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REVIEW – CANCER RESEARCH

Molecular targeted treatment and drug delivery system for gastric cancer

Lanxin Jiang[1,2] · Xiaomin Gong[1,3] · Wangdi Liao[1] · Nonghua Lv[1] · Runwei Yan[1]

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Abstract

Gastric cancer is still a major cancer worldwide. The early diagnosis rate of gastric cancer in most high incidence countries is low. At present, the overall treatment effect of gastric cancer is poor, and the median overall survival remains low. Most of the patients with gastric cancer are in an advanced stage when diagnosed, and drug treatment has become the main means. Thus, new targeted drugs and therapeutic strategies are the hope of improving the therapeutic effect of gastric cancer. In this review, we summarize the new methods and advances of targeted therapy for gastric cancer, including novel molecular targeted therapeutic agents and drug delivery systems, with a major focus on the development of drug delivery systems (drug carriers and targeting peptides). Elaborating these new methods and advances will contribute to the management of gastric cancer.

Keywords Gastric cancer · Molecular targeted therapy · Drug delivery systems · Drug carriers · Targeted peptides

Introduction

The incidence and mortality of cancer are increasing rapidly worldwide. It is estimated that there were 18.1 million new cases and 9.6 million cancer deaths worldwide in 2018. Gastric cancer is a major cancer worldwide. There were over 1 million new cases and an estimated 783 thousands deaths of gastric cancer in 2018, which making gastric cancer the fifth most commonly diagnosed cancer and the third leading for mortality (Bray et al. 2018).

The incidence rate of gastric cancer remains high especially in Eastern Asia and Eastern Europe. The early diagnosis rate of gastric cancer in most high incidence countries is low. Most patients have been diagnosed as advanced, and drug treatment has become the main means. But traditional chemotherapy has limited efficacy and short duration. At present, the overall treatment effect of gastric cancer is poor, and the median overall survival remains low. Therefore, further research and development of new targeted drugs and strategies is the key to improve the therapeutic effect of gastric cancer. In the past few decades, researches on new drugs targeting at dysfunctional signaling pathways in gastric cancer have become a hot topic. At the same time, the development of a smart drug delivery system is also very important for improving the therapeutic effect of gastric cancer.

In this review, we summarize the new methods and advances of targeted therapy for gastric cancer, including novel therapeutic agents and drug delivery systems, with a major focus on the development of drug delivery systems (drug carriers and targeting peptides).

Therapeutic agents for gastric cancer

Different gene mutations, epigenetic changes and dysfunction of molecular signaling pathways in gastric cancer have been reported. Currently, some of these aberrant molecules and signaling pathways are used as novel therapeutic targets of gastric cancer. Herein, we reviewed the novel agents

Lanxin Jiang and Xiaomin Gong contributed equal to this work.

✉ Runwei Yan
Runwei_Yan0202@hotmail.com

[1] Department of Gastroenterology, Key Laboratory of Digestive Diseases of Jiangxi Province, The First Affiliated Hospital of Nanchang University, Nanchang 330006, China

[2] Department of Medical Inspection Technology, School of Public Health, Nanchang University, Nanchang 330006, China

[3] Clinical Medicine, The First Affiliated Hospital of Nanchang University, Nanchang 330006, China

which are used for targeted therapeutics in advanced gastric cancer, some of which are already in clinical application, while others have obtained promising positive results in clinical trials. Furthermore, we also summarized some novel therapeutic targets for gastric cancer that are still in the exploration, such as miRNA-based and gene therapy (Fig. 1).

Targeted drugs for clinical application

With the efforts of researchers, some targeted medicines are applied to clinical treatment. Based on the data from targeted therapeutic clinical trials in gastric cancer, trastuzumab, by virtue of its excellent improved overall survival (OS) and progression-free survival (PFS), become the first-line therapy for human epidermal growth factor receptor 2 (HER2) positive patients. In addition, some agents with different target spot, such as ramucirumab and apatinib, with the lower OS and PFS are apply to second- or third-line therapy. Pembrolizumab, the programmed death-1 (PD-1) inhibitor, is also applied as second-line treatment in microsatellite instability (MSI)-high cancers and third-line therapy in programmed death ligand 1 (PD-L1)-positive cancer. Otherwise, the TAS-102 was also put into application for pretreated gastric cancer patients. And napabucasin is used for clinical treatment as an orphan drug (Selim et al. 2019b).

Trastuzumab is a humanized monoclonal antibody which arrests the cell cycle at G1 and targets the extracellular binding domain of the HER2 receptor. The TOGA trail, a phase III study, had shown that the median overall survival increased from 11.1 months (in chemotherapy alone group, $n = 290$) to 13.8 months (in the trastuzumab plus chemotherapy group, $n = 294$). What's more, a post-hoc analysis showed in subgroup with high HER2 protein expression, median overall survival was improved to 16.0 months by trastuzumab plus chemotherapy, while it was 11.8 months by chemotherapy alone. Unsurprisingly, based on the significantly improved dates of median overall survival, overall tumor response rate, time to progression and duration of response, trastuzumab has been approved by the FDA in 2010 for patients with gastric or gastroesophageal junction adenocarcinoma (GEJC) (Bang et al. 2010). Recently, a subpopulation analysis of the JACOB trial, a phase III study, was conducted to investigate outcomes in Chinese patients with HER2-positive GC/GEJC after pertuzumab in combination with trastuzumab and chemotherapy treatment. The results showed that adding pertuzumab to trastuzumab and chemotherapy as first-line treatment made both OS and PFS improved (Liu et al. 2019a).

Ramucirumab is a fully human monoclonal antibody, binding to the vascular endothelial growth factor receptor 2 (VEGFR-2), blocking the connection with VEGF. The REGARD was a phase III trial, results showed an increased OS in patients with ramucirumab than placebo (5.2 m versus 3.8 m). And the ramucirumab group was also benefited more in PFS (2.1 m versus 1.3 m) (Fuchs et al. 2014). While, the RAINBOW, a phase III trial, showed a significantly prolonged OS (9.6 m versus 7.4 m), PFS (4.4 m versus 2.9 m) and response rate (28% versus 16%) in the ramucirumab plus paclitaxel group compared within the placebo plus paclitaxel group (Wilke et al. 2014). FDA approved that addition ramucirumab to paclitaxel as second-line therapy for gastric cancer patients. Apatinib is a small tyrosine kinase inhibitor (TKI) developed in China that targets VEGFR-2. The phase III study, which recruited patients from 32 centers in China with advanced gastric cancer, showed an excellent improvement in OS (6.5 months versus 4.7 months) and PFS (2.6 months versus 1.8 months) (Li et al. 2016). Based on these positive results, in October 2014, apatinib was approved for metastatic GC/GEJC after second-line chemotherapy progression by the China FDA. In June 2017, the

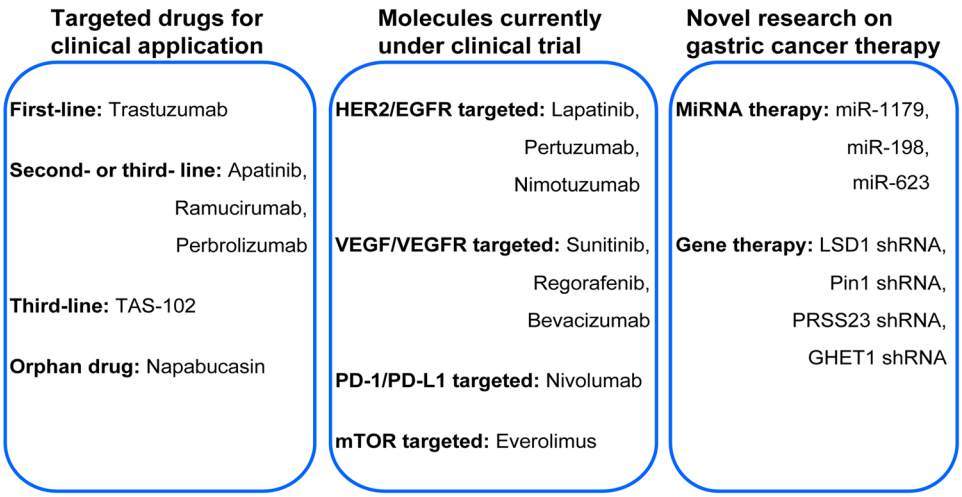

Fig. 1 Promising targeted drugs, molecules and novel research for gastric cancer therapy

apatinib got the approval from the US FDA as an orphan-drug for advanced gastric cancer therapy.

Pembrolizumab is a monoclonal antibody that impedes the binding of PD-1 to PD-L1. The phase II clinical KEYNOTE-059 trial showed the encouraging efficacy and stable safety of the pembrolizumab in advanced GC/GEJC (Fuchs et al. 2018). Based on this study, pembrolizumab was approved by US FDA for the therapy of PD-L1-positive, second or more lines pretreated gastric cancer patients.

Moreover, TAS-102 is an oral treatment composing of thymidine analog trifluridine and tipiracil hydrochloride, a thymidine phosphorylase inhibitor (Temmink et al. 2007). A phase III trial TAGS showed a dramatically prolonged OS in the TAS-102 plus best supportive care group than in the placebo plus best supportive care group (5.7 m versus 3.6 m) in advanced gastric cancer patients who have accepted two chemotherapy or more (Shitara et al. 2018). TAS-102 was approved by the US FDA as a third-line treatment for advanced gastric cancer patients. In particular, Napabucasin (BBI608) is a molecule, with the capacity of inhibiting STAT3 and cancer stem cells (CSC) (Li et al. 2015d). In a phase II study, addition napabucasin to weekly paclitaxel showed incentive signs of anti-tumor activity in patients with advanced gastric cancer (Becerra et al. 2015). Based on this study, napabucasin was approved as an orphan drug destination by the US FDA for patients with advanced gastric cancer.

Taken together, trastuzumab is currently the best-targeted drug for gastric cancer. But the positive rate of HER2 in gastric cancer patients is only 10% to 20%, which greatly affects the application of trastuzumab. Therefore, the exploration and discovery of new and more effective gastric cancer-targeting drugs is still the current research hotspot.

Molecules currently under clinical trial

Plenty targeted pathways have been explored for gastric cancer therapy, such as HER2, VEGFR, fibroblast growth factor receptor (FGFR), programmed death-1 (PD-1) and (PD-L1), epidermal growth factor receptor (EGFR) and mammalian target of rapamycin (mTOR). And some of which show good prospects on gastric cancer treatment (Lazar et al. 2016; Selim et al. 2019a).

Lapatinib (an oral TKI) and nimotuzumab (a humanized IgG1 monoclonal antibody) both target EGFR. A phase III trial TRIO-013/LOGIC displayed no difference in OS between lapatinib plus capecitabine and oxaliplatin (CapeOx) group and placebo plus CapeOx group, whereas the increased OS was showed in the subgroup with lapatinib plus CapeOx (Hecht et al. 2016). A phase II trial, with two groups including nimotuzumab plus Irinotecan group and Irinotecan alone, investigated the effect of nimotuzumab in advanced gastric cancer patients, showed no difference in OS and PFS between this two groups, whereas, the prolonged OS and PFS was displayed on the EGFR 2 + /3 + subgroup (Satoh et al. 2015).

There are some promising agents in clinical trials that targeted VEGF or VEGFR, such as bevacizumab, regorafenib and sunitinib. A phase III double-blind study (AVAGAST), showed a dramatically improved median PFS in bevacizumab plus fluoropyrimidine-cisplatin group compared to in placebo plus fluoropyrimidine-cisplatin group (6.7 m versus 5.3 m) (Ohtsu et al. 2011). A phase II placebo-controlled trial, designed to evaluate the efficacy and safety of regorafenib (an oral inhibitor of VEGFR) in advanced gastric cancer patients, demonstrated that the regorafenib group had a significant prolonged median PFS (2.6 m versus 0.9 m) (Pavlakis et al. 2016). A phase II trial was conducted to investigate the effect and security of sunitinib (an oral tyrosine kinase inhibitor of VEGFR) in combination with docetaxel in metastatic gastric cancer, showed a dramatic improved objective response in the sunitinib plus docetaxel group than in the docetaxel alone group (Yi et al. 2012).

Nivolumab is a monoclonal antibody that prevents the PD-1 receptor (Brahmer et al. 2010). The phase III study ATTRACTION-2 (ono-4538-12), conducted to evaluate the effect and security of nivolumab in GC/GEJC therapy, showed a significantly improved median OS in the nivolumab group compared within the placebo group (5.26 m versus 4.14 m) (Kang et al. 2017).

Everolimus is an oral mTOR inhibitor. The randomized, double-blind, placebo-controlled, phase III GRANITE-1 study demonstrated that there was no significant difference in OS (primary end point), however, the median OS was improved in the everolimus group (5.4 m versus 4.3 m) (Ohtsu et al. 2013).

Novel research on miRNA therapy for gastric cancer

In recent years, microRNAs get the researchers' attention by their excellent targeting function. MicroRNAs are a large family of small, endogenous, non-coding RNAs with a length of approximately 19–21 nucleotides (Lu and Rothenberg 2018). MiRNAs participate in gene regulation via binding the 3′-untranslated region (3′-UTR) of the target genes, which leads to the degradation of mRNA or inhibition of translation. Notably, emerging evidences demonstrated that miRNA could therapeutically be a promising factor for patients with gastric cancer.

Immediately after discovering the decreased expression of miR-1179 in gastric cancer patients, Li et al. demonstrated that the proliferation of gastric cancer could effectively be restrained by over-expressed miR-1179 (Li and Qin 2019). MiR-198, which directly targeting and silencing fibroblast growth factor receptor 1 (FGFR1), was down-regulated in gastric cancer and possessed anti-cancer capacity (Gu

et al. 2019). Similarly, recovered the expression of down-expressed miR-623 could inhibit cell proliferation and inverse the drug resistance to 5-Fluorouracil in gastric cancer (Jiang et al. 2018).

These studies raised the possibility that these miRNAs could be promising targets to develop novel therapeutic strategies for the treatment of gastric carcinoma.

Novel research on gene therapy for gastric cancer

Gene therapy is an emerging targeting therapy in gastric cancer treatment, as the research goes on, more and more gene sites are discovered. Lysine-specific demethylase 1 (LSD1) is the first histone lysine demethylase discovered, which belongs to the family of amine exidases. Zhang et al. uncovered that LSD1 was highly expressed in gastric carcinoma and facilitated gastric cancer cell proliferation, migration and invasion (Zhang et al. 2019b). Down-regulated the expression of LSD1 could suppress the proliferation of gastric cancer cells and blocked VEGF-C/PI3K/AKT signaling pathway (Pan et al. 2019). These studies indicated that LSD1 was a promising candidate for gastric cancer therapy.

On the other hand, Pin1 (the unique proline isomerase) was found observably up-expressed in gastric carcinoma, which might be related to clinical-pathological parameters and poor prognosis. Down-regulation of Pin1 expression prevented gastric carcinoma growth and arrested PI3K/AKT and Wnt/β-catenin oncogenic pathways (Zhang et al. 2019c).

The level of serine protease PRSS23 protein was dramatically increased in gastric cancer tissues, and the lower expression of PRSS23 revealed a better prognosis. Knockdown of PRSS23 (with PRSS23 shRNA) could inhibit the gastric cancer development via restraining EIF2 signaling (Han et al. 2019). These findings showed that PRSS23 was a promising target for the treatment of gastric cancer.

Notably, the high expression level of lncRNA GHET1 in gastric cancer facilitated cell proliferation, invasion and closely related to poor prognosis (Yang et al. 2014). Knockdown of lncRNA GHET1 inhibited AGS cell proliferation, migration and invasion, as well as stimulated cell apoptosis (Huang et al. 2017a). These results suggested that lncRNA GHET1 could be a potential molecular target for gastric cancer therapy.

Drug carriers used in the treatment of gastric cancer

Chemotherapy is the major treatment for advanced gastric carcinoma, but chemotherapy for gastric carcinoma is facing the challenge of maximizing the therapeutic concentrations and low systemic distribution. In addition, sensitive immune response and physiological mucosal barriers also hinder the accumulation of drugs in tumor tissues. To solve these challenges, high doses of drugs are needed, which brings new problems, such as drug resistance. In view of these, researchers have turned to intelligent drug delivery system to improve the concentration of drugs in tumor tissue.

Nanocarriers for the treatment of gastric cancer

Nanotechnology, a multidisciplinary research field, provides a splendid, paradigm-breaking chance in carcinoma treatment by providing intelligent drug delivery systems (Cuenca et al. 2006) and it aims at material which is 1–100 nm scale. Since the basis laid down for nanotechnology to deliver therapeutic agents over 40 years ago (Strebhardt and Ullrich 2008), many nanocarriers have emerged. Some nanocarriers had been eliminated due to their fatal shortcomings. For example, although viral carrier possessed the property of high transfection efficiency, but its clinical use was markedly limited by the genotoxicity, inferior loading efficiency and noteworthy immunogenicity (Liu et al. 2009; Tanaka et al. 2006). However, others such as nanoparticles (NPs) have gained wide spread applications in gastric carcinoma treatment because of their unique characteristics in drug delivery. For example, drug capsulation within nanoparticles could lengthen plasma circulation time, allow for better drug payloads and alleviate off-target toxicity. In addition, a single nanoparticle is capable of encapsulate multifarious synergistic drugs and its surface can be functionalized with various ligands which target carcinoma-related biomarkers (Muntimadugu et al. 2017). Moreover, they themselves also play a role in fighting against gastric carcinoma.

Up till now, there are various types of nanoparticles that commonly used in drug delivery of gastric carcinoma, such as liposome, micelle, solid lipid nanoparticles, magnetic nanoparticles, chitosan nanoparticles and PLGA nanoparticles, etc. Their advantages and limitations are summarized in Table 1.

Liposome described as early as 1965 is the archetypal, simplest form of nanocarrier, with a spherical structure in which an aqueous core was encapsulated in the lipid layer (Bangham et al. 1965). It has been explored widely as a delivery system for biologics, gene therapies and chemotherapeutic drugs. At present, most scholars will choose liposomes with multiple modifications, which called multifunctional liposome. PTX encapsulating in a novel multifunctional liposome system, which using ginsenosides as the membrane stabilizer and chemotherapy adjuvant, revealed splendid tumor growth suppression in a gastric carcinoma xenografted model and exceeded most reported PTX formulations, including Lipusu® and Abraxane® (Hong et al. 2019).

Polymeric nanoparticles are promising drug carriers, among which PLGA nanoparticles, biopolymer

Table 1 Nanoparticles that commonly used in drug delivery of gastric carcinoma

Nanoparticle type	Advantages	Limitations	References
PLGA NPs	Excellent biocompatibility and biodegradability Suitable pharmacokinetics and controllable degradation rate Minimal toxicity	Their angiogenic nature may negatively affect anticarcinogen curative effect Poor release of acid-labile drugs	Bonelli et al. (2012); Chereddy et al. (2018); Mohammadian et al. (2016)
Silk fibroin NPs	Good biocompatibility and biodegradability Negligible toxicity Controlled degradation, size, shape and drug loading	Rely on passive accumulation	Mottaghitalab et al. (2015); Wu et al. (2013)
Chitosan NPs	Anti-gastric carcinoma activity good biocompatibility and biodegradability Safe and serum stability	Rely on passive accumulation	Chen et al. (2017); Qi et al. (2005)
micelle	In vivo serum stability Longer circulation time	Limited drug loading capacity Drug premature release	Li et al. (2012)
Liposome	Good biocompatibility and bioavailability Good biological distribution Low drug toxicity	Drug storage and leakage problems Short shelf life	Bulbake et al. (2017); Das and Huang (2019)
Solid lipid nanoparticles (SLNs)	Good biocompatibility Sustained drug release Effortlessly encapsulation of lipophilic anti-carcinoma drugs	Low encapsulation of Hydrophilic drugs Nonuniform drug release	Wang et al. (2014b); Yingchoncharoen et al. (2016)
Magnetic NPs	Magnetic targeting capacity Chemohyperthermia ability Can be modified for custom drug administration	Unknown security Burst drug release Low stability	Chenthamara et al. (2019); Jiang and Chan (2012)
Carbon nanotubes	High surface area Biocompatibility Thermodynamic properties	Limited aqueous solubility Toxicity	Chenthamara et al. (2019); Taghavi et al. (2017)

nanoparticles and micelles are widely used. Poly (lactic-co-glycolic acid) (PLGA) nanoparticle was one of the polymeric nanoparticles approved by the FDA/EMA and there were some studies about this carrier in gastric carcinoma (Fernandes et al. 2019; Liu et al. 2019b). A double-targeting hybrid nanoparticle system, consisting of a PLGA particle core and a lipoid shell, allowed SN38 agent to be specifically delivered towards human solid gastric tumor cells via targeting the CD44 and HER2 and thus exhibited extraordinary antitumor efficacy (Yang et al. 2016). Coincidentally, PLGA-based nanoparticles, which were decorated with polyethylene glycol and engrafted with a human Fab, were safe and possessed enhanced circulation time (Kennedy et al. 2018).

Biopolymer nanoparticles are promising drug carriers due to their biocompatibility and biodegradability. Chitosan nanoparticles and silk fibroin nanoparticles were two representative biopolymer nanoparticles in the treatment of gastric carcinoma. Chitosan nanoparticle was one of the commonly used gene carriers and was also approved by the FDA/EMA for drug delivery. BRAF siRNA encapsulated chitosan NPs in BGC823 cells not only remarkably down-regulated BRAF expression but also inhibited cell invasion (Huo 2016). Furthermore, Chitosan NPs can also be used to synthesize complex for targeting the delivery of epigallocatechin-3-gallate (Lin et al. 2015) as well as prepare chitosan/heparin nanoparticle for cytolethal distending toxin (CDT) targeted delivery to gastric carcinoma (Lai et al. 2014). Silk fibroin (SF) based nanoparticle conjugated with cRGDfk and Chlorin e6 was fabricated to load 5-FU for both chemotherapy and photodynamic therapy (PDT) of gastric carcinoma, showing active tumor targeting, certified sustained release and promising PDT potential in gastric MGC-803 cells (Mao et al. 2018). Similarly, PTX-SF-NPs (encapsulating PTX into SF nanoparticles), with 130 nm in diameter, could be taken up by SGC-7901 and BGC-823 cell lines efficiently and had a significant antitumor effect for gastric carcinoma in vivo (Wu et al. 2013).

Micelles have been widely used in drug delivery due to their in vivo serum stability, longer circulation time and many other advantages. Polymeric micelles incorporated with KRN5500, a water-insoluble anticarcinogen, achieved no vascular damage and liver toxicity compared with KRN5500 alone (Matsumura et al. 1999). Meanwhile, Micelles can also be modified to improve delivery efficiency.

Li et al. developed a unique temperature-sensitive immunomicelle in which PLGA played the role of drug loading reservoir in the micellar core and anti-Her2 Fabs served as targeting ligands conjugated onto the micellar surface. This doxorubicin-loaded immunomicelle showed significantly enhanced cytotoxicity, evidently increased intratumoral accumulation and improved in vivo stability as well as promising tumor inhibition in gastric carcinoma bearing mice (Li et al. 2012). Moreover, a unique SN-38 (an active metabolite of irinotecan)-releasing polymeric micelle, called NK012, revealed stronger anticarcinoma efficacy compared with irinotecan in orthotopic gastric carcinoma mice mode (Koizumi et al. 2006; Nakajima et al. 2008). Despite all the progress that has been made, the characteristic of releasing drugs earlier on arrival at the target site and the small micellar size still hampered its application in gastric carcinoma treatment.

In recent years, magnetic nanoparticles have been widely studied in hyperthermia and targeted imaging of gastric carcinoma as well due to their special magnetic properties (Li et al. 2015a; Ruan et al. 2012). For example, silver nanoparticles which synthesized by using *Artemisia turcomanica* leaf (Mousavi et al. 2018), *Dysosma pleiantha rhizome* (Karuppaiya et al. 2019) or *Artemisia marschalliana Sprengel* (Salehi et al. 2016) extract as well as gold nanoparticles (Wu et al. 2016) can fight against gastric carcinoma. Au nanoparticles conjugating Tmab on its surface showed stronger antitumor effects against both HER2-postive Tmab-sensitive (NCI-N87) and HER2-postive Tmab-resistant (MKN7) gastric carcinoma cell lines (Kubota et al. 2018). In addition, these nanoparticles can also be used for drug delivery, such as doxorubicin (Fang et al. 2019; Ma et al. 2015), 5-fluorouracil (Liu et al. 2014b) and *Cardiospermum halicacabum* (Li et al. 2019). Furthermore, drug-embedded magnetoliposomes achieved simultaneous chemotherapy and hyperthermia in mice implanted with human MKN45 gastric carcinoma cells (Yoshida et al. 2010, 2012).

Additionally, there were many other nanoparticles that used in the treatment of gastric carcinoma, including solid lipid nanoparticles (Muller et al. 2000), carbon nanotubes (Taghavi et al. 2017; Yao et al. 2014). mesoporous silica nanoparticles (Fang et al. 2018; Hu et al. 2019), CeO_2 nanoparticles (Li et al. 2014), calcium carbonate nanoparticles (He et al. 2008) and cerium oxide nanoparticles (Xiao et al. 2016). But more research is needed on these nanocarriers.

Exosomes, a novel promising drug delivery system

Exosome which gained its first description in 1981 (Trams et al. 1981), has made a dramatic breakthrough in the treatment of gastric cancer in recent years. Exosomes are lipid bilayer vesicles that contain a variety of bioactive molecules, such as nucleic acids, lipids, and proteins, ranging in size from 30 to 150 nm (Wang et al. 2019). Exosomes originate from multivesicular bodies (MVBs), which can be secreted by almost all eukaryotic cells (Abak et al. 2018; Colombo et al. 2014). Exosomes transmit information between cells by carrying components such as proteins and nucleic acids. The membranes of exosomes are rich in cholesterol, sphingolipids, fittsfceramides, phosphatidylserine, and saturated fatty acids, which play an important role in the cellular microenvironment (Colombo et al. 2014). Exosomes contain nucleic acids (DNA, mRNA, microRNA), proteins and lipids, etc. (Becker et al. 2016). Compared to the traditional drug carriers, exosomes as a novel drug delivery system have many advantages: firstly, they have small particle size, strong permeability in the body, and are easy to penetrate the biological barrier (Fitts et al. 2019); secondly, the protein phospholipid bilayer structure on the surface of exosomes can efficiently package and transport various drugs to recipient cells (Allahverdiyev et al. 2018); thirdly, they have good stability in human blood (Rufino-Ramos et al. 2017); finally, they are endogenous substances, greatly reducing the risk of toxicity and immunogenicity (Allahverdiyev et al. 2018). Therefore, in recent years, exosomes as drug carriers and therapeutic systems for clinical treatment has become a research hotspot. Emerging evidences indicate that exosomes play a critical and robust role in the diagnosis and treatment of gastric carcinoma.

On account of the excellent stability and distinctive expression mode, exosomes are highlighted the probability to apply in gastric cancer diagnosis and prognosis as novel and promising biomarkers. Some studies had shown exosomal lncRNAs (such as LINC0015, HOTTIP and lncUEGC1) was highly expressed in patients with gastric cancer or early gastric cancer, with the stable feature and precise diagnosis, might be the potential biomarkers for gastric cancer (Li et al. 2015b; Lin et al. 2018; Zhao et al. 2018). Similarly, it had been reported that exosomal miRNAs could also be used as biomarkers for the diagnosis and prognosis of gastric cancer. The expression of miR-451 up-regulated in exosomes derived from tumor tissues was able to predict poor prognosis in post-operation gastric cancer patients (Liu et al. 2018). Exosomal miR-1246 in the serum of gastric cancer patients was typically increased, indicating that miR-1246 might also be a promising candidate for gastric cancer diagnosis (Shi et al. 2019).

In addition to being biomarkers for the diagnosis and prognosis of gastric cancer, the important characteristics of exosomes suggested that they can also be used as a delivery system of biomolecules and chemotherapeutic drugs for gastric carcinoma therapy. At present, the most commonly used donor cells of exosomes are immature dendritic cells (DC), mesenchymal stem cells (MSc) or model cells (such as HEK293T cells).

Some studies reported that exosomes delivering miRNA inhibitor were a new approach for the treatment of gastric cancer. MiR-374a-5p was overexpressed in gastric cancer serum, which predicted poor prognosis. Exosome delivered miR-374a-5p inhibitor could induce cell apoptosis and inhibit chemoresistance of gastric cancer via increasing Neurod1 expression (Ji et al. 2019). Macrophage-released exosomes were the capacity of delivering miR-21 inhibitor into BGC-823 gastric cancer cells, suppressing migration and promoting apoptosis (Wang et al. 2015a). Furthermore, Exosome-anti-miR-214 could reverse the cisplatin (DDP)-resistance, preventing migration and inducing apoptosis in gastric carcinoma (Wang et al. 2018).

Other studies showed that exosome-mediated delivery of protein targeted biomolecules could also be a new strategy for gastric cancer therapy. Exosome carrying Gastrokine 1 (GKN1) could suppress cell proliferation and induce apoptosis in both AGS and MKN1 gastric cancer cells. The tumor volume and tumor weight of MKN1 xenograft nude mice significantly reduced after exosomes carrying GKN1 treated (Yoon et al. 2018). Hepatocyte growth factor (HGF) could promote the growth of tumor cells and vascular cells. HGF-siRNA loaded exosomes could inhibit the proliferation and migration of gastric cancer cells and vascular cells in vitro, and suppressing the tumor growth and angiogaenesis in vivo (Zhang et al. 2018).

Targeting peptides for gastric cancer therapy

Unfortunately, drug carriers such as nanoparticles did not significantly improve the therapeutic effect, only about 1% of the nanoparticles accumulated in the tumor (Wilhelm et al. 2016). Even though the modification of drug carriers with targeted ligands can successfully overcome the high interstitial pressure and penetrate into tumor tissues, most of the ligands are broad-spectrum ligands and lack specificity for gastric carcinoma.

Therefore, the targeting peptides, which can localize tumor vessels, target gastric cancer or gastric cancer biomarkers, and thus improve the efficiency of targeted therapy for gastric cancer, have attracted the attention of scientists. Phage display library is a potent tool to gain targeting peptides with specific binding properties on the basis of biopanning procedure (Smith 1985). During the past two decades, a series of peptides having affinity to gastric carcinoma have been screened, including RGD (Arap et al. 1998), GX1 (Zhi et al. 2004), GEBP11 (Liang et al. 2006), LSP-5 (Lee et al. 2007), iRGD (Sugahara et al. 2009), TCP-1 (Li et al. 2010), AAD (Zhang et al. 2012), GMBP1 (Kang et al. 2013), GP-5 (Wang et al. 2014a) and RP-1 (Zhang et al. 2015). These targeting peptides can be used to improve the efficiency of targeted therapy for gastric cancer through various ways (Fig. 2).

Targeting peptides modify the drug carrier to promote the ability of gastric cancer targeting

For many therapies (such as chemotherapy and gene therapy), efficient carriers can improve the therapeutic effect (Fang et al. 2014; Yin et al. 2014). Targeting peptides can modify the carriers so that the carriers can better target gastric cancer.

RGD (Arg-Gly-Asp) was a commonly used targeting peptide for several kinds of tumor. Many studies had reported that RGD modified drug carriers possessed high affinity to gastric cancer. Wei Wang et al. employed RGD to modify

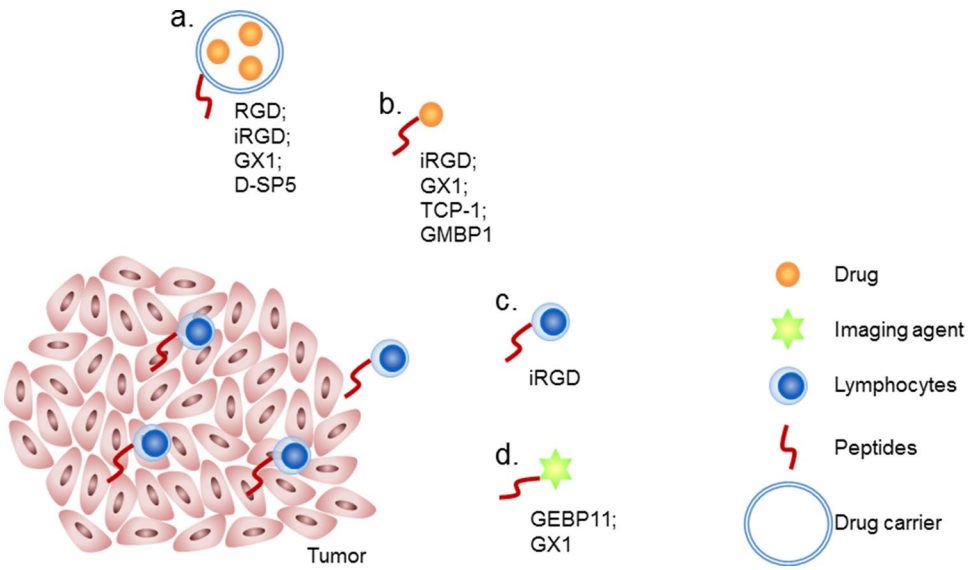

Fig. 2 The functions of targeting peptides in improving the therapeutic effect for gastric cancer. **a** Targeting peptides can modify the drug carrier. **b** Targeting peptides can directly combine with the drugs. **c** Targeting peptides can enhance lymphocyte infiltration. **d** Targeting peptides can bind with imaging agent

Pluronic triblock copolymers which encapsulated with activating protein 2 family expression plasmids (RGD@P123@AP-2α). This composite showed targeted and continuous inhibitory effect of gastric carcinoma cells growth both in vivo and in vitro via increasing AP-2α protein expression (Wang et al. 2015b). In addition, anti-EGFR-iRGD, a fusion protein constructed and expressed by Huizi Sha et al., consisting of peptide iRGD (internalizing-RGD) as well as an EGFR single-domain antibody. It could improve the permeability and efficacy of anticarcinogen on monolayer cells (2 dimensional), multicellular spheroids (3 dimensional) and tumor-bearing mice (Sha et al. 2015b). Further, they used this fusion protein to fabricate an erythrocyte membrane-derived targeting nanosystem (anti-EGFR-iRGD-RBCm-PTX or PRP), in which RBCm-derived microvesicles guaranteed promising carriers and lipid insertion method improved the active targeting ability, displaying improved gastric carcinoma suppression (Chen et al. 2018).

GX1 (CGNSNPKSC) was another peptide utilized to form a targeting delivery system. Immunohistochemistry analysis of human tissues and murine revealed its specifical ability of binding to human gastric carcinoma endothelial cells; moreover, GX1 labeled with $^{99}Tc^{m}$, 64Cu and Cy5.5 was also firmly targeted to gastric carcinoma both in vivo and in vitro (Chen et al. 2012a, b; Hui et al. 2008). A GX1-mediated delivery system (GX1-Ad5-AL) could notably restrain the migration and the proliferation of SGC-7901 cells, as well as the proliferation of HUVEC (Xiong et al. 2015). In addition to this, the GX1-DGC nanoparticles (GX1 conjugating with chitosan derivative nanoparticles DGC) could deliver hydrophobic docetaxel (DCT) toward gastric carcinoma vasculature. GX1-DGC-DCT showed potentiated antitumor activity in tumor-bearing models but no obvious toxicity to healthy L929 cells (Zhang et al. 2019a).

Moreover, apart from using peptides screened by phage display library to directly modify the carrier, there were studies that remoulded peptides to better modify the carrier. Retro-inverso peptide D-SP5 was remoulded from peptide L-SP5. D-SP5-conjugated micelles showed potentiated tumor homing and displayed increased tumor cytotoxic efficacy in KB tumor xenografts than L-SP5 micelles (Li et al. 2013). Thereafter, D-SP5-PEG-PEI was found to be a safe and efficient carrier for antitumor gene therapy for gastric cancer (Li et al. 2015c).

Targeting peptides directly combine with drugs to improve their therapeutic effects

Excluding modifying drug carriers, some targeting peptides can also be directly combined with drugs to improve their therapeutic effects of gastric carcinoma. They can work in the following ways: enhancing drug efficacy, synthesizing new agents and directly anti-angiogenesis.

In terms of enhancing drug efficacy, there were many studies. Anti-EGFR-iRGD could enhance the curative effect of drugs broadly in high-EGFR-expressing gastric carcinoma (Sha et al. 2015a). Zhang et al. also found iRGD peptide could help 5-FU to penetrate into tumors (Zhang et al. 2017). Besides, a novel peptide named GX1-RPAKPAR (GXC) was consisting of GX1 and a kind of CendR peptide RPARPAR. CendR peptides screened by phage display technology guaranteed improved penetration of tumor cells via binding to NRP-1, a protein which could facilitate proliferation, migration as well as invasion of gastric carcinoma cells (Teesalu et al. 2009). Co-administration of GXC peptide with Adriamycin could potentiate the therapeutic efficacy of anticarcinogen in SGC-7901 xenograft models (Jin et al. 2018). Analogously, peptide TCP-1 which could be used as a targeting probe against gastric carcinoma vasculature (Li and Cho 2012) enabled normalized gastric carcinoma blood vessels and potentiated antitumor efficiency of 5-FU (Lu et al. 2017). It was worth mentioning that peptide GMBP1 could enhance the efficacy of drugs in a specific way. GMBP1 could bind to GRP78 peptide, a gastric MDR tumor-specific expression protein, displaying its capability to reverse gastric carcinoma cells MDR phenotype and enhance drug efficacy (Kang et al. 2013; Wang et al. 2015c).

In addition to this, synthesizing new agents was another pattern. A recombinant protein called KLA-iRGD was reported as a promising antineoplastic agent for MKN45 gastric carcinoma (Huang et al. 2017c), in which KLA peptide enabled the swelling and permeabilization of mitochondrial as well as apoptosis-promoting (Chu et al. 2015; Ellerby et al. 1999), and iRGD guaranteed high penetration. Another recombinant protein called sTRAIL-iRGD was consisting of CRGDKGPDC and sTRAIL, in which sTRAIL could induce programed cell death in various tumors (Liu et al. 2014a). The antineoplastic effect of sTRAIL-iRGD in tumor cells (2D), multicellular spheroids (3D), and mice was assessed. And its property of restricted systemic toxicity and high selectivity was ultimately confirmed (Huang et al. 2017b).

As angiogenesis plays an important role in tumorigenesis and metastasis, the unique anti-angiogenesis properties makes GX1 a promising strategy for gastric cancer treatment (Folkman 1971). GX1 could directly bind to TGM2, reduce the GTP-binding activity of TGM2, suppress its downstream pathway (NF-κB/HIF1α), and thus inhibit angiogenesis (Lei et al. 2018). Compared with rmhTNF-α alone, GX1-rmhTNF-α displayed better selectivity, higher antineoplastic activity and lower systemic toxicity. This demonstrated that GX1 could act as a targeted guider as well as an antiangiogenic agent in human gastric cancer's diagnosis and treatment (Chen et al. 2009).

Targeting peptides enhance lymphocyte infiltration to promote antitumor effect

As a novel treatment method, immunotherapy has recently led to dramatic clinical responses towards gastric carcinoma (Takimoto et al. 2017; Wrzesinski et al. 2010). The effective transport of lymphocytes into tumor microenvironment is the key to the success of effective anti-tumor immunotherapy.

Studies have shown that targeting peptides can enhance the therapeutic effect of gastric carcinoma by enhancing the infiltration of lymphocytes. Anti-EGFR-iRGD could effectively potentiate the infiltration of lymphocytes in gastric cancer and promote the anti-tumor activity both in vitro and in vivo (Zhu et al. 2018). Besides, iRGD modification could also boost the infiltration of lymphocytes in tumor site via binding to its receptor neuropilin-1 (Ding et al. 2019).

Targeting peptides bind with imaging agent to improve the treatment effect

Primarily, targeting peptide could achieve targeted radionuclide therapy via labeling with radionuclides. ^{131}I-2PEG-$(GEBP11)_3$, a bifid PEGlylated GEBP11 trimer labeled with iodine 131, showed higher tumor accumulation and significant inhibitory effect on tumor growth. These results suggested that ^{131}I-2PEG-$(GEBP11)_3$ could be a potential radioactive targeting drug of gastric cancer and 2PEG-$(GEBP11)_3$ could be an underlying drug delivery carrier (Zhang et al. 2013).

Furthermore, peptide-based targeting molecular probe (CyIC-GX1) was of great use for gastric carcinoma targeting and imaging in vivo, which suggested the combination of vasculature-targeted peptide with fluorescence imaging technology might enhance early detection and the anti-angiogenesis therapeutic effect for gastric cancer (Xin et al. 2013).

Conclusion

Most of the patients with gastric cancer were in an advanced stage when diagnosed, and were mainly treated with drugs. However, the current treatment is limited, and the efficacy needs to be improved. To solve these challenges, biomedical researchers have done a lot of work in the research of molecularly targeted treatments and the development of drug delivery systems in recent years.

Trastuzumab, which targets HER2 receptor, is the most effective molecular targeted drug for gastric cancer at present and is approved as a first-line treatment for HER2-positive advanced gastric cancer. However, HER2-positive rate is seen about 10–20% in gastric cancer patients. So, more novel targeted therapies are still being explored, including the search for novel pathways and targets, and the optimization of the compatibility of targeted drugs with chemotherapy drugs.

In recent decades, drug delivery systems for gastric cancer have been widely investigated, including drug carriers and targeted peptides to improve the treatment of gastric cancer. At present, nanoparticles are commonly used drug carriers for gastric cancer, among which Poly (lactic-co-glycolic acid) (PLGA) nanoparticle is one of the polymeric nanoparticles approved by the FDA/EMA. Several peptides have been screened for targeting gastric cancer therapy. Among them, iRGD and GX1 have outstanding effects, because they not only have a high affinity for gastric cancer tissue, the former can help to synthesize new drugs, the latter can directly inhibit angiogenesis. Because of many incomparable advantages than traditional carriers, the development of exosomes as a new delivery carrier is promising. In particular, engineering exosomes, such as targeted peptides modified exosomes, will have great potential in the treatment of gastric cancer.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

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