Nanomedicine strategies for sustained, controlled, and targeted treatment of cancer stem cells of the digestive system

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Abstract
Cancer stem cells (CSCs) constitute a small proportion of the cancer cells that have self-renewal capacity and tumor-initiating ability. They have been identified in a variety of tumors, including tumors of the digestive system. CSCs exhibit some unique characteristics, which are responsible for cancer metastasis and recurrence. Consequently, the development of effective therapeutic strategies against CSCs plays a key role in increasing the efficacy of cancer therapy. Several potential approaches to target CSCs of the digestive system have been explored, including targeting CSC surface markers and signaling pathways, inducing the differentiation of CSCs, altering the tumor microenvironment or niche, and inhibiting ATP-driven efflux transporters. However, conventional therapies may not successfully eradicate CSCs owing to various problems, including poor solubility, stability, rapid clearance, poor cellular uptake, and unacceptable cytotoxicity. Nanomedicine strategies, which include drug, gene, targeted, and combinational delivery, could solve these problems and significantly improve the therapeutic index. This review briefly summarizes the ongoing development of strategies and nanomedicine-based therapies against CSCs of the digestive system.

Key words: Nanomedicine; Cancer stem cells; Digestive system; Drug delivery; Gene delivery

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Core tip: There are reviews in the literature contributed to the applications of nanotechnology for the detection and treatment of gastrointestinal diseases. However, this is a first review to report the current development of strategies and nanomedicine-based therapies against cancer stem cells of the digestive system.

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INTRODUCTION

Currently, gastrointestinal cancer is the second leading cause of cancer-related deaths worldwide. Despite some progress achieved in cancer treatment, the current therapies have limitations with respect to their ability to prevent tumor metastasis and relapse. Recent scientific studies have found that a small proportion of cancer cells (0.01%-4%) can proliferate indefinitely. These cells are similar to adult stem cells with respect to their proliferation, self-renewal, and differentiation into other cells; therefore, they were named cancer stem cells (CSCs) [1]. CSCs were first isolated from acute myeloid leukemia by Bonnet et al. [2] in 1997. It was not until 2003 that CSCs in solid tumors were studied when Al-Hajj et al. [3] identified CSCs with a phenotype of CD44+/CD24-/low/Lineage- in breast cancer. This provided strong evidence for the existence of CSCs in solid tumors and theoretically supported the possible identification of CSCs in other solid tumors. Subsequently, CSCs were identified in a variety of tumors, including tumors of the digestive system, such as gastric cancer [4], liver cancer [5], and colon cancer [6,7].

CSCs have many characteristics similar to those of stem cells, for example, the self-renewal and differentiation abilities, and some common signaling pathways, including the Wnt/l-β-catenin, Notch, and Hedgehog pathways [6,7-9]. However, CSCs also exhibit some unique characteristics because of abnormally regulated genetic mechanisms: (1) quiescence, conventional anticancer therapies always kill rapidly proliferating cancer cells, but have less effect on quiescent CSCs [10,11,12]; (2) high tumorigenicity, only a handful of CSCs can lead to tumor development, whereas the same number of non-CSCs are unable to form done or tumors in vivo [13,14,15]; (3) resistance, CSCs highly express membrane transport proteins of the ATP binding cassette (ABC) family, which can transport and efflux a variety of materials, including metabolites, drugs, toxic substances, endogenous lipids, peptides, nucleotides, and sterols, which accounts for the drug efflux and drug resistance of CSCs [16,17,18,19]; (4) high levels of anti-apoptotic molecules [20]; and (5) enhanced DNA repair ability [21-23]. Conventional therapies including chemotherapy, radiotherapy, biotherapy, and thermal therapy mainly focus on the differentiation and proliferation of cancer cells rather than those of CSCs, resulting in an increase in the CSCs fraction, which can lead to metastasis and recurrence [24,25]. Consequently, the development of effective therapeutic strategies against CSCs plays a key role in increasing the efficacy of cancer therapy.

In recent years, the applications of nanomaterials and nanotechnology in CSC-targeted therapy have received more and more attention. As an emerging interdisciplinary field, nanotechnology can provide materials and tools with unique physical and chemical properties and biological functions for CSC-targeted therapy. In this review, we briefly discussed the properties of CSCs and the conventional strategies against CSCs of the digestive system, as well as a summary of the latest achievements in the nanomedicine approaches for CSC therapy in the digestive system.

CANCER STEM CELLS OF THE DIGESTIVE SYSTEM

Normal gastrointestinal tissues comprise a specific class of stem cells, named gastrointestinal stem cells, which are adult stem cells, with a capacity to self-renew and replicate. They can differentiate into any type of cells in the gastrointestinal tract and play an important role in the regeneration of gastrointestinal mucosa and maintenance of tissue homeostasis. It seems that gastrointestinal stem cells may undergo mutation and can transform into CSCs, which, in turn, participate in the initiation and progression of the gastrointestinal tumors [26]. However, Houghton found that Helicobacter pylori induced chronic inflammation in the gastric tissue of C57BL/6 mice and this inflamed tissue included bone marrow-derived cells, which could develop into intraepithelial carcinoma through dysplasia [27]. The exact origin of gastrointestinal CSCs is unknown: They may be derived directly from the mutation of normal stem cells, or it may be that mature cells acquire tumor formation potential and transform into CSCs.

The identification of CSCs plays an important role in the evaluation of the prognosis of patients and serves to guide treatment. Currently, the main method used for the isolation of CSCs is based on the surface markers (such as membrane proteins, adhesion molecules, and receptors) that distinguish CSCs from non-CSCs, which can be sorted by flow cytometry or magnetic-activated cell sorting (MACS). In recent years, great progress has been made in the study of gastrointestinal CSCs and their markers, which can theoretically support the diagnosis and treatment of gastrointestinal tumors. In addition, the identification of specific cellular markers of gastrointestinal CSCs has become a research focus. So far, some possible markers of gastrointestinal CSCs have been evaluated, such as CD24, CD133, CD44, CD166, stage-specific embryonic antigen (SSEA), Oct-4,
and Sox-2. CD133 and CD44 are the main markers of gastrointestinal CSCs. However, recent studies of CSC phenotypes have presented a new challenge \[28,29\]: CSCs are of different phenotypes and it is urgent and necessary to target all subsets of CSCs within the tumor to prevent a relapse. Thus, there is a need to investigate more cell surface markers in addition to CD133 and CD44, for the identification of gastrointestinal CSCs.

**STRATEGIES AGAINST CSCS OF THE DIGESTIVE SYSTEM**

The current failure in the treatment of gastrointestinal cancer is attributable to drug resistance and recurrence after therapy in most cases, in which CSCs are thought to play a crucial role. Therefore, strategies targeting CSCs may bring new hope for the treatment of gastrointestinal cancer \[19,30\]. Currently, several strategies have been proposed to target CSCs of the digestive system (Figure 1). For example, specific surface markers and altered signaling pathways are attractive therapeutic targets. Induction of the differentiation of CSCs and targeting of the tumor microenvironment or niche are also efficient strategies. Inhibition of ATP-driven efflux transporters that are overexpressed on the CSCs surface, is believed to increase the sensitivity of the tumor to chemotherapeutic drugs. Other strategies, such as anti-telomerase therapy and modulation of abnormal metabolism, are also worth evaluating.

**Targeting cell surface markers**

CSCs express some unique surface markers that distinguish them from other cells; therefore, strategies targeting these specific surface markers can eradicate CSCs of the digestive system, which is an effective approach for the treatment of gastrointestinal cancer. Aptamers, which are oligonucleotide or peptide molecules that can specifically bind to a desired site and penetrate the cancer cells, have been found to target the CSCs surface markers. Shigdar et al\[31\] isolated the first RNA aptamer against epithelial cell adhesion molecule (EpCAM), a putative marker of gastric, colorectal, and liver CSCs. In addition, monoclonal antibodies have been developed to block CSC surface markers. Haraguchi et al\[32\] demonstrated that CD13 is a marker for liver CSCs and treatment with anti-CD13 antibody suppressed the self-renewal and tumor-initiating ability of dormant CSCs. Smith et al\[33\] reported that a murine anti-human CD133 antibody conjugated to a potent cytotoxic drug, monomethyl auristatin F, selectively targeted CD133\(^+\) cells, which is a marker for gastric and liver CSCs. Other surface markers, including CD44\[34\] and CD58\[35\], have been also utilized to specifically eradicate the CSCs of the digestive system.

**Inhibition of CSCs-related signaling pathways**

The normal function of stem cells depends on the normal regulation of a variety of signaling pathways. Dysregulation of the signaling pathways results in abnormal proliferation and differentiation. Therefore, inhibition of CSCs-related signaling pathways is an effective method for cancer therapy. The common CSCs-related signaling pathways include: (1) Wnt/\(\beta\)-catenin pathway: Implicated in the maintenance and proliferation of CSCs\[36\]. Cai et al\[37\]
suggested that the Wnt/β-catenin pathway is essential for the self-renewal of cancer stem-like cells in human gastric cancer. Another study also suggested the same role for the Wnt/β-catenin pathway in gastric CSCs and showed that salinomycin (SAL) could inhibit gastric tumor growth by suppressing Wnt/β-catenin signaling in CSCs. The Wnt/β-catenin pathway plays an important role not only in gastric CSCs, but also in colon and liver CSCs. Song et al. demonstrated that small molecules could target the Wnt signaling pathways in CSCs for the treatment of colorectal cancer; (2) notch pathway: Required for the maintenance of gastrointestinal stem cells. Luo et al. suggested that the Notch pathway promotes CSCs activity in hepatocellular carcinoma (HCC). Wang et al. demonstrated that the Wnt/β-catenin and Notch signaling pathways play important roles in the activation of liver CSCs; and (3) hedgehog pathway: Implicated in the unchecked self-renewal and the development of metastatic tumors. Song et al. suggested that the Sonic Hedgehog pathway is essential for the maintenance of the cancer stem-like cells in human gastric cancer. A study that investigated the molecular mechanisms of curcumin and curcumin analogs against colorectal CSCs suggested the involvement of signaling pathways, including Wnt/β-catenin, Sonic Hedgehog, Notch, and PI3K/Akt/mTOR.

**Differentiation therapy**

Differentiation therapy of tumors refers to treatment of malignant tumors via induction of cell differentiation. The abnormal differentiation of CSCs is one of the important causes of cancer development, thus, inducing the differentiation of CSCs is an important method for cancer therapy. Hepatocyte nuclear factor-4α (HNF-4α), a central regulator of differentiated hepatocyte phenotype, suppresses tumorigenesis and tumor development by inducing the differentiation of the hepatocarcinoma cells, especially CSCs, into mature hepatocytes. Lombardo et al. found that bone morphogenetic protein 4 (BMP4) induces the differentiation of colorectal CSCs and increases the antitumor effects of 5-fluorouracil and oxaliplatin. Zhang et al. verified that sophoridine has the ability to suppress HCC and CSCs and could act as a differentiation therapy drug.

**Targeting the tumor microenvironment or niche**

The microenvironment is an important condition for the survival of cells, which plays an important role in the regulation of the proliferation and differentiation of cells. The stem cell microenvironment, called niche, includes the niche cells, extracellular matrix, and soluble factors derived from the niche cells. CSCs are also believed to reside in niches, which maintain the principle properties of CSCs, preserve their phenotypic plasticity, protect them from the immune system, and facilitate their metastatic potential. Targeted therapy against this microenvironment is of great significance for the treatment of cancer. Vermeulen et al. proposed that colon cancer stemness was partly orchestrated by the microenvironment. Hypoxia, which influences the liver CSC microenvironment, has been identified as a major cause of hypervascularization in HCCs. Targeting hypoxia is an effective strategy to manipulate the niche of the quiescent, drug-resistant cells. Several studies have indicated that angiogenesis can be related to CSC survival and drug resistance and shown that vascular endothelial growth factor (VEGF) is one of the most specific and critical regulators of angiogenesis, which promotes CSC activity by governing both the microvasculature formation and the intrinsic self-renewal pathways. Targeting VEGF with inhibitors or antibodies can lead to normalization of the tumor vasculature, disruption of the CSC niche, and inhibition of tumor growth.

**Targeting the ATP-driven efflux transporters**

CSCs express high levels of ABC transporters, such as ABCB1, ABCG2, and ABCB5, which represent the three principal multidrug-resistance (MDR) genes that have been identified in tumor cells. These transporters actively efflux the drugs outside the cells, conferring resistance to chemotherapeutic drugs. Xie et al. suggested that the overexpression of ABCG2 is responsible for chemotherapy failure in colon cancer. Inhibition of ABCB1 (MDR1) expression, which encodes P-glycoprotein (Pgp), can increase the sensitivity of HCC cells to anticancer drugs, such as doxorubicin and daunorubicin. Pgp’s cousin, ABCB5, is another ABC transporter implicated in the drug resistance of CSCs in different tumor types. For example, Cheung et al. found that the expression of granulin-epithelin precursor (GEP) and ABCB5 in liver CSCs was associated with chemoresistance and reduced the survival rates of patients with HCC. However, inhibition of ABC transporters is likely to have significant side effects, and the ability to overcome MDR clinically is rather limited. Therefore, targeted and combined therapy may be required to circumvent drug resistance and nanomedicine may show tremendous potential to overcome MDR.

**Other strategies**

**Anti-telomerase therapy:** Telomerase activation leads to telomere maintenance, which plays an important role in the immortality of CSCs. Compared to the normal cells, the telomerase activity in CSCs is higher and the length of the telomere is shorter. Anti-telomerase therapy can specifically shorten the CSCs telomere, causing replicative senescence, apoptosis, and cell cycle arrest with little damage to the normal cells. Several anti-telomerase agents, such as the antisense oligonucleotide inhibitor GRN163L and immunotherapies that use dendritic cells (GRVAC1), hTERT peptide (GV1001), or cryptic peptides (Vx-001), are currently in clinical trials for treatment of various tumors and are speculated to efficiently target CSCs. A recent study has implied that co-inhibition of telomerase and tankyrase 1, which elongates the telomere, may be a rational strategy for telomere-directed gastric cancer therapy.
**Targeting the metabolism:** Recently, there is growing evidence that metabolism and stemness are highly intertwined processes in tumors\[^{48}\]. For example, gastrointestinal CSCs showed higher inducible nitric oxide synthase (iNOS) expression, lower reactive oxygen species (ROS) production, and a different metabolic profile with respect to non-CSCs. Aerobic glycolysis blockade, oxidative stress-based therapies, and nitric oxide synthase inhibition target the gastrointestinal CSCs and could have profound anticancer effects\[^{49}\].

**NANOMEDICINE-BASED ANTI-CANCER THERAPIES AGAINST CSCs OF THE DIGESTIVE SYSTEM**

As discussed above, conventional therapies may not successfully eradicate CSCs owing to various problems, including solubility, stability, rapid clearance, poor cellular uptake, and unacceptable cytotoxicity. Thus, more and more attention has been drawn to the application of nanomedicine\[^{70-72}\]. Nanomedicine can be defined as the application and further development of nanotechnology to solve the problems faced in medicine, i.e., to diagnose, treat, and prevent diseases at the cellular and molecular levels\[^{73-75}\]. Nanomedicine is characterized by a size of less than 200 nm in general, which is smaller than the traditional medicine, thus, it has the advantages of large specific surface area, high surface reaction activity, and high adsorption capacity. Moreover, it can be optimized in the aspects of drug loading, pharmacokinetic properties, and biocompatibility by different modifications of the particle surface. In conclusion, nanomedicine has the following characteristics: Sustained, controlled, and targeted drug delivery, improved drug stability, prolonged half-life of drugs, good biocompatibility, etc. Consequently, nanomedicine strategies for sustained, controlled, and targeted treatment of CSCs of the digestive system may offer superior outcomes leading to efficient cancer therapy (Figure 1).

**Drug delivery**

One important application of nanomedicine is the transport of chemotherapeutic drugs with poor solubility, stability, or severe side effects. For example, the monocarboxylic polyether antibiotic, SAL, which primarily functions as a highly selective potassium ionophore, has been shown to affect various CSCs, including liver, gastric, and colorectal CSCs\[^{76-79}\]. However, it exhibits poor aqueous solubility and severe nervous and muscle toxicity, which hinder its clinical applications\[^{80,81}\]. Therefore, various studies incorporate SAL into nanocarriers to address these issues. For instance, Yao et al\[^{82}\] developed a gastric CSC-targeted drug delivery system (SAL-SWNT-CHI-HA complexes), which could enhance the bioavailability and cytotoxic activity of SAL. In our previous study, we developed novel iRGD (internalizing Arg-Gly-Asp peptide)-conjugated DSPE-PEG2000 nanomicelles (M-SAL-iRGD) for delivery of SAL to both liver cancer cells and CSCs. M-SAL-iRGD possessed a small size of around 10 nm and a drug encapsulation efficacy higher than 90%. It showed a superior tumor penetrating ability and therapeutic efficacy\[^{83}\]. Similarly, curcumin has extraordinary anticancer properties; however, it has a limited application in the treatment of cancer owing to its insolubility, instability, and poor pharmacokinetics, which greatly hamper its in vivo efficacy\[^{84-86}\]. Wang et al\[^{87}\] developed a novel nanoparticle formulation in which curcumin was encapsulated in stearic acid-g-chitosan oligosaccharide (CSO-SA) polymeric micelles to overcome these hurdles. Curcumin-loaded CSO-SA micelles could increase curcumin accumulation in cancer cells and were effective in inhibiting colorectal CSCs both in vitro and in vivo. In another study, Wang et al\[^{88}\] used the CSO-SA micelles to deliver a standard chemotherapy for colorectal cancer treatment (oxaliplatin). This could also increase oxaliplatin accumulation in both colorectal cancer cells and tissues and could effectively eradicate colorectal CSCs.

**Gene delivery**

Nucleic acids, especially small interfering RNAs (siRNAs) and microRNAs (miRNAs), can effectively target genes overexpressed in CSCs and involved in the maintenance of stemness and tumorigenicity. However, their characteristics, such as negative charge, high molecular weight, and low stability, limit their application. Therefore, nanomedicines have been developed to condense them for effective delivery. For instance, a novel non-cytotoxic and pH-sensitive anti-EpCAM monoclonal antibody-labeled CSCs-targeted block copolymer vesicle was synthesized as a nanocarrier for anticancer drugs and siRNA. The polymer vesicles showed good pH-regulated drug release capability and excellent stability in water, PBS, and 40% fetal bovine serum. The EpCAM-positive CSC-targeted vesicles showed a high delivery efficacy of both the anticancer drug, doxorubicin hydrochloride (DOX-HCl), and siRNA to the CSCs\[^{89}\]. Similarly, Kim et al\[^{90}\] developed a tumor-targeted nanodelivery platform (scL) and showed that systemic administration of scL carrying the wtp53 gene was able to induce tumor growth inhibition and promote the death of both CSCs and non-CSCs in subcutaneous colorectal cancer xenografts. Nanomedicine for siRNA delivery can also sensitize CSCs to chemotherapeutic drugs. For example, Liu et al\[^{91}\] designed a novel siRNA delivery carrier system with multidrug resistance gene (MDR1)-targeted siRNA (siMDR1) and showed that it effectively reduced the expression of MDR1 in human colon CSCs, resulting in a significant increase in the chemosensitivity to paclitaxel.

Recent studies have indicated that miRNAs are important regulators of CSCs\[^{92}\]. For example, miR-34, a transcriptional target of p53, inhibits the biological properties of gastric CSCs. Restoration of miR-34 expression in gastric CSCs inhibits sphere formation in vitro and tumor regeneration in vivo\[^{93}\]. Liu et al\[^{94}\] developed gelatinase-stimulated PEG-Pep-PCL nanoparticles to
deliver miR-200c, which were reported to inhibit CSC-like properties. The miR-200c nanoparticles enhanced the radiotherapy efficacy, reduced the expression of CD44, and the percentage of CD44+ gastric cancer cells. Meanwhile, other CSCs properties, including invasiveness and resistance to apoptosis, could be suppressed by miR-200c nanoparticles.

**Targeted delivery**

In addition to its ability to improve drug stability and biocompatibility, nanomedicine can also be modified to direct or guide the therapeutic agents to CSCs. Since CSCs express specific cell surface biomarkers, it may be a promising strategy to use these biomarkers for targeted drug delivery. Hyaluronic acid (HA), a glycosaminoglycan widely found in the extracellular matrix, can specifically recognize its receptors, CD44, and has been identified as a potent targeting ligand to tumors possessing CD44-overexpressing cells. Yao et al. developed SAL-loaded chitosan (CHI)-coated single-walled carbon nanotubes (SWNTs) functionalized with HA, which facilitated the uptake of SWNTs into the gastric CSCs via CD44 receptor-mediated endocytosis. In addition, anti-CD44 antibodies could also be used for CSC-targeted therapy. Wang et al. developed doxorubicin-loaded anti-CD44 antibody-functionalized liposomal nanoparticles, which specifically targeted CD44+ cells of HCC to mitigate the side effects of conventional chemotherapy. In a recent study, CD90+ LCSCs were isolated by magnetic-activated cell sorting from HCC cells. Therefore, Yang et al. prepared a CD90-targeted thermosensitive magnetoliposomes (TM)-encapsulated 17-allylamino-17-demethoxgeldanamycin (17-AAG), which is a heat-shock protein 90 (HSP90) inhibitor, to sensitize the CD90+ LCSCs to magnetic hyperthermia and enhance its antitumor effects in vitro and in vivo.

**Combinational delivery systems**

As described above, nanomedicine-based single drug delivery systems are effective in targeting the CSCs in the digestive system. However, various CSCs-targeted drugs that are not highly cytotoxic as compared to the conventional chemotherapeutic drugs, are not very effective in reducing the bulk cancer cells, which can spontaneously and stochastically turn into CSCs again. Therefore, combinational delivery of chemotherapeutics and CSC-specific agents for eliminating both the cancer cells and CSCs is a promising method to improve cancer treatment. Liu et al. developed doxorubicin-loaded anti-CD44 antibody-mediated liposomal nanoparticle loaded of doxorubicin and siNotch1 into both non-CSCs and CSCs of SMMC7721. The combined drug delivery system could remarkably augment drug delivery into tumor tissues, thus, substantially suppressing the tumor growth (Table 1).

Additionally, nanomedicine is crucial for the delivery of dual drugs with predictable ratios at the tumor site to achieve a synergistic effect. Mayer et al. co-encapsulated irinotecan and floxuridine at a 1:1 molar ratio inside 100-nm-diameter liposomes composed of distearoylphosphatidylycholine/distearoylphosphatidylglycerol/cholesterol (7:2:1 molar ratio). The liposomes maintained the drug ratio in the plasma after injection, and delivered the formulated drug ratio directly to the tumor tissue of the colorectal cancer. In another study, vincristine and topotecan were successfully co-encapsulated at therapeutically relevant levels in the same nanoliposome (LipoVib). The nanoliposomes controlled the drugs’ “biofate” and maintained a fixed drug ratio in

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**Table 1** Nanomedicine-based therapies against cancer stem cells of the digestive system

| Tumor types | Nanomedicine | Ref. |
|-------------|--------------|------|
| Drug delivery | SAL-loaded carbon nanotubes functionalized with HA | [82] |
| Gastric cancer | SAL-loaded iRGD-conjugated DSPE-PEG2000 nanomicelles | [83] |
| Liver cancer | Curcumin-loaded CSO-SA micelles | [87] |
| Colorectal cancer | Oxaliplatin-loaded CSO-SA micelles | [88] |
| Gene delivery | Anti-EpCAM-monovalent-antibody-labeled block copolymer vesicle | [89] |
| Liver cancer | Wnt3 gene loaded s.c. nanocomplex | [90] |
| Colorectal cancer | MDRI siRNA loaded lipid nanoparticles | [92] |
| Gastric cancer | miR-200c loaded gelatinase-stimuli PEG-Pep-PCL nanoparticles | [94] |
| Targeted delivery | SAL-loaded carbon nanotubes functionalized with HA | [82] |
| Liver cancer | Anti-CD44 antibody-mediated liposomal nanoparticle loaded of doxorubicin | [96] |
| Gastric cancer | CD90-targeted thermosensitive magnetoliposomes-encapsulated 17-AAG | [97] |
| Combinational delivery | Nanoparticle co-loaded miR-200c and DOC | [99] |
| Liver cancer | Micellar nanoparticle co-delivering platinum (IV) prodruk and siNotch1 | [100] |
| Colorectal cancer | Liposomes co-encapsulated irinotecan and floxuridine | [101] |
| Colon cancer | Nanoliposomes co-encapsulated vincristine and topotecan | [102] |
vivo, displaying an enhanced therapeutic efficacy against colon cancer[122].

CONCLUSION

The CSCs theory revealed more facts about cancer, but the CSCs in the digestive system are still not fully understood. There is a need for further investigation of the new markers, abnormal metabolism, and signal transduction pathways of CSCs, which will improve our strategies to target CSCs. In this review, we summarized the current strategies against CSCs of the digestive system. Nanomedicines have been shown to effectively deliver drugs and genes to target CSCs of the digestive system. A number of studies have shown that there is a significant increase in the therapeutic outcome with nanomedicine. However, there are still great challenges limiting the effective application of nanomedicine in clinical practice. One of the most important challenges is the biological safety issues. There is still no clear evidence that the nanomaterials can be effectively metabolized in vivo and will not accumulate to cause side effects. In addition, it is difficult to determine the safe dose of nanomedicine because of the lack of clear evaluation criteria.

Although there are still some difficulties preventing the wide application of nanomedicine in clinical practice, there is a reason to believe that, with the progress of nanotechnology and the in-depth research of CSCs, there is a reason to believe that, with the progress of nanotechnology and the in-depth research of CSCs, the unique advantages of nanomedicine will create good conditions for the development of personalized therapy for cancer patients and will finally be capable of conquering cancer of the digestive system.

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