Review Article

Stem Cell INVESTIGATION

Cancer stem cells and nanotechnological approaches for eradication

Gholam Basati[1], Mojtaba Khaksarian[2], Saber Abbaszadeh[3], Hamed Esmaeil Lashgarian[4], Abdolrazagh Marzban[5]

[1]Clinical Microbiology Research Center, Ilam University of Medical Sciences, Ilam, Iran; [2]Razi Herbal Medicine Research Center & Department of Physiology, [3]Student Research Committee, [4]Department of Biotechnology, School of Medicine, Hepatitis Research Center, [5]Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran

Contributions: (I) Conception and design: G Basati; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: M Khaksarian, S Abbaszadeh; (V) Data analysis and interpretation: M Khaksarian, S Abbaszadeh; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Abdolrazagh Marzban. Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran. Email: marzban86@gmail.com.

Abstract: Cancer stem cells (CSCs) are currently known as the main cause of tumor recurrence. After chemotherapy is completed, CSCs proliferate and then differentiate to generate new tumor tissues. Similar to normal stem cells, this non-uniformly distributed cell population in the tumor tissue has self-renewal capacity and is responsible for survival of the tumor and difference in its genetic and metabolic characteristics. Followed by gene instability in CSCs, new phenotypic markers are aberrantly expressed in CSCs subpopulation. Hence, some of the surface markers and metabolic pathways that are upregulated in CSCs may be applied as specific targets for development of diagnostic and therapeutic approaches. In this review article, the distinctive properties of CSCs including signal pathways implicated in self-renewal and surface markers were discussed. Moreover, targeting CSCs based on their specific properties using nanodrugs was reviewed.

Keywords: Cancer stem cells (CSCs); self-renewal; nano-formulations; surface markers

Received: 14 August 2019; Accepted: 08 October 2019; Published: 28 November 2019.
doi: 10.21037/sci.2019.10.07
View this article at: http://dx.doi.org/10.21037/sci.2019.10.07

Introduction

After the theory of the presence of stem cells in the population of tumor cells was introduced by Bonnet *et al.* (1), several studies were conducted on how these cells were generated (2,3). In this regard, researchers sought to characterize cancer stem cells (CSCs) from cancer cell populations. Although these efforts gained relative success in the early stages of cancer, it failed to isolate a homogeneous population of CSCs in advanced stages (4,5) (*Figure 1*).

Subsequently, while observing a heterogeneous subpopulation in leukemia, researchers identified a small, clonogenic cell population whose characteristics were similar to those of blood stem cells. Given the clonogenic and heterogeneous nature of tumors, they suggested that there was a rare cell population in cancers that acted like stem cells and was responsible for tumor growth and metastasis. In fact, the results showed that CSCs could be derived from normal stem cells or from committed progenitor cells that had obtained self-renewal capacity (6,7). These cells are highly similar to normal stem cells with respect to self-renewal and metabolic characteristics (2). However, there are certain differences between CSCs and normal stem cells. These lead to different types of cancer cells with varying metabolic activity, and in different stages of tumor evolution, guarantee tumor survival under severe conditions, even under the influence of strong

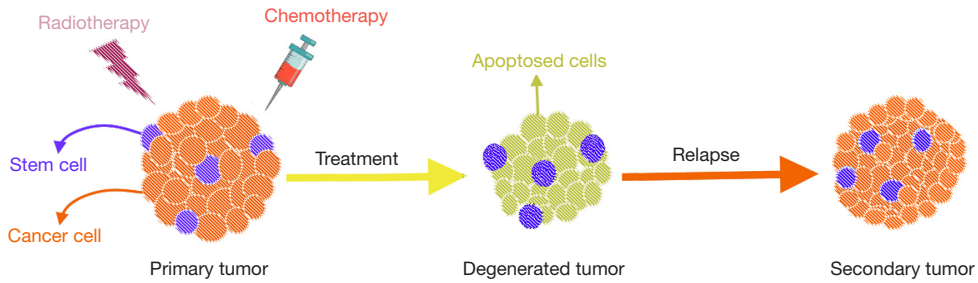

Figure 1 A schematic of the classical therapeutic approaches against a tumor growth. In the heterogeneous differentiation model, CSCs having potential of resistance to radiation and chemotherapy can cause recurrence of the tumor. CSCs, cancer stem cells.

chemotherapy drugs (8). Many studies have shown that CSCs are generated from genetic changes occurring in a cell population, and following the formation of these cells, the gene expression profile in cancer cells changes (9). With the changes in the genetic or epigenetic profiles of CSCs, new distinctions were emerged in the molecular metabolism, surface markers profile and signaling pathways, which were shown to be involved in self-renewal, drug resistance, proliferation and differentiation (10,11).

Currently, extremely few drugs with definitive outcomes have been developed with high efficacy against CSCs, such as salinomycin, cisplatin, doxorubicin, vincristine, paclitaxel and their synthetic derivatives, which have a highly disruptive impact on various cancer cells (12-17). Because of the non-specific toxicity of these drugs in all cells, only targeted nano-formulation drugs have the potential to target CSCs and break drug-resistance in cancer cells. Many nano-formulations have been developed as combinations of chemical and biological derivatives such as plant bioactive products and microbial secondary metabolites that might play a dual role in cancer treatment. For example, curcumin and its analogues, which are used in clinical cancer studies due to their anticancer and prophylactic effects, are able to decrease the side effects of chemotherapy and radiotherapy on normal tissues (12,18,19).

Another challenge lies in drug delivery to brain tumors that are strictly protected by brain-blood barrier (BBB). Actually, the BBB has been constituted of highly regulated structure that does not allow drugs present in blood circulation to be enter the brain tissue. Thus, many efforts have been conducted to develop effective drug delivery systems that are able to across the BBB. In this regard, to efficiently deliver therapeutic molecules to the tumor location in the brain, various nanopharmaceutical systems have been formulated such as lipid-based nanoparticles, hydrophobic nanocarriers, functionalized compatible polymeric nanoparticles etc (20-25).

Developing nanotechnology-based therapeutic systems have improved many of the known limitations of anticancer drugs, such as low water solubility, stability and non-specific toxicity (19,26). Additionally, these nanodrug formulations have indicated high potential of controlling the release of anti-tumor drugs and protecting them from rapid metabolization and elimination. The controlled release of drugs, rational design of specific targeting of cancer cells and accurate diagnostic techniques of these cells can help to treat cancer (27,28). In this respect, by detecting specific properties of CSCs, various formulations were developed via designing effective nanodrugs, which specifically target CSCs in tumor tissues (29,30).

This review paper discussed key pathways involved in the development and survival of tumor cells that may be appropriate targets for the design of antitumor drugs based on nanoscale formulations.

Targeting active genes in CSCs

New approaches to target genes that implicate in drug resistance, self-renewal and in CSCs are developed based on gene silencing by specific RNA inhibitors such as siRNAs, miRNAs and LncRNAs (31-35). For example, *MDR1* gene silencing in drug-resistant tumors can reduce the expression of P-gp transporters and increase the efficacy of chemotherapy (36). The low sustainability and accumulation of these therapeutic molecules have led to many efforts in recent years to design nanodrug delivery systems. For example, in a study of siRNA against Signal transducers and activators of transcription (STAT3) in PEI-PLGA nanoparticles as a part of a combination treatment, paclitaxel-siRNA was used for A549/T12

(paclitaxel-resistant cell line) (37). In another study, a lipid based nanocarrier was used to effectively deliver siRNA to lung cancer cells, A549 (38). In one other study, two siRNA including STAT3 and GRP78 were delivered using polycation-functionalized nanoporous silicon microparticles, resulting in suppressed STAT3 expression in MDA-MB-231 breast cancer cells and reduced self-renewal capacity of CSCs in tumor tissues (39).

CSCs targeting via specific surface markers

By characterizing the metabolic pathway, genetic profile, resistance pattern and microenvironmental condition in CSCs, many efforts were conducted to target these specialized factors via nanodrug delivery (40). Many surface biomarkers, specific to CSCs, such as Cx43, CD44, CD133 and $CD34^+$ can be used as targets for cancer treatment (38,41-43). Therefore, one of the most effective strategies for targeting various tumor cells is to link nano-formulations of drugs to specific antibodies against tumor markers. To treat pancreatic and breast cancer, efficient nano-magnetic particles in combination with gentamicin and in conjugation with anti-CD44 were applied for targeting CD44 marker in the surface of adult cancer cells (ACCs) and CSCs. This nano-formulation successfully eliminated complete tumor cells, especially CSCs (44). In addition, an efficient formulation of nano-curcumin was found to significantly inhibit anchorage-independent clonogenic growth and also reduce the stem cell population CD133 in medulloblastoma and glioblastoma (45). In another study, vincristine/silver nanoparticles conjugated to an anti-ABCG1 antibody was exploited for targeting myeloma cancer cells, which resulted in a synergetic cytotoxic effect on tumor cells in mice (46). Yang *et al.* (2014) applied an efficient formulation as a combination of γ-Fe2O3 nanoparticles and paclitaxel that was conjugated with anti-ABCG1 for inducing apoptosis gene expression and downregulation of the NF-κB gene in multiple myeloma CSCs (47).

Thus, with the advent of CSCs manifesting unique properties such as self-renewal ability and overexpression of surface markers, these specific surface markers are found to be ideal targets for designing novel drug formulations that are able to select and eliminate CSCs subpopulation (28,48,49).

These studies have led to the identification of a wide range of markers on the surface of CSCs. Some of the most specific markers for CSCs in human and animal cells are introduced in *Table 1*.

Signaling pathways for drug targeting

Molecular signaling pathways that control the homeostasis of normal stem cells are tightly regulated. These regulations are disrupted by changes occurring in many cancerous cells. Numerous studies have demonstrated that abnormalities in the cell regulatory system play a critical role in the promotion of self-renewal, cell survival, proliferation and differentiation of CSCs. During the tumor progression, the ability to self-renew CSCs may be increased, weakened or even missed through subsequent mutations (55,87,88). In fact, these signaling pathways may activate some genes involved in the formation of CSCs and relapse of cancer after chemotherapy. The signal network involved in the development of cancer covers many pathways, which express numerous cell surface markers, i.e., cell membrane proteins (89). These tumor markers are useful indicators for the design of diagnostic tests and also important targets for targeting antitumor medications drugs.

As CSCs can survive radiation and chemotherapy, specific identification of all tumorigenic components can represent an effective therapeutic strategy for targeting tumor integrity. In this regard, many efforts have been adopted to identify mechanisms of signaling involved in self-renewal, differentiation and proliferation. *Table 2* shows some signaling pathways including Hedgehog, Notch, Wnt/β-catenin, BmiI1, PTEN and TGF-β, which might be responsible for proliferation, proliferation, malignancy, drug resistance and tumor recurrence.

These signal pathways are currently attractive targets for drug delivery to tumor tissues, especially CSCs. Many efforts are made to disrupt signals associated to tumor progression as well as to self-renewal and differentiation of CSCs, which may lead to complete removal of a tumor.

One of the most important signal pathways is the Wnt/β-catenin pathway that is known as an essential activator of several transcription factors responsible for survival, self-renewal and differentiation properties of normal stem cells. It also appears that the Wnt/β-catenin signaling pathway can play a pivotal role in the formation of CSCs and establishment of their self-renewal capacity (90-92). In this regard, the role of the Wnt signaling pathway has been significantly confirmed in recurrence of breast cancer and myeloid leukemia as well as in progression of liver fibrosis alteration (93-96). In this context, Mao *et al.* (2014) showed that suppression of the Wnt signaling pathway led to the inhibition of the proliferation of CD44+Oct4–CSC subclone (97).

Table 1 Main specific markers that were found to be present over the various CSCs

Types of CSC origin	Specific marker	Reference
Prostate cancer	$CD133^+$/alpha2 beta 1 integrin/$CD44^+$, BMI-1, CD49f, integrins α2/β1, SCA-1, OCT3/4	(50,51)
Brain cancer	Cx43, $CD133^+$, CD44, CD163, $CD15^+$, $CD49f^+$, $CD90^+$	(52-57)
Colorectal cancer	$CD133^+$/$CD26^+$, $CD133^+$/$CD44^+$/$ALDH1^+$, $EpCAM^+$/$CD44^+$, $CD166^+$, $CD44^+$/$CD24^+$, $Lgr5^+$/$GPR49^+$, $CD133^+$, $CD44^+$, $CD166^+$, $E\text{-}CAM^{hig}$	(58-61)
Acute myelogenous leukemia and Ph1-acute lymphogenous leukemia	$CD34^+$, $CD38^-$, CD44, $CD123^+$, $CD90^-$, $CD19^+$	(1,62-64)
Chronic myeloid leukemia	$CD34^+$, $CD38^-$, $CD123^+$, $CD26^+$	(65,66)
Blast-crisis CML	$CD34^+$, $CD38^+$, $CD123^+$	(63)
Bone sarcomas	Stro-1^+, $CD105^+$, $CD44^+$, NKX2	(67,68)
Pancreatic cancer	$CD133^+$, $CD44^+$, $CD24^+$, ESA^+	(69,70)
Breast cancer	$CD44^+$, $CD24^-$/low, ESA^+, $CD49^{hi}$, $ALDH1^+$, $CD133^+$, $EpCAM^+$	(71-73)
Head and neck squamous cell carcinoma	$CD44^+$, $ALDH^+$, CD44/CD133	(74-76)
Gastric cancer	$CD133^+$, $CD44^+$, Lgr5, $CD90^+$, $CD71^-$	(40,77,78)
Melanoma	$CD20^+$, $CD133^+$, $ABCB5^+$, nestin, $CD271^+$	(48,79)
Hepatocellular carcinoma	$CD133^+$, $CD90^+$, $CD90^+$/CD45, $EpCAM^+$, $CD13^+$, $CD133^+$/$CD49f^+$, $CD44^+$	(80-82)
Ovarian cancer	$CD44^+$, $MyD88^+$, $CD133^+$	(83,84)
Lung cancer	$ALDH1^+$, Sca1CD45-PecamCD34, $CD133^+$, $CD90^+$	(85,86)

CSCs, cancer stem cells; CML, chronic myeloid leukemia.

Table 2 Signaling pathways involved in the self-renewal process of some CSCs

Tumor type	Signal pathway	Reference
Breast	Wnt/β-catenin, Hedgehog, Notch, PI3K/Akt/PTEN/mTOR, NF-κB, Jak/STAT	(74,75)
Glioblastoma	Hedgehog, Notch, PI3K/Akt/PTEN/mTOR, cAMP-Epac, NF-κB, Jak/STAT	(29,76-78)
Leukemia	Wnt/β-catenin, Hedgehog, PI3K/Akt/PTEN/mTOR	(79)
Gastrointestinal	NF-κB, Wnt/β-catenin	(80)
Liver fibrosis	Wnt/β-catenin, Jak/STAT	(81,82)
Prostate	Jak/STAT, PI3K/Akt/PTEN/mTOR,	(40,83)
Lung	PI3K/Akt/PTEN/mTOR, Wnt/β-catenin	(84,85)
Osteosarcoma	Notch, Wnt/β-catenin, PI3K/Akt/PTEN/mTOR, RANKL/RANK	(86,87)

Another important signal pathway is Hedgehog that regulates several genes during the development of embryogenesis in normal cells. Evidence shows that the abnormal activation of Hedgehog pathways promotes tumor cells to produce CSCs clone and enhance chemo-resistance and survival via induction of self-renewal capacity in CSCs (98). Since the crucial role of Hedgehog pathways has been well documented by several studies, nanodrugs targeting the regulatory molecules of Hedgehog pathways are good candidates for cancer therapy. In this respect, several nano-based drug formulations including nanopolymers containing anticancer drugs, siRNA, miRNA and drug-gene combination systems have been designed that target various molecules of Hedgehog

pathways in CSCs and/or ACCs (99-102).

The Jak/STAT pathway is a modulatory pathway that induces multiple signal cascades involved in self-renewal, proliferation and differentiation of CSCs. To inhibit the abnormal expression of Jak/STAT mediators, many efforts have been made through specific targeting by using nanosize molecules carrying different anticancer drugs or delivering some types of genes for suppressing oncogenes and/or activating apoptosis genes (34,37).

The Notch pathway is composed of five ligands (DLL1–4 and JAG1–2) and four receptors (Notch1–4) making up an integral transmembrane protein. Activation of the Notch pathway occurs through binding the related ligands to receptors on the surface of adjacent cells (48,61,103). This pathway contributes to development of embryonic stem cells and guarantees CSCs survival in cancer cells when Notch signaling is enriched by aberrant upregulations of related genes (80). On the other hand, with inhibition of the Notch pathway, self-renewal, clonogenic potential, chemoresistance and radioresistance ability significantly decrease (104).

The PI3K/Akt/PTEN/mTOR network pathway is evolutionarily conserved molecular network that has shown to possess a strategic role for controlling proliferation and differentiation. Recent studies have demonstrated the role of the PI3K/Akt/mTOR signaling pathway in tumor metastasis, propagation, and angiogenesis. Activation of PI3K increases the chemoresistance capacity of cancer cells occurring by overexpression of multidrug resistance protein 1 (MDRP-1) (32). PTEN acts as a negative regulator in PI3K/Akt signaling that can inhibit metastasis and autophagy by inhibiting the Akt/mTOR pathway. Additionally, PTEN signaling effectively contracts the PI3K activity leading to inactivation of self-renewal capacity as well as radio and chemoresistance functions in CSCs (99). Therefore, the PI3K/Akt/PTEN/mTOR network pathway appears to be an ideal target for cancer therapy using nano-based drug formulations (41,99,105).

Another important pathway contributing to development of CSCs properties including self-renewal, proliferation and differentiation properties is NF-κB complex that consists of five proteins with dimmers active feature. This complex is normally inhibited in cells by an inhibitor called IκB protein (61). Activation of NF-κB takes place by binding ligands such as TNF-α, IL-1β and bacterial cell ghost, resulting in ubiquitination/degradation of the IκB inhibitor and then in release of NF-κB, migration to nucleus and activation of gene transcription. Mutation in NF-κB has been shown to cause malignancies in several cancer cells such as gastrointestinal, thoracic, and head and neck malignancies as well as breast cancer and other tumors (106).

As can be reviewed in *Table 1*, signaling pathways contribute to acquisition of CSCs properties and consequently enhance survival with self-renewal and promote recurrence of the tumor after a conventional therapeutic regime such as radiation and chemotherapy. Currently, many researchers have focused on designing various nano-vehicles such as nanoparticles, nanocapsules and nanoemulsions, nanobiopolymers, nanolipid particles, graphene-based nanocomposites, etc. These formulations have been applied for loading various anticancer drugs, herbal drugs, and chemical and bacterial toxins for targeting tumor cells (107-110). Additionally, nano-vehicles have been documented to be efficient carriers for gene delivery into tumor cells to induce apoptosis pathways and inactivate resistance genes. *Table 3* presents some nano-vehicles applied for targeting tumor tissues, which are capable of eliminating CSCs.

Removal of CSC niche

Various abnormalities in the tumor tissues have offered some advantages such as radiation and drug resistance, tumor growth promotion, invasion and malignancy for cancer cells. Tumor microenvironment is highly abnormal region that caused by metabolic changes such as acidic pH, hypoxic condition, redox potential change, up-regulation of secreted proteins and hyperthermia. This unique condition can be applied to design drug formulations based on nanotechnology, which specifically target tumor cells (121-123).

Several studies are being conducted to develop various physico-chemical methods for destruction of cancer cells and their environments. In some of them, the goal is to release nanoparticles containing the drug, which is followed by photodynamic therapy with radiation (114). In various studies, gold nanoparticles of 10–20 nm in diameter modified with specific antibodies against EGFR1 or MUC1 have been used (124). Radiation to gold nanoparticles causes a localized increase in temperature around the tumor, leading to rapid destruction of cancer cells, in which these nanoparticles accumulate (125). Wolf *et al.* (2015) have recently used goserelin-conjugated gold nanorods to increase radiosensitization for effective internalization of gold nanoparticles to prostate cancer cells through

Table 3 Nano-formulations of anticancer drugs for targeting different cancers.

Formulation type*	Tumor type**	Function***	Reference
Paclitaxel (Ptx) loaded in folic acid-PLGA	Ovarian cancer	Induction and high expression of apoptotic factors in CSCs	(13)
Gemcitabine combined with iron oxide magnetic NPs and functionalized with anti-CD44 antibody	Human pancreatic cancer and breast cancer	Inhibition of proliferation in both CSCs	(44)
Acetazolamide alone or combined with temozolomide	Glioblastoma multiforme	Removal of CSCs in exposing with the combined treatment	(111)
Lawsone encapsulated in noisome	Breast cancer	Encapsulation increased antitumor activity of lawsone against MCF-7 cells	(112)
Difluorinated curcumin encapsulated in liposome	Head and neck cancer	Inhibition of proliferation in cisplatin resistant CSCs	(76)
Salinomycin in combination with graphene oxide-AgNPs (RGO)	Human ovarian cancer	Combined formulation increased apoptosis levels in the cells 5-fold more than single therapy	(113)
Salinomycin Encapsulated in PEG-PLA copolymer	Pancreatic cancer	Increase of cell mortality through induction of apoptosis	(14)
Magnetic-nanoemulsion of chloroaluminum phthalocyanine combination to hyperthermia and photodynamic therapy	Mesenchymal stem cell	Reduction of cell viability by photodynamic therapy in combination to magnetic nanoparticle/chloroaluminum phthalocyanine formulation	(114)
AgNPs combined with vincristine and functionalized with anti-ABCG2 monoclonal antibody	Myeloma cancer (mice)	Inhibiting the growth of myeloma CSCs $CD44^{+}CD24^{-}$ CSC	(46)
Graphene oxide (GO) nano-therapy	Breast, ovarian, prostate, lung, pancreatic and glioblastoma (brain)	Inhibition of signal transduction pathways (Wnt, Notch and STAT-signaling) by striking effects and differentiating the CSCs	(91)
cisplatin and demethoxycurcumin loaded in amphiphilic carboxymethyl-hexanoyl chitosan	Lung cancer	MDR lung CSCs were significantly targeted by CD133-biofunctionalized nanoparticles and inhibit using drugs	(12)
Doxorubicin encapsulated in liposome	Liver cancer	Induction of apoptosis in HepG2 cells by activating caspase-3	(16)
microRNA-34a delivery using nano-vesicle	Gastric cancer	Targeting tumor cells by gene delivery and inhibiting the growth in CD44-positive tumor-bearing mouse models	(31)
Magnetic nanoclusters (MNC) exposure	Breast cancer	Hyperthermia mediated magnetic field progressed apoptotic cell death	(115)
A cocktail of Ptx, the thioridazine and the PD-1/PD-L1 inhibitor loaded in micelle-liposome double-layer structure	Breast and lung cancer	Suppressing the metastasis process in lung cancer cells and Inhibition of the growth of breast cancer cells	(116)
mesoporous silica nanoparticle (MSN) with anti-CD133 antibody linked to MSN along with thermal treatment	Breast adenocarcinoma cancer	Nano-delivery system efficiently inhibits the tumor growth	(117)
Ptx and siRNA loaded in polymeric nanostructure containing PEI(1200), polyethylene glycol and a lipid carrier	Colon cancer	Silencing the multidrug resistance gene (MDR1) by siRNA exhibited synergistic effect with Ptx	(32)

Table 3 *(continued)*

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Formulation type*	Tumor type**	Function***	Reference
miRNA delivery by poly-β-amino ester nanoparticles	Glioblastoma	Co-delivery of two miRNAs, miR-148a and miR-296-5p, using the nanopolymer functionalized-bioreducible amino ester group enhanced survivability of mice bearing glioblastoma	(33)
Combination of nanoquinacrine (NQC) and GW280264 (ADAM-17 inhibitor loaded in PLGA	Cervical cancer (CC)	Combination treatment of the cells with NQC and GW280264 decreased the proliferation and invasion rates, induced nectin-4 expression resulting in metastasis inhibition and the activation of base excision repair (BER) pathway	(118)
Gene delivery (PCPS-STAT3 siRNA and PCPS-GRP78 siRNA) using polycation-functionalized Nanoporous silicon microparticles (PCPS)	Breast cancer	Delivery of PCPS-STAT3 siRNA and PCPS-GRP78 siRNA reduced STAT3 expression in MDA-MB-231 breast cancer cells, causing remarkable reduction of CSCs in the tumor tissue	(34)
Ptx encapsulated in liposome	Ovarian cancer	Intraperitoneal delivery of nanoliposome-Ptx shifted metabolic program toward the oxidative phosphorylation and resulted in the suppression of CSCs	(119)
Zinc sulfide (ZnS) nanoparticles	Breast cancer	ZnS nanoparticles exhibited high potential of inhibition against migration and invasion of CSCs	(120)
Disulfiram in combination with copper, CI-isobologram, 5-FU and sorafenib encapsulated in PLGA	Liver cancer	DS-PLGA combined with copper, significantly inhibited the liver CSCs. CI-isobologram exhibited significant synergistic cytotoxicity against liver cancer when co-delivered with (5-FU)-DS-PLGA or sorafenib-DS-PLGA	(96)
Gamma-Fe_2O_3@DMSA in combination with Ptx and anti-ABCG2 monoclonal antibody	Multiple myeloma cancer	Ptx and anti-ABCG2 antibody remarkably inhibited the growth of $CD138^-CD34^-$ cells through elevation of expression of caspase-9, caspase-8 and caspase-3, and down-regulation of NF-κB were observed in CSCs	(47)
Epirubicin absorbed on nanodiamonds	Hepatic cancer	Epirubicin-nanodiamonds showed an enhanced cytotoxicity against both CSCs and non-CSCs *in vitro* and *in vivo*	(17)
Ptx and STAT3 siRNA loaded in PLGA-PEI	Lung cancer	PLGA-PEI-Ptx-S3SI efficiently suppressed STAT3 expression and induced the activation of apoptosis pathway in A549 and A549/T12	(37)

*, the first column demonstrates various types of nanoformulations that obtained from current therapeutic systems; **, second column shows tumor cells or tissues that were treated by nanodrugs; ***, third column summarized function of nano-vehicles. NPs, nanoparticles; CSCs, cancer stem cells; AgNPs, silver nanoparticles; RGO, reduced graphene oxide; CI, combination index; 5-FU, 5-fluorouracil.

interaction between goserelin with related receptors (126). In a study on treatment of breast cancer spheroids, lipid and polymer nanoparticles containing drugs were used along with ultrasonic waves. Effective treatment for solid tumors requires uniform distribution of anticancer drugs in all parts of the tumor, and the lethal concentration of the drug should be delivered to all resistant cells and CSCs (127). However, penetration of lipid and polymer nanoparticles into hypoxic and necrotized areas of solid tumors, which contain a large number of CSCs, is a major challenge (128).

Perspective of CSCs

With the assumption of the CSC hypothesis as the major cause of recurrence, heterogeneity and drug resistance of cancer, many researchers concluded that achievement of an effective treatment strategy for complete eradication of tumor masses by focusing on CSCs behavior could be the only way to permanent success in cancer therapy. In fact, such unclear issues related to CSCs refer to aberrant expression of some key genes involved in regulation and integrity of genome and epigenome (35,129,130). In

some tumors, which genetic changes do not occur at the phenotype surface, genetic differences can be detected among cancer cells subpopulations through genomic profiling studies, which can provide a rational solution for targeting CSCs inside the tumor masses (10). However, it should be noted that despite recent advances in CSCs, due to the highly complicated behavior of CSCs, for targeting this rare population, an in-depth knowledge is needed about details of specific features of CSCs so that a successful therapeutic outcome could be obtained.

Conclusions

For treating cancer, the disease must be first recognized well, which can be accelerated and facilitated by identification of CSCs. Many researchers believe that instead of concentrating on the treatment of solid tumors, we must focus on the metastasis and complete removal of cancer cells, and in this way, strategies should be utilized to overcome drug resistance and combination therapies. Nanomedicine has a high potential to accelerate the development of effective strategies for treating drug resistance and recurrent cancers. Despite known advances in drug delivery systems and development of nano-based approaches, serious barriers have remained unresolved, including inappropriate absorption and distribution in tumor tissues, obstruction by limbs and reticuloendothelial system macrophages after systemic administration and limited oral bioavailability of these therapies *in vivo* conditions. It is hoped that the new therapeutic strategies based on nanotechnology could pave the way for eradication of cancer, which is currently a serious concern worldwide.

Acknowledgments

The authors are appreciated to Lorestan University of Medical Sciences, Razi Herbal Medicines Research Center, researcher staffs for kindly contribution in all preparation of review article.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/sci.2019.10.07
Cite this article as: Basati G, Khaksarian M, Abbaszadeh S, Lashgarian HE, Marzban A. Cancer stem cells and nanotechnological approaches for eradication. Stem Cell Investig 2019;6:38.