ISSN 1948-0210 (online)

World Journal of *Stem Cells*

World J Stem Cells 2023 June 26; 15(6): 502-653

Published by Baishideng Publishing Group Inc

WJSC

World Journal of Stem Cells

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Stem Cells

ISSN
ISSN 1948-0210 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Shengwen Calvin Li, Carlo Ventura

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-0210/editorialboard.htm

PUBLICATION DATE
June 26, 2023

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World J Stem Cells 2023 June 26; 15(6): 514-529

DOI: 10.4252/wjsc.v15.i6.514

ISSN 1948-0210 (online)

REVIEW

Advances of nanotechnology applied to cancer stem cells

Miao Yue, Ting Guo, Deng-Yun Nie, Yin-Xing Zhu, Mei Lin

Specialty type: Cell biology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Kanaoujiya R, India; Nath L, India

Received: December 28, 2022
Peer-review started: December 28, 2022
First decision: February 14, 2023
Revised: March 1, 2023
Accepted: April 18, 2023
Article in press: April 18, 2023
Published online: June 26, 2023

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Abstract

Cancer stem cells (CSCs) are a small proportion of the cells that exist in cancer tissues. They are considered to be the culprit of tumor genesis, development, drug resistance, metastasis and recurrence because of their self-renewal, proliferation, and differentiation potential. The elimination of CSCs is thus the key to cure cancer, and targeting CSCs provides a new method for tumor treatment. Due to the advantages of controlled sustained release, targeting and high biocompatibility, a variety of nanomaterials are used in the diagnosis and treatments targeting CSCs and promote the recognition and removal of tumor cells and CSCs. This article mainly reviews the research progress of nanotechnology in sorting CSCs and nanodrug delivery systems targeting CSCs. Furthermore, we identify the problems and future research directions of nanotechnology in CSC therapy. We hope that this review will provide guidance for the design of nanotechnology as a drug carrier so that it can be used in clinic for cancer therapy as soon as possible.

Key Words: Cancer stem cells; Nanotechnology; Nanoparticles; Nanodrug delivery systems; Drug resistance; Therapy

Core Tip: Cancer stem cells (CSCs) have the potential to self-renew, proliferate, and differentiate. CSCs play a key role in the occurrence, development, recurrence, and metastasis of tumors. Due to the good compatibility and biodegradability of nanomaterials, they are applied to target CSCs for drug delivery, photothermal therapy, and magnetic hyperthermia to treat cancer.

Citation: Yue M, Guo T, Nie DY, Zhu YX, Lin M. Advances of nanotechnology applied to cancer stem cells. *World J Stem Cells* 2023; 15(6): 514-529
URL: https://www.wjgnet.com/1948-0210/full/v15/i6/514.htm
DOI: https://dx.doi.org/10.4252/wjsc.v15.i6.514

INTRODUCTION

Cancer is a major threat to people's health and life worldwide[1]. One of every eight deaths is caused by cancer[2,3]. Current cancer treatments mainly include surgical intervention, radiation therapy, and chemotherapy, which often kill healthy cells and are harmful to patients. Therefore, researchers are seeking better ways to eliminate cancer cells, with less side effects. Some researchers are working on the use of various macrocyclic ligands for cancer therapy, making ruthenium an ideal choice over other transition metals due to its special chemical properties[4]. However, what plagues most cancer treatments is the presence of a small number of cancer stem cells (CSCs) in tumor tissues[5,6], which have the potential for self-renewal, unlimited proliferative capacity, and multidirectional differentiation [5,7]. These cells are in the G0 phase and hypoxic microenvironment and play a key role in tumorigenesis, progression, recurrence, and metastasis. The presence of CSCs in solid tumors such as breast cancer (BC)[8,9], human leukemia[10,11], colorectal cancer[12,13], glioblastoma multiforme (GBM)[14], and ovarian cancer[15] has been reported, and it has been confirmed that CSCs play an important role in the development of tumors.

CSCs have inherent properties such as phenotypic plasticity, drug efflux transporters, overexpression of antiapoptotic proteins, an efficient DNA repair system and a persistent stemness profile that make them resistant to conventional therapies such as chemotherapy and radiation[16-18]. In general, CSC resistance mainly occur through stem cell pathways including the hedgehog[19,20], Notch[21,22], Wnt/β-linked protein[23,24], Nanog[25,26], nuclear factor kappa B (NF-*k*B)[27], and epidermal growth factor receptor pathways[28]. They express ATP-binding cassette (ABC) transporter proteins that can abrogate potential drug damage. CSCs also activate DNA repair capacity within tumor cells and are resistant to cell death[29], which helps to prevent the recruitment of apoptotic factors[5,30]. Therefore, the development of effective anticancer strategies to specifically kill tumor cells and tumor stem cells will be central to cancer therapy.

In recent years, the popularity of nanotechnology has promoted the development of nanodrug delivery systems (NDDS), and various nanodrug carriers have been applied to the treatment of tumors. Due to their small size, biocompatibility, and biodegradability, nanoparticles (NPs) help to fully exploit the function of NDDSs as drug delivery systems/drug carriers, including as imaging agents and for photothermal therapy (PTT), recognition, and drug and gene delivery[31]. As the carrier of active drugs in the drug delivery model, NDDSs can ensure the specific release of active drugs in the patient's body, improve drug solubility and bioavailability and prolong maintenance to improve drug efficacy[32]. Nanocarriers offer remarkable specificity in targeted delivery through active and passive targeting mechanisms (Figure 1)[33,34]. In active targeting, NPs are conjugated to antibodies, peptides, aptamers, and other small molecules[34]. Drug delivery using NP targeting reduces toxicity in healthy cells, prevents drug degradation, and has the advantages of better specificity, biocompatibility, less cytotoxicity, extended half-lives, controlled drug release, and high drug loading capacity for NP-based cancer treatments compared to traditional chemo-cancer treatments[35]. In passive targeting, enhanced permeability and retention (EPR) effects result in NPs circulating slowly in the tumor microenvironment and being more concentrated there than in healthy tissue[36]. Some commonly used nanocarriers (Figure 2) include lipid and micelle-based NPs, polymer/non-polymer NPs, nanobinding, carbon nanotubes (CNTs), graphene oxide (GO), nanocapsules, dendritic macromolecules, polymer micelles, and quantum dots (QDs), which are used to enhance the effectiveness of therapeutic interventions by delivering nontoxic large payloads[37-39]. Recent advances in nanotherapeutics have led to the development and exploration of various nanomaterial carriers for efficient drug/therapeutic delivery.

CSCs have been identified as playing a central role in the setbacks currently faced in clinical trials and research. Therefore, designing a system that can target them at the cellular and system levels is the most promising avenue in the evolution of therapeutic design. By reviewing the application of nanotechnology in CSCs, we hope to provide guidance for the design and in-depth study of nanotechnology drug carriers so that they can be applied in clinic to treat cancer.

NANOTECHNOLOGY FOR CSC SORTING

To better understand the molecular basis of the contribution of CSCs to tumor progression, metastasis, and treatment resistance, many studies have identified biomarkers on the surface of CSC populations to distinguish them from the majority of tumor cells. Magnetic-activated cell sorting (MACS) is a CSC

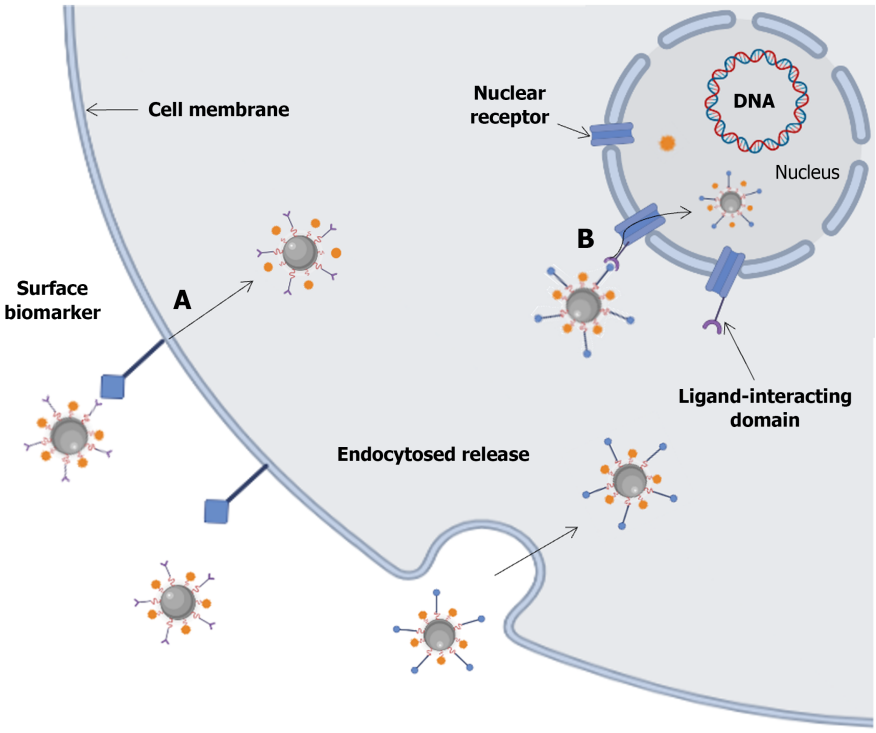

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Figure 1 Different mechanisms of nanocarriers. A: Targeting through surface biomarkers; B: Targeting through the ligand-interacting domain on the nuclear receptor (created with BioRender).

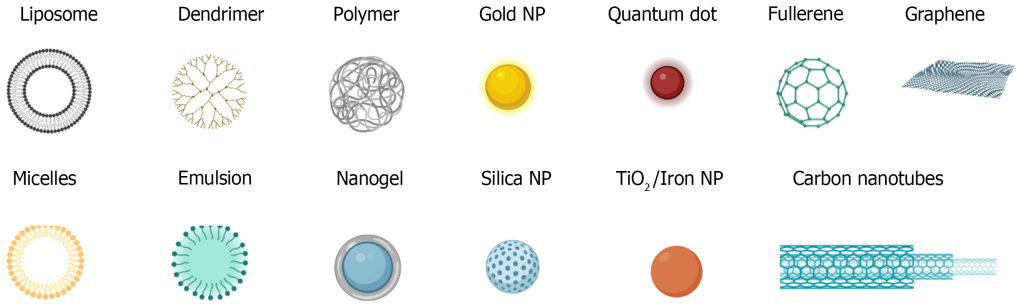

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Figure 2 Different types of nanoparticles (created with BioRender). NPs: Nanoparticles.

sorting technique. Magnetic NPs have unique magnetic activity and are one of the most actively studied NPs, usually ranging in diameter from 1 to 100 nanometers. Basically, magnetic NPs are classified as magnetically manipulated substances, consisting mainly of iron oxides or other metals (iron, nickel, or cobalt). MACS microbeads are superparamagnetic particles coupled to highly specific monoclonal antibodies. The cell surface-specific antigens are combined with stem cell markers such as CD44, CD133, and epithelial cell adhesion molecule (EpCAM), connected to the magnetic bead, and the cells labeled with the conjugated magnetic bead is separated by providing a uniform magnetic field to sort out the corresponding CSC population (Figure 3).

KINDS OF NANODRUG DELIVERY SYSTEMS

To date, nanomedicine has been focused on identifying alternatives to tumor therapy, with researchers focusing on the design of various nanocarriers, which have been used to load various anticancer drugs and herbal medicines to target tumor cells. In fact, according to the National Institutes of Health, there have been clinical trials involving the use of nanotechnology in CSC therapy (Table 1). Because the mechanisms of multidrug resistance are very complex and varied, targeting one mechanism alone does not address clinical needs. Nanocarriers have good stability, a high encapsulation rate and a high drug

Table 1 Clinical trials of advances in nanotechnology applied in cancer stem cells

Identifier	Trial name	Enrollment
NCT04907422	Cluster of differentiation 24-gold nanocomposite expression using quantitative polymerase chain reaction	60
NCT04907422	Nonconjugated cluster of differentiation 24 expression using quantitative polymerase chain reaction	60

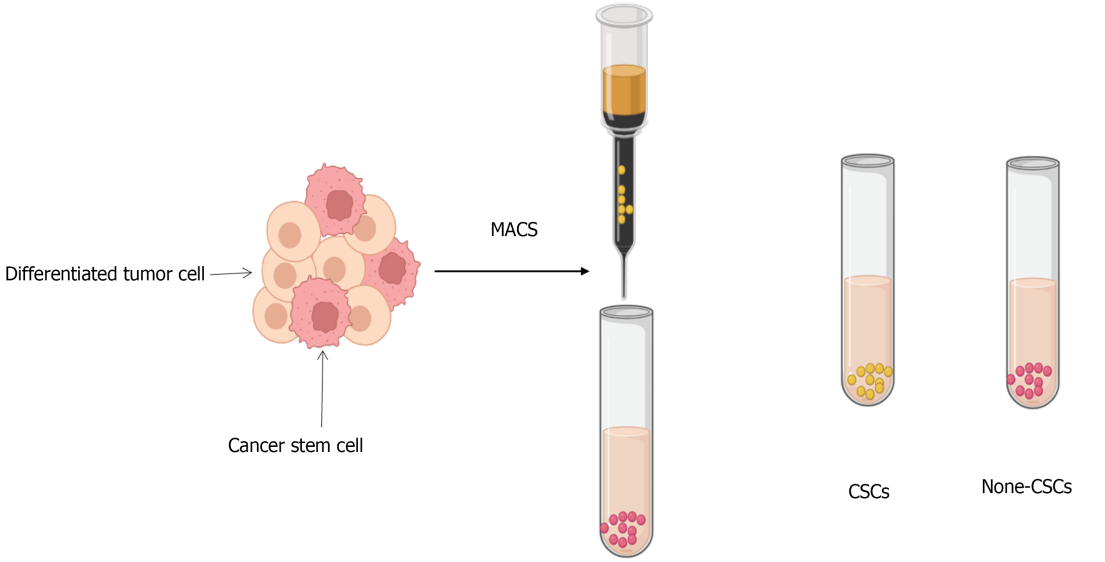

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Figure 3 Magnetic-activated cell sorting (created with BioRender). CSCs: Cancer stem cells; MACS: Magnetic-activated cell sorting.

loading rate and have been proven to be effective carriers for genes and drugs delivered to tumor cells. This delivery induces apoptotic pathways and inactivates resistance genes for targeting tumor tissue to eliminate CSCs. According to the classification of nanotechnology used to target CSCs, they can be divided into Polymeric NPs(PNPs), liposomes, gold (Au) nanorods (GNRs), QDs, CNTs, GO, PTT, and magnetic fluid hyperthermia (Table 2).

PNPs

PNPs can enhance the therapeutic effects of drugs, reduce the drug resistance of CSCs, and improve the therapeutic effects of chemotherapy drugs. The following is a summary of the classification of PNPs through different antibody-ligand recognition (Figure 4), mesoporous silica ($mSiO_2$) NPs (MSNs), and other nanodrug delivery systems.

CD44

CD44[40,41] is a non-kinase transmembrane glycoprotein that is overexpressed in several cell types, including CSCs. Hyaluronic acid (HA) has become a research hotspot in drug release due to its simple chemical structure and inherent properties of targeting CD44. Kesharwani *et al*[42] designed a novel HA copolymerized styrene maleic acid and the effective anticancer agent 3,4-difluoromethylcurcumin to form nanomicelles. CD44+/CD133+/EpCAM+ pancreatic CSCs showed better uptake of HA-engineered nanomicelles and a better anticancer effect on CD44+ pancreatic CSCs. Furthermore, these nanomicelles significantly inhibited the expression of NF-κB, thereby reducing its proliferation and invasion. Debele *et al*[43] conjugated HA with hydrophobic 6-mercaptopurine (MP) and introduced doxorubicin (DOX) into colon cancer cells and colon CSCs through ligands. The inhibitory effect of the synthesized bisensitive polymer drug conjugate (HA-SS-MP) micelles on tumor growth was significantly higher than that of free drugs. In *vitro* cytotoxicity of HA-SS-MP and DOX-loaded HA-SS-MP micelles was great for CSCs (HCT116-CSCs). Gu *et al*[44] prepared mineralized HA-SS-tetracylecyl nanocarriers (M-HA-SS-TA) from oily, hydrophobic, and unstable sulforaphane (SFN), which showed a good response to highly reduced and weakly acidic tumor niches. The SFN nanomaterials (SFN/M-HA-SS-TA) can release SFN rapidly. Compared to free SFN, SFN/M-HA-SS-TA rapidly releases SFN in response to tumor niches, showing stronger inhibition of breast CSC (BCSC)-like properties (invasions, self-renewal, and tumor growth) *in vitro* and *in vivo*. However, magnetic fluid hyperthermia (MFH) mediated by anti-CD44 antibody-modified superparamagnetic iron oxide NPs (SPIONPs) can kill CSCs, and significantly inhibit the growth of transplanted Cal-27 tumors in mice[45].

Table 2 Nanocarrier systems for cancer stem cells

Nanocarrier	Therapeutic agent	Cancer type	Delivery model	Cell line	CSC marker	Ref.
PNPs	CDF	Pancreas	HA-SMA could be engineered to form nanomicelles with a potent anticancer agent, CDF	MiaPaCa-2, AsPC-1	CD44	[42]
	DOX	Colon	HA-SS-MP	HCT116	CD44	[43]
	SFN	Breast	SFN/M-HA-SS-TA	MDA-MB-231, Hs578t, MCF7, MCF10A	CD44	[44]
	SN-38	Colon	CD133Ab-NP-SN-38	HCT116	CD133	[47]
	ITGA5	Breast	ITGA5-targeting NPs	MDA-MB-231	-	[48]
	DOX, tariquidar	Breast	mSiO2-dPG	MCF-7	-	[55]
	DOX, tariquidar	Cancer cell	TTNV	Hela, A547	CD44	[56]
	DS	GMB	PLGA	U87MG, U251MG, U373MG	ALDH	[57,58]
	miR-148a, miR-296-5p	GMB	nano-miRs	GBM1A	Oct4/Sox2	[60]
	TPZ	Breast	MSN	MCF-7	CD133	[54]
	Cyclopamine	Prostate	HPMA	RC-92a/hTERT	CD133	[57]
	HPI-1	Liver, pancreas	HPI-1 was loaded with PLGA-PEG NPs	Huh7, Pa03C	CD133	[58]
	RNA drugs	Liver	ET-tMNV	hep3B	EpCAM	[52]
	DOX, Cyc	Breast	HA-SS-PLGA	MCF-7 MDA-MB-231	CD44	[64]
	LDN193189	Liver	Fe_3O_4-OA-DHCA-PEI-HA	-	CD44	[61]
	DOX	Breast	Gold NPs coupled to adriamycin by nitrogen condensation bond	sk-3	-	[62]
	ZnS	Breast	ZnS	MCF-7	CD44	[63]
	DOX, all-trans retinoic acid	Liver	PLGA-b-PEG	Hepa1-6	EpCAM	[51]
	Epiampicin, arsenic trioxide	Liver	Nanomicelles	hepG2	CD44	[97]
	Resveratrol	Oral	NP	H-357	-	[69]
	Cisplatin	Liver	PEI-modified MSN	Huh7	CD133	[53]
Liposomes	SAL, DOX	Liver	Nanoliposomes	HepG2	CD133	[73]
	TRAIL, SAL	Cancer cell	Liposomes	CSCs	-	[72]
	DOX	Liver	HLs	HepG2	EpCAM, CD133	[74]
	DOX, SAL	Liver	Redox-triggered dual-targeted liposomes	Huh7	CD133EpCAM	[48]
	DTXPL, TEL	Lung	DOX loaded with polyethylene glycolized liposomes	NCI-H460	CD133	[76]
Gold nanorods	-	Head, neck	SPIONPs	Cal-27	CD44	[45]
	PKF, SAHA	Breast	PKF and SAHA loaded on the corona of GNPs	MCF-7	-	[81]
	-	Liver	CD133-targeting aptamers modified on the surface of quantum dots and gold NPs with partially complementary paired	Huh7	CD133	[82]

			RNA (ssRNA)			
	DOX	Liver	EpCAM antibody conjugated onto lipophilic Au-NR	Hepa 1-6	EpCAM	[51]
	siRNA	Breast	Glu-NP	MDA-MB-231	GLUT1	[84]
	SAL	Breast	SAL-conjugated gold NPs, SAL-AuNPs	MCF-7	CD44	[86]
	HA	Breast	HA-capped AuNPs	MDA-MB-231	CD44	[86]
	Teleglenastat	Brain	Au-PEG-CD133-CB-839	GBM-1, NCH-644	CD133	[83]
GO	SAL	Ovarian	rGO-Ag	A2780	ALDH, CD133	[93]
CNTs	Paclitaxel	Breast	Multiwalled carbon nanotubes	HMLER	CD44	[45]
	-	brain	CD133 monoclonal antibody onto chitosan-modified CNTs	GBM tissues	CD133	[89]
	Paclitaxel, SAL	Breast	CD44 antibody hydrazone-linked onto SWCNT with pH-activated release system	MDA-MB-231	CD44+	[91]
	SAL	Glioblastoma	SAL-SWCNT-CHI-HA	AGS	CD44+	[90]

CD: Cluster of differentiation; CDF: 3,4-Difluorobenzylidene curcumin; anti-CD133 antibody-conjugated SN-38-loaded nanoparticles CNTs: Carbon nanotubes; CSCs: Cancer stem cells; Cyc: Cyclophosphamide;CB-839:telaglenastat; dPG: Dendritic polyglycerol; DOX: Doxorubicin; DTXPL: Docetaxel liposome; EpCAM: Epithelial cell adhesion molecule; ET: EpCAM-targeted; Fe_3O_4-OA-DHCA-PEI- HA: Mgnetic nanocubes were synthesized and modified with PEI and HA; GBM: Glioblastoma multiforme; GO: Graphene oxide; GLS1: Glutaminase 1; Glu-NP: Glucose-installed sub-50-nm unimer polyion complex-assembled gold nanoparticle; HA: Hyaluronic acid; HA-SMA: Hyaluronic acid conjugate of copoly (styrene maleic acid); HA-SS-MP: Hyaluronic acid-SS-mercaptopurine; HPMA: N-(2-hydroxypropyl) methylacrylamide; HLs: Hybrid lipo plastids;ITGA5: Integrin subunit alpha 5; MNVs: Milk-derived nanovesicles: M-HA-SS-TA: Mineralized HA-SS-tetracylecyl nanocarrier; miR: MicroRNA; $miSO_2$: Mesoporous silica; MSNs: Mesoporous silica nanoparticles; MWCNTs: Multiwalled carbon nanotubes; NPs: Nanoparticles; PEG: Polyethylene glycol; PKF: PKF118-310; PLGA: Poly(L-lactide-co-glycolide); PNPs: Polymeric nanoparticles; PDT: Photodynamic therapy; ROS: Reactive oxygen species; rGO-Ag: Reduced graphene oxide–silver nanocomposite; SAHA: Vorinostat; SAL: Salomycin; SFN: Sulforaphane; siRNA: Small interfering RNA; SWCNT: Single-walled carbon nanotubes; SPIONPs: Superparamagnetic iron oxide NPs; SAL-SWCNT-CHI-HA:CHI-coated SWCNTs loaded with SAL and functionalized with HA;TEL: Telmisartan; TPZ: Tirapazamine; TRAIL: Tumor necrosis factor-associated apoptosis-inducing ligand; TTNV: Targeted theranostic nano vehicle; ZnS: Zinc sulfide.

CD133

The CD133 antigen is a five-fold transmembrane single-chain glycoprotein that exists on the surface of tumor stem cells. It is a key molecule that regulates the fate of stem cells and a functional marker of stem cells. It can be used to detect and isolate CSCs in various solid tumors[46]. NPs with SN-38 (anti-CD133 antibody-conjugated SN-38-loaded nanoparticles (CD133Ab-NPs-SN-38)), a topoisomerase inhibitor conjured by anti-CD133 antibody, targets CD133+HCT116 cells and inhibits colony formation. The CD133-targeted NP delivery system can eliminate CD133-positive cells[47]. The Wnt/β-catenin pathway plays critical roles in CSC generation and maintenance as well as in normal stem cells. Integrin subunit alpha 5-targeting NPs attenuate β-catenin and significantly reduce triple-negative BC (TNBC) metastasis and may provide a facile and unique strategy of specially attenuating β-catenin *in vivo* for treating metastatic TNBC[48]. Codelivery of DOX and salomycin (SAL) REDOX-triggered double-targeted liposomes CEP-LP@S/D can be used for the synergistic treatment of liver cancer. The system is based on the binding of CD133- and EpCAM-targeting peptides to form Y-shaped CEP ligands that anchor to the liposome surface and allow selective targeting of CD133EpCAMlCSC[49].

EpCAM

EpCAM, considered to be a homogenous cell-cell adhesion glycoprotein, is expressed in epithelial and circulating tumor cells (CTCs), as well as CSCs[50], and is involved in the regulation of cell adhesion, proliferation, migration, dryness, and the epithelial-to-mesenchymal transition (EMT) of cancer cells. Locatelli *et al*[51] coloaded GNRs and adriamycin (Adr) to label EpCAM by targeting the surface of CSCs and killed CSCs under laser ablation. Ishiguro *et al*[52] used RNA nanotechnology to pair milk source nanocapsules (MNVs) with synthetic oligonucleotide aptamers that could bind to EPCAM with high affinity and specificity and loaded small interfering RNA (siRNA) onto β-catenin. The EpCAM-targeted (ET) therapeutic MNV has been prepared. These ET-TMNVs can target EPCAM-positive stem cell populations and effectively release siRNAs within cells that inhibit β-catenin expression and tumor growth. For polymer nanomicelles (GNRS-1/curc@Pms) made from biocompatible poly(L-lactide-co-

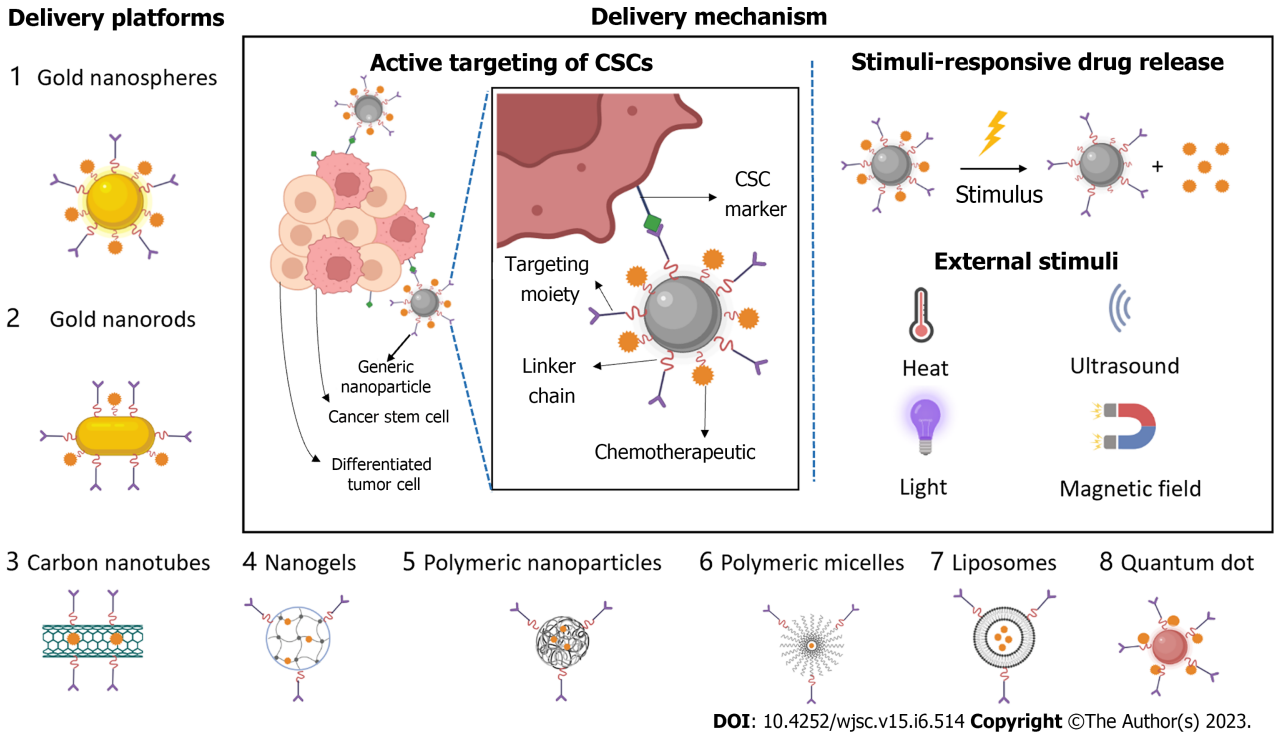

Figure 4 Nanoparticle-mediated targeted drug delivery to cancer stem cells (created with BioRender). CSCs: Cancer stem cells.

glycolide)-block-poly(ethylene glycol) (PLGA-b-PEG) copolymer as drug carriers for Adr and GNRs, when Adr/GNRs@Pms-antiEpCAM with EpCAM antibodies are modified, they are delivered to specific tumor stem cells and increase the drug concentration at the tumor site, thereby killing the entire tumor stem cell population[51].

MSN

MSN drug loading[53] can significantly enhance the cytotoxicity of anticancer drugs with low potency. Therefore, the positive polymer polyethylenimine (PEI) is usually coated and chemically modified to introduce a positive charge on the surface of MSNs, which can effectively bind the DNA structure, siRNAs, and other nucleic acids, thus enhancing their uptake by cells. The PEI-modified MSN was used for double delivery of the chemotherapy drug cisplatin, and the DNA encoding the hepatocyte nuclear factor 4 alpha transcription factor was used for gene therapy of liver cancer. This therapy inhibited the proliferation of CD133+ HUH7 cells, reduced the proportion of CSCs, and reduced the expression of dry-related genes. The nuclear targeting system of MSNs by Li *et al*[54] can directly target CSCs and enter the nucleus through anti-CD133 surface modification and heat-triggered exposure of the TAT polypeptide under an alternating magnetic field (AMF). Combined with hyperthermia and hypoxia-activated chemotherapy, the release of nuclear-targeted drugs eventually leads to complete apoptosis of CSCs. CSC-specific targeting of $mSiO_2$-dendritic polyglycerol (dPG) nanocarriers delivered the chemotherapy drug DOX and the P-glycoprotein (P-gp) inhibitor tariquidar (Tar) to reverse multidrug resistance (MDR) and enhance chemotherapy efficacy in bCSCs[55]. A targeted theranostic nano vehicle (TTNV) was designed using manganese-doped MSNs with an ideal surface area and pore volume for loading optimized ratios of antitumor DOX and the drug efflux inhibitor Tar. This strategically framed TTNV, which is chemically coupled with folic acid and HA, as a dual-targeted entity to promote folate receptor (FR)-mediated cancer cells and CD44-mediated CSC uptake, respectively[56].

Other nanodrug delivery systems

The N-(2-hydroxypropyl) methylacrylamide (HPMA) cyclopamine delivery system, as a selective macromolecular therapy for CSCs, has improved drug solubility and reduced systemic toxicity, allowing it to effectively remove CD133+ tumor stem cells in prostate tumors. HPI-1 was loaded with PLGA-PEG NPs to solve the problem of poor water solubility and effectively eliminate CD133+ CSCs in pancreatic and liver cancer[57,58].

GBM stem cells (GSCs) are the leading cause of chemotherapy failure in GBM. PLGA NP-encapsulated disulfiram effectively inhibited *in situ* and subcutaneous GSC xenografting in mouse models[59]. Although we are increasingly understanding GBM at the molecular level, treatment options are still limited. We have developed bioreducible poly(β-aminoester) NPs that exhibit high intracellular delivery efficacy and low cytotoxicity that have the ability to escape from endosomes and facilitate the

release of cytoplasmic environment-triggered cargo for the delivery of microRNAs to tumor-reproducing human CSCs[60]. In the study by Wang *et al*[61], a high temperature thermal breakdown approach was used to create composite magnetic nanocubes modified by PEI and HA. The ferric oxide nanocubes recognized hepatocellular carcinoma (HCC) stem cells *via* receptor-ligand binding of HA and CD44 (HA receptor), while loading small molecule LDN193189 inhibited the expression of stemness-related genes octamer-binding transcription factor 4 and Nanog. Double pH-sensitive polymeric drug-conjugated NPs showed enhanced inhibition of the progression of drug-resistant SK-3 CSCs, whereas AuNPs conjugated to Adr *via* nitrogen reduction bonds overcame resistance by avoiding P-gp efflux, thereby delivering more DOX to tumor stem cells. This mechanism resulted in the elimination of all tumor cell subpopulations and prevented the potential reaggregation of CSCs[62]. Tran *et al*[63] inhibited the transfer of MCF-7-SCs by inhibiting the EMT process, revealing the potential role of nanozinc sulfide in inhibiting the migration and invasion of bCSCs, which opened up a new way of thinking and provided a potential approach for the treatment of BC.

It has also been shown that the constructed amphiphilic polymer, HA-cystine-PLGA, can be used to deliver DOX and cyclopamine to CD44-high-expressing bCSC subpopulations and a large number of BC cells, and allow on-demand release. The dual delivery particles effectively reduce the number and size of tumor spheroids, and HA shows targeting effects on bCSCs[64].

Gao *et al*[65] proposed a novel intravenous photodynamic therapy (PDT) platform based on stem cell simulation of SUCNPs@mSiO2 for tumor targeting and enhanced PDT efficacy. Due to the coating of the stem cell membrane, the prepared nano SUCNPs@mSiO2 has good stability and biocompatibility. Moreover, it has the ability to be intravenously injected and escape immunity, extend the blood circulation time, and improve the tumor targeting function of stem cells, paving the way for the development of photosensitizers with bioactive cell components, such as SUCNPs@mSiO2, as a platform for targeting PDT. Sorafenib and glucose oxidase were integrated into the N-acetylgalactosamine-modified zeolite imidazolate framework (ZIF-8), designated SG@GR-ZIF-8, and this nano preparation exhibited significant antimetastatic HCC activity against C5 WN1 cells, a liver CSC-like cell line with tumorigenic and lung metastatic activity[66]. PT chemotherapy synergy was achieved by loading crocodile-based PT agents with natural cytotoxic heat shock protein (HSP) inhibitors that had high potency biradical characteristics into a redox-sensitive chitosan (CHI) matrix. Within solid tumors, PEG shells that prevent nano-assembled mono nuclei from phagocytosing were cleared quickly to expose the positively charged CHI, and the isolated peptide iRGD was further activated. This step drives tumor penetration of CHI NPs and allows CSC targeting by selective identification of CD44 proteins. Due to the inhibition and chemosensitization of HSPs, the designed nano assembly can completely eliminate CSCs and non-CSCs, thereby inhibiting tumor growth and metastasis[67]. Chen *et al*[68] used PLGA/d-alpha-tocopherol PEG 1000 succinate (TPGS) NPs for the first time with the combination of chemotherapy drugs and ATP-binding cassette (ABC) transporter inhibitors (ATIs) and used TPGS and PLGA to prepare NPs. Due to the overexpression of ABC transporters in CSCs, the combination of ATIs and chemotherapy drugs can overcome the multidrug resistance of CSCs. PLGA/TPGS NPs were prepared for the codelivery of DOX and extracellular lipopeptide composite to reach the tumor site with an optimized synergistic ratio, and resveratrol NP reduces cancer activity and decreases inflammation in CSC-rich oral cancer[69]. In addition to active targeting strategies, relying on intelligent changes in nanodrug size to penetrate deep into tumor tissues and improve the clearance rate of CSCs is also an important strategy for efficient reversal of MDR. On this basis, a special morphologically tunable nanodrug was developed, which integrated chemotherapy and immune checkpoint blocking therapy for large tumor cells and CSCs into drug delivery systems. As NPs are transferred from circulation to tumor tissue, particle size shrinks, favoring pharmacokinetics and cellular uptake while enabling sequential drug release when needed. The nanomedicine reduced the proportion of CSCs and enhanced the therapeutic effect on tumors, thereby prolonging the survival time of mice[70].

Liposomes

Liposomes are spherical vesicles consisting of one or more concentric phospholipid bilayer layers that enclose a water core. Liposomes are both nontoxic and biodegradable, making them powerful drug delivery systems. They improve the therapeutic effect of drugs by stabilizing compounds, overcoming barriers to cell and tissue uptake, and increasing the biological distribution of drugs at target sites in the body while minimizing systemic toxicity[71].

Tumor necrosis factor-associated apoptosis-inducing ligands (TRAILs) have received much attention for their favorable ability to activate apoptosis in cancer cells by interacting with death receptors (DRs). However, CSC-like cells lack or express low levels of the death receptor DR and are highly resistant to apoptosis mediated by TRAIL, limiting therapeutic efficacy. The liposomal component of the plasmid DNA encoding TRAIL and SAL enables cancer cells to express TRAIL as protein generators, and more importantly, to upregulate DR expression through SAL-induced CSCs, making drug-resistant CSCs sensitive to TRAIL-triggered apoptosis. This liposome-based programmable drug codelivery system shows the potential to effectively eliminate CSCs and inhibit CSC-rich tumor growth in mouse models of colon tumors *in situ*[72].

Gong *et al*[73] prepared and characterized SAL-loaded nanoliposomes (SLNs), DOX-LNs (DLNs) and SAL and DOX simultaneously delivered nanoliposomes (SAL/DOX). Novel SDLNs and SLN-DLNs are used to deliver SAL and DOX to HCC cells and CSCs. Hybrid lipo plastids (HLs) are nanosized liposome particles that can be prepared by the ultrasonic mixing of capsule and micelle molecules in buffer solution. The inhibitory effect of HLs on the growth of the CSC subpopulation of HCC cells (HepG2) has proven that HLs are a new type of nanomaterial that can be used to target CSCs in the treatment of HCC[74]. Dual-targeted liposomes CEP-LP@S/D selectively target CD133EpCAMlCSCs. Upon arrival at CSCs, CEP-LP@S/D liposomes undergo cytoplasmic endocytosis, in which high concentrations of glutathione break the disulfide bonds, thereby degrading the liposomes[75]. The combination of docetaxel liposome (DTXPL) and telmisartan (TEL) increased the cytotoxicity of H460 WT 3D cells two-fold. In H460 WT and DTX-resistant CD133+ xenograft tumor models, tumors treated with the combination of DTXPL and TEL showed reduced tumor volume, increased apoptosis, and downregulated CSC marker expression[76].

Lipid nanocapsule (LNC) encapsulated with paclitaxel and SAL can induce apoptosis in bCSCs, which is enhanced by the codelivery of paclitaxel and SAL. Synergistic cytotoxic effects on cells, non-bCSCs, and bCSCs, as well as effective reduction in tumor mammary globular growth by encapsulating both paclitaxel and SAL, suggest that LNCs have potential for the treatment of BC[77].These studies demonstrate the great potential of nanoliposome-targeted drug delivery to tumor stem cells.

GNRs and QDs

GNRs are pseudo-one-dimensional rod-like NPs, which have become one of the emerging materials of interest in recent years due to their anisotropic shape and adjustable plasma properties[78]. QDs, also known as nanocrystals, are NPs composed of II-VI or III-V elements that are rich in energy electrons and quantum-confined holes[79]. QDs are widely studied as biomedical imaging probes due to their unique optical and electronic properties. They are usually nanoscale semiconductor microcrystals and are widely used to improve the efficacy of fluorescent markers in bioimaging[80].

PKF118-310 (PKF) and vorinostat (SAHA) loaded on GNP corona Protein corona (PC), a AuNP system with protein corona coating for simultaneous delivery of PKF and SAHA resulted in a reduction of stem cell populations and Snail marker in MCF7 bCSCs[81]. Coloaded with GNRs and Adr, EpCAM was labeled by targeting the surface of CSCs to kill CSCs under laser ablation[54]. A novel fluorescent on nano aptamer sensor for the quantitative detection of CD133 has also been designed. By hybridization of CD133-targeting aptamers modified on the surface of QDs and AuNPs with partially complementary paired RNA (single-stranded RNA), the distance between the QDs and AuNPs is shortened, resulting in fluorescence resonance energy transfer between them so that the fluorescence of the QDs is quenched by AuNPs. The QD fluorescence recovery aptamer sensor is a sensitive and reliable sensor for the detection of CD133, providing a simple and promising detection tool for CSC markers[82]. Inhibition of glutamine decomposition may be an effective anti-CSC strategy. The glutaminase 1 (GLS1) inhibitor telaglenastat (CB-839) was loaded into Au pegylated NPs (Au-PEG-CD133-CB-839) equipped with covalently coupled CD133 aptamer. In an *in vitro* exposure to a CD133-positive brain tumor model, Au-PEG-CD133-CB-839 reduced the activity of CD133-positive cancer cells in a dose-dependent manner [83]. Glucose-installed-targeted NPs (Glu-NPs) demonstrated higher cellular uptake of siRNA payload in globular BC (MBA-MB-231) cell cultures compared to glucose-uncoupled control NPs (MeO-NPs). Glu-NPs, a promising nanocarrier design for CSC-targeted cancer therapy, caused significantly enhanced gene silencing in CSC-rich MDA-MB-231 tumor tissue in situ after systemic administration to tumor-bearing mice[84]. Liu *et al*[85] reported that SAL was conjugated with biocompatible AuNPs coated with PEG showed specific targeting ability and high antitumor efficacy against CD24 Low/CD44high subsets in BC cells. The biodegradable naturally negatively charged polysaccharide HA is used to synthesize AuNPs, while HA can act as a capping agent based on its hydroxyl group, thereby stabilizing newly produced AuNPs. HA-functionalized AuNPs exhibit excellent physical properties and high cell uptake and have a strong inhibitory effect on MDA-MB-231 cells and CSCs. In particular, synergistic chemothermal therapy with HA-capped AuNPs combined with NIR irradiation has shown more effective therapeutic results in terms of cytotoxicity, apoptosis, and necrosis compared with chemotherapy alone[86].

The disadvantage of metallic nanomaterials lies in their toxicity. Reactive oxygen species(ROS) generation, influence on cell structures and other characteristics of metallic NPs toxicity are similar to other NPs, and the toxicity is related to size, shape, dimensionality, surface charge. Therefore, metallic NPs should be carefully examined before used in clinic.

CNTs

The high surface-to-volume ratio, enhanced electrical conductivity, strength, biocompatibility, ease of functionalization, and optical properties of CNTs have led to their consideration as novel drug and gene delivery vehicles. CNTs are cylindrical tubes formed from sp2 hybrid carbon atoms, which can range in size from 1 nanometer to several microns. CNTs can be divided into single-walled CNTs (SWCNTs) and multiwalled CNTs (MWCNTs) according to the number of layers formed in them[87].

BCSCs have strong resistance to traditional hyperthermia, while PTT mediated by amino-modified multiwalled CNTs on the surface can effectively kill bCSCs[88]. CD133 is a currently recognized CSC marker for GBM. CNTs can be targeted to CD133-positive cells of GBM (GBM-CD133+) through a CD133 antibody. Wang *et al*[89] grafted a CD133 monoclonal antibody onto CHI-modified CNTs. Then, CSCs were effectively killed by PTT. The gastric CSC-specific targeted drug delivery system (SAL-SWNT-CHI-HA complex) is also based on CHI-coated SWCNTs loaded with SAL and functionalized with HA to selectively eliminate gastric CSCs[90]. SWCNTs facilitate active targeting due to their needle shape, significant transmembrane penetration, EPR effects, high drug loading capacity, and ease of functionalization of biological agents (*i.e.* antibodies). Surface functionalization with polymers such as PEG helps overcome the limitations of the original NTs, providing good water solubility, prolonging blood circulation, and reducing the toxic effects of SWCNT-based nanocarriers. The potential therapeutic effect of the combination of paclitaxel and SAL in BC and CSCs is mediated by a pH-responsive release mechanism near the acidic tumor microenvironment *via* a hydrazone junction[91].

GO

Driven by the achievements of CNTs, graphene, and GO are new types of drug nano carriers used to support a variety of therapeutic drugs, anticancer drugs, insoluble drugs, antibiotics, antibodies, *etc.*

GO is alleged to specifically target CSCs rather than normal cells and to induce CSC differentiation and inhibit tumor sphere formation in multiple cell lines, including breast, ovarian, prostate, lung, pancreas, and GBM cell lines, by inhibiting several key signaling pathways, including the Wnt, Notch, and signal tranducer and activator of transcription signaling pathways[92].

Choi *et al*[93] synthesized reduced graphene-silver nanocomposites (rGO-Ag) using the R-phycoglobin biomolecular mediated method. These composites have a toxic effect on ovarian CSCs (OvCSCs) and can reduce the survival rate of OvCSCs by decreasing the mitochondrial membrane potential and expression of apoptotic genes, leading to mitochondrial dysfunction and possibly apoptosis. RGO-Ag may be a novel nanotherapeutic molecule for specifically targeting highly tumorigenic ALDH+CD133+ cells and clearing CSCs.

PTT

PTT uses metal NPs to eradicate CSCs and stimulate a hyperthermal physiological response by converting light into heat[94]. MSNs under an alternating magnetic field eliminate CSCs by blocking the hypoxia signaling pathway and heating, thus effectively inhibiting tumor growth[56,95]. Burke *et al*[86] found that bCSCs have strong resistance to traditional hyperthermia, and PTT mediated by amino-modified multiwalled CNTs on the surface can effectively kill bCSCs. Wang *et al*[87] grafted CD133 monoclonal antibody onto CHI-modified CNTs. CD133 is currently recognized as a CSC marker for GBM, and CNTs can be targeted to GBM-CD133+ through the CD133 antibody. Then the CSCs were effectively killed by PTT. NPs loaded with bimodal metal cages and photodynamic therapys (PDT) PDTs target CSCs by reducing cell mobility under laser irradiation[96]. Researchers developed a CSC-specific-targeted, retinoic acid (RA)-loaded Au nanostar-dPG nanoplatform for the efficient eradication of CSCs. The nanocomposites possess good biocompatibility and exhibit effective CSC-specific multivalent-targeted capability due to HA decorated on the multiple attachment sites of the bioinert dPG. With the help of CSC differentiation induced by RA, the self-renewal of bCSCs and tumor growth were suppressed by the high therapeutic efficacy of PTT in a synergistic inhibitory manner[97]. Based on PTT properties of CNTs and metallic materials, nanoplatform functions with chemotherapy and PTT can be designed to produce synergistic effects.

Researchers have utilized MnO_2@Ce6 NPs and a PDT-based approach that improved tumor microenvironment-related therapeutic resistance by modulating the tumor microenvironment with excess hydrogen protons and water, resulting in subsequent radiation of CSCs[98]. Haldavnekar R *et al*. introduced nickel-based functionalized nanoprobe-facilitated surface-enhanced Raman scattering for the prediction of cancer dissemination by CSC-based surveillance[99]. MoS_2 nanosheets and a moderate PTT treatment were applied to target a CSC surface receptor (*i.e.* CD44) and modulate its downstream signaling pathway. The treatment showed attenuated self-renewal capacity, more response to anticancer drugs, and less invasiveness[100].

Although PTT can inhibit tumor growth by eliminating tumor stem cells, it is usually difficult to completely eradicate tumors due to the limited penetration depth of near-infrared (NIR) light. Therefore, combining PTT with other therapies is expected to overcome these challenges.

Magnetic fluid hyperthermia

MFH uses the good magnetic thermal conversion ability of magnetic NPs under the influence of an external alternating magnetic field to rapidly heat the internal tumor, forming a high-temperature zone, to kill tumor cells or induce their apoptosis[101].

When anti-CD44 antibody-modified SPIONPs are prepared, SPIONP-mediated hyperthermia can kill CSCs, and MFH significantly inhibits the growth of transplanted Cal-27 tumors in mice[59]. Nuclear targeting systems coated with MSNs of superparamagnetic iron oxide-based NPs can directly target CSCs and can be used to combine thermotherapy and hypoxia-activated chemotherapy with nuclear-

targeted drug release under an alternating magnetic field, ultimately leading to complete apoptosis of CSCs[73]. Biomimetic magnetic NPs induce apoptosis of stress-escape CSCs and inhibit their proliferation and metastasis *in vitro* and *in vivo* by the combined therapeutic effects of DOX chemotherapy and magnetic MSNs MFH under the action of an alternating magnetic field[102]. Antibody-modified NPs targeting lung CSCs enhance cellular uptake *in vitro* and prolong tumor accumulation *in vivo*. Due to the combined effects of hyperthermia and chemotherapy treatment, up to 98% of lung CSCs are killed by AMF within 30 min of application outside the body. In *in vivo* models, this combination therapy significantly inhibited tumor growth and metastasis in mice carrying lung CSC xenografts with minimal side effects and adverse reactions[103]. In summary, MFH shows great potential in targeting tumor stem cells.

FUTURE PERSPECTIVES AND CHALLENGES

The discovery of CSCs has made us gradually realize the complexity of tumors. CSCs are the roots of tumor occurrence, drug resistance, and postoperative recurrence. Therefore, the eradication of CSCs is of great significance for the treatment of cancer. At present, theoretical research on tumor stem cells is still in the initial stage, and many problems have not been solved. For example, CSCs and normal stem cells have very similar self-renewal, multidirectional differentiation, signaling pathways, and cell surface markers. How to effectively kill CSCs without damaging normal stem cells needs further research. Some regulatory mechanisms and biological behaviors of tumor stem cells have not been fully clarified. It is believed that with the continuous deepening of CSC research, more targets and a theoretical basis will be provided for clinical treatment.

In addition to effective drugs targeting CSCs, it is also necessary to consider the heterogeneity of CSCs to eliminate tumor cells and CSCs more effectively, inhibit recurrence and improve the survival rate of patients. Although great progress has been made in research on the molecular mechanism of cancer, cancer detection and treatment, and the treatment methods have been continuously improved, there is still a lack of effective treatments for cancer. The targeting, slow release, good biocompatibility, and stability of nanomaterials will play a huge role. In addition, nanotargeting technology is used to track the biological characteristics of CTCs[104]. The physical and chemical properties of each component of the tumor microenvironment are different from those of normal tissues, and the tumor microenvironment plays a huge role in the process of tumor occurrence and development, which makes the tumor microenvironment an important target for nanomaterial-targeted therapy[105]. Although there are still several difficulties in the wide application of nanomaterials in clinical practice, the most important of which is biosafety, there is still no convincing evidence that nanomaterials can be effectively metabolized in the body without accumulation and causing toxic side effects. In addition, how to improve the linking efficiency of targeted molecules and nanomaterials, the activity of targeted molecules after linking, the stability of the binding of targeted substances and drug carriers, and the metabolic pathways and toxicity of nanomaterials *in vivo* have not yet been solved. However, the strong ability shown in the early stages makes us hypothesize that nanomaterials for CSC-targeted therapy have broad prospects as a new generation of tumor treatment. With the continuous deepening of CSC research and the rapid development of nanotechnology, these fields will potentially overlap and provide a strong guarantee for cancer treatment.

CONCLUSION

Cancer is a huge barrier for researchers due to its high mortality rate and resistance to treatments. For example, multidrug resistance, recurrence, and the spreading nature of cancer cells make cancer extremely difficult to treat. CSCs are the main reason for inducing the characteristics of drug resistance and the regenerative ability of tumor cells. Therefore, the targeted system of cancer treatment began to turn to stem cell research. As an emerging field, nanotechnology is mainly applied to materials and carrier structures with diameters between 1 and 100 nanometers. Because nanomaterials have similar dimensions, they differ in composition, structure, hydrophobicity, magnetism, immunogenicity, and other properties. CSC therapies based on these unique properties have been extensively studied, but only a few have entered clinical trials. To better improve clinical translation, further research on targeted drug delivery of nanocarriers is needed to reduce toxicity, enhance permeability and retention, and minimize the shielding effect of the protein corona. By rationally designing and constructing new NDDS to accurately target CSCs that have developed drug resistance, the efficiency of reversing multidrug resistance and inhibiting tumor growth can be effectively improved, providing a tremendous opportunity to improve cancer treatment or prognosis, which will ultimately improve the survival rate of cancer patients.

FOOTNOTES

Author contributions: Yue M wrote the original draft of the manuscript; Guo T and Nie DY drew the charts; Zhu YX wrote and edited the final paper; Lin M was responsible for the overall direction of the paper and for editing of the manuscript.

Supported by Natural Science Foundation of Nanjing University of Chinese Medicine China, No. XZR2020093.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

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S-Editor: Yan JP
L-Editor: Filipodia
P-Editor: Cai YX

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