENT AND PREVENTION STRATEGIES

$CD44^+$ and gastric cancer treatment

Cancer onset, development, drug resistance and metastasis are all associated with gastric stem cells. GCSC-targeted therapy has received increasing attention[49-51,55]. $CD44^+$ is a cell surface adhesion molecule and is the earliest marker for gastric stem cells[43-44]. $CD44^+$ cells have stronger drug resistance and express more genes related to cancer invasion, such as MMP-1, MMP-2, EGFR and COX-2[28]. Isolated GCSCs are the ideal model for targeted therapy for gastric cancer. GCSCs highly express CD44v9. Silencing of CD44v9 expression is a novel pathway for treating gastric cancer[56]. Compared with $CD44^-$ cells, $CD44^+$ cells have high expression of Notch1. With the specific drug β-Elemene interfering Notch1 expression, the proliferation of $CD44^+$ cells and xenografts and vessel survival are all inhibited[43-44,57]. The ERK → CD44 → STAT3 signaling cascade promotes GCSC proliferation. Interfering with this signal inhibits proliferation of gastric stem cells[58]. The sonic hedgehog (SHH) signal is necessary for maintaining tumorigenesis of primary cancer tissue stem cells. Interfering with SHH signaling can increase gastric stem cell sensitivity to chemotherapy, and thus inhibit xenografts in nude mice[59]. It is believed that phosphoglycerate kinase (PGK)1 is activated in gastric cancer cell lines and inhibits the differentiation of gastric stem cells. shRNA PGK1 in $CD44^+$ cells promotes GCSC differentiation and inhibits xenograft growth in nude mice. With targeted silencing of PGK1 induction, GCSC differentiation is regarded as an effective therapeutic target for gastric cancer[60]. Adipose-tissue-derived stem cells can regulate $CD44^+$ cell surface integrated protein α2/β2 and Wnt signaling *via* cell surface adhesion molecules, and thus increase sensitivity of CSCs to chemotherapy. This suggests that adipose-tissue-derived stem cells can be used as a "living vehicle surface" for gastric cancer therapy. Targeted overexpression of miR-200c can silence the expression of TUBB3 in tumors, reduce expression of CD44 and invasive marker molecule E-cadherin, increase drug sensitivity of gastric cancer cells, and inhibit xenograft growth[61].

Other biomarkers and gastric cancer treatment

CD133 and ALDH are often regarded as marker molecule of GCSCs. Expression of CD133 is positively correlated with malignancy of gastric cancer. The overexpression of *SOX17* gene by silence-regulated CD133 inhibit the growth of gastric cancer, suggesting that regulating expression of CD133 is the target for treating gastric cancer[62]. ALDH may activate Notch1 and SHH signaling and promote proliferation of GCSCs, leading to development of drug resistance. Interfering with ALDH expression and activity and downstream signals can be used as a target for treating gastric cancer[53]. $CD71^-$ and $CD71^+$ cells have stronger xenograft ability. $CD71^-$ cells can be used as an effective target for gastric cancer research[63]. TR3, an orphan receptor, is also regarded as a necessary molecule for maintaining activity of GCSCs. Silencing TR3 reduces expression of stem-cell-associated genes *Oct-4* and Nanog, as well as invasion-associated gene *MMP-9*, and inhibits colonization of cancer cells, invasion and metastasis, xenograft growth, and drug resistance. Silencing TR3 is a novel effective target for treating gastric cancer[64]. Meanwhile, Lgr5, CD26, Musashi-1, CD24, CD54, Sox2, Nanog, and Nestin have been used as diagnostic marker molecules on GCSCs[46,65-67]. Overexpression of Sox2 in CSCs shows that Sox2 plays an important role in maintaining the stem cell characteristics of CSCs. Targeting silencing of Sox2 significantly inhibits colonization and drug resistance of GCSCs *in vitro*[52]. Moreover, SP cells express a many drug-resistance-associated proteins, including ABCG2, Bcl-2, multidrug resistance, and Bmi-1[47,48,68]. In addition, trastuzumab has recently been reported as a humanized monoclonal antibody that selectively acts on the extracellular region of human epidermal growth factor receptor (HER)2. Trastuzumab is mainly used for the treatment of gastric cancer with overexpression of HER2[69,70]. Ramucirumab is another newly humanized IgG1 monoclonal antibody. It acts as a receptor antagonist that binds to the extracellular region of vascular endothelial growth factor (VEGF) receptor 2, thereby blocking the interaction between VEGF ligands A C and D, and inhibiting activation of the receptor. Ramucirumab has shown promising results in an international, randomized, multicenter, placebo-controlled, phase Ⅲ clinical trial for advanced gastric cancer[71,72]. All the above results suggest that GCSC-targeted therapy is a novel direction for treating and preventing gastric cancer.

SUMMARY AND FUTURE DIRECTION OF RESEARCH

CSC theory is developing rapidly. The presence of GCSCs and their significance are acknowledged widely. Novel GCSC markers were discovered gradually, bringing great opportunities for therapy of gastric cancer. However, our knowledge of GCSCs is currently insufficient and

more research is needed in the following areas. (1) isolation and culture of GCSCs. Impure stem cells and differentiation *in vitro* have resulted in an inability to perform long-term culture to study the mechanism of generation and development of GCSCs. Further research into the isolation and continuous culture of GCSCs might provide a opportunity to understand better the biological properties of stem cells; (2) mechanism of generation and development of GCSCs. Studies should investigate further the microenvironment and signaling pathways of GCSCs, as well as the regulatory mechanism associated with the development, drug resistance, recurrence and metastasis of gastric cancer. This will demonstrate the relationship between GCSCs and gastric cancer in detail; and (3) to determine specific markers of gastric cancer. These markers could be used in clinical studies to develop new chemotherapeutic agents against cancer cells. These agents could target the specific markers of GCSCs or the microenvironment and related signal transduction pathways of GCSCs.

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