

REVIEW ARTICLE

Application of Nanotechnology in Targeting of Cancer Stem Cells: A Review

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Cancer is increasingly apparent as a systems-level, network happening. The central tendency of malignant alteration can be described as a two-phase procedure, where an initial increase of network plasticity is followed by reducing plasticity at late stages of tumor improvement. Cancer stem cells (CSCs) are cancer cells that take characteristics associated with normal stem cells. Cancer therapy has been based on the concept that most of the cancer cells have a similar ability to separate metastasise and kill the host. In this review, we addressed the use of nanotechnology in the treatment of cancer stem cells.

Keywords: Cancer stem cell, Nanomaterial, Targeting, Markers, Signaling pathway

Introduction

Progress in preclinical and clinical cancer research has brought new diagnostic and therapeutic options for cancer patients that would provide significant improvements in the treatment and prevention of cancer (1). The most life-threatening aspect of the cancer is metastasis that spreads

cancer cells from their original tissues to other ones (2). Cancerous tissues include collections of heterogeneous cell populations that are different in their apparent state of differentiation (3). These heterogeneous populations contain particular types of “tumor-initiating” cells arisen from mutations of normal stem cells (4). Stem cells are undifferentiated cells which were found in multi-cellular organisms. They have three main properties including differentiation, self-renewal, and homeostatic control (3). Accordingly, tumor-initiating cells were called “cancer stem cells” that have the capacity for self-renewal, being able to differentiate into any cell, and the proliferative ability to expand malignant cells (4). Although the exact cause of cancer is unknown, the understanding of the balance between self-renewal and differentiation is an essential way to prevent cancer formation and the therapeutic utilisation of stem cells in human diseases. Current cancer therapies including radiotherapy, surgery, and chemotherapy intend to destroy or kill every cell of the body (5). Cancer stem cells (CSCs) do not destroy easily with con-

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ventional methods of cancer treatment such as chemotherapy and radiation. Although, anticancer drugs can lessen tumor size, but do not kill cancer stem cells. Though CSCs might only create up a small part of a tumor, their resistance to drugs lets them persist. Therefore, the identification of tumor-initiating cancer stem cells (CSCs) is of significant interest in cancer research and suggests varied approaches (6). In the last few decades, nanotechnology and nanomaterials have found essential roles in cancer diagnosis and treatment for better early detections and also, more efficient drug delivery to the tumor cells. This review aims to highlight the opportunities and challenges for integrating the nanoscience with cancer biology and thereby, researches regarding the advanced nano-based detecting systems for cancer stem cells.

Cancer Stem Cell

Cancer is defined as a biological condition with an uncontrolled division of the natural body cells. Until now, the complete treatment of cancer as a disease is difficult and costly. One reason for this difficulty relates to the presence of specific receptors on the surface of the cancer cells that pump the drugs out of the cells. Therefore, it is difficult to find a drug to eliminate these cells. However, all cells involved in tumor development are not equally dangerous. The leading cause of cancer is a group of dividing cells with high power and high resistance to the drugs that they called CSCs. CSCs are the cells in tumors or blood that are known particularly with the ability to turn into all cell types that are found in the host body. CSCs were identified and characterized in the 1990s, when a stem cell biologist, John Dick, said that his team had isolated scarce cells in the blood of people with leukemia that seemed to have a crucial role in cancer (7). Most researchers believe that CSC, in addition to leukemia, exists in solid tumors such as prostate, breast, and pancreas cancers. They can renew and keep themselves in the tumor masses (8-10). CSCs differentiate into several types of cells through the renewable process that can be the reason for the tumor formation. Such tumor cells as a distinct population remain and cause the disease to recur, metastasis and tumor development.

Some of the characteristics of the CSCs are similar to normal stem cells. These cells have extraordinary capability of self-renewal, differentiation and proliferative potential. The CSCs have been identified in tumor tissues and cell cultures by detecting the expressions of specific protein markers, such as CD133, CD44 and CD24 (11-13). Table 1 shows the markers of cancer stem cells in a variety

of solid tumors (6, 10, 12, 14-31). The CSCs have the potential to be adapted to different environments. Therefore, the high flexibility of the CSCs can be used as a high potential for changing the plasticity and rigidity of their network (32). Environmental changes would often be strong enough for increasing the tumorigenicity of cancer stem cells (33). Generally, studies and trials have shown that the CSC self-renewal potential is determined by the high proliferative potential with a loss of regular differentiation program and high efficiency in response to environmental changes. The CSCs have two main phenotypes include the proliferative and quiescent state that characterized by symmetric and asymmetric cell divisions. The cancer stem cells with proliferative phenotypes have symmetric cell division and are less aggressive and could be classified as a plasticity network (34).

On the other hand, the CSCs with the quiescent phenotype have asymmetric cell division with dynamic properties and are classified as a rigid network (35). The CSCs with quiescent phenotype may be the main factor in the metastasis that would appear years after surgical treatment of a primary tumor. Protection of the CSCs against therapeutic agents and their resistance to the treatment process can be obtained by, quiescence, expression of ABC (ATP-binding cassette) drug pumps, increased expression of anti-apoptotic proteins and resistance to DNA damaging agents (Fig. 1).

It can be concluded that the tumor cells without the CSC marker would be killed by chemotherapy, resulting in tumor regression, but the cells with the CSC markers are resistant to the treatment and their number would be risen in a tumor (36-38). Surface markers of the CSC, in many types of cancers, are shown in Table 1.

The percentage of CSCs are different in many types of cancers (39, 40) and there are relations between the num-

Table 1. Cancer stem cell markers in a variety of solid tumors

Type of cancers	Markers	References
Leukemia	CD34 ⁺ /CD38 ⁻ /CD96	(10, 15, 16)
Breast cancer	CD44 ⁺ /ESA ⁺ /CD24 ⁻ /ALDH1	(10, 12, 17)
Brain cancer	CD133 ⁺	(18, 19)
Multiple myelomas	CD138 ⁻	(20, 21)
Pancreatic cancer	CD44 ⁺ /CD24 ⁺ /ESA ⁺	(6, 22)
Colon cancer	CD133 ⁺	(23)
Liver cancer	CD133 ⁺ /CD90 ⁺	(24, 25)
Prostate cancer	CD44 ⁺ /CD133 ⁺	(26, 27)
Lung cancer	CD133 ⁺	(28)
Ovarian cancer	CD133 ⁺ /CD44 ⁺ /CD117 ⁺ / CD24 ⁺	(29-31)

ber of CSCs and patient prognosis (41, 42). Studies have demonstrated that cancer therapy could target the tumor cell mass and create a partial regression of a tumor, but the CSCs could make and develop new tumor clones, therefore, identification and directed targeting against this kind of stem cells have been reported to be more effective (Fig. 2) (40, 43). Cancer therapy, based on this hypothesis, was reported to decrease mechanisms of resistance to conventional chemotherapeutic drugs and radiation therapy. The new design of cancer therapeutic drugs could eliminate the CSCs by interfering with the specific pathways (44-48).

Scientists and researchers have suggested that comprehension of disorders in signal pathways or too much activation is one of the most vital importance for anticancer targeting of the CSCs. Wnt, Notch and Hedgehog signaling pathways have critical roles in the reappearance and maintenance of cancer stem cells (49). Wnt marks a group of signaling proteins that bind to surface receptor molecules on the target cells. Activation of Wnt target genes happens by β -Catenin. Also activated Wnt/ β -Catenin signaling has been reported to be a key feature of epithelial cancers, epithelial-mesenchymal transition (EMT), and maintenance of the CSCs of melanoma, breast, colon, liver and lung cancers (50).

Notch signaling pathway has a critical role in the cell-fate decision, tissue patterning, morphogenesis (51), and maintenance of the glioblastoma and breast cancer stem cells (52). A reported study about Notch signaling

pathway suggested that Notch inhibition in glioblastoma could decrease cancer stem cells via an endothelial cell intermediate (53).

Studies have suggested that the Hedgehog (Hh) signaling can regulate many cancer stem cells including glioblastoma, pancreatic adenocarcinoma, breast cancer, multiple myeloma, and chronic myeloid leukemia (CML) (20). Hh signaling has been found to play multiple roles in development, homeostasis and disease by activating the 7-pass transmembrane protein Smoothened (Smo), to send an intracellular signal. Due to that, the most advanced types of Hh antagonists are Smo-targeted (54, 55). Targeting the signal pathways including the Wnt, Notch, and Hh may improve current strategies for cancer therapy. Although, anti-cancer treatment can reduce tumor size, survived CSCs would trigger tumor formation again. This type of relapse causes metastasis and more resistant to treatment. Therefore, most currently available cancer treatments such as hormone therapy, radiotherapy and chemotherapy, would not be useful in the elimination of cancer stem cells (5). Specific targeting of tumor stem cells has been suggested to be an efficient alternative for cancer treatment (10, 11).

Cancer Treatment with Nanotechnology

Today, cancer mortality is one of the most common causes of death. The application of nanotechnology in

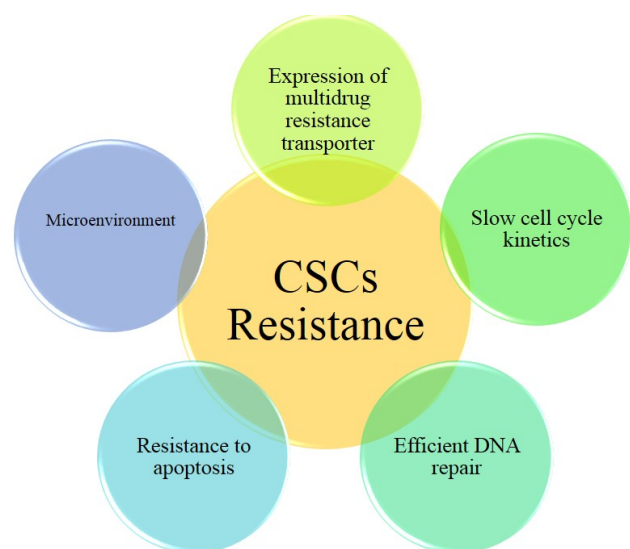


Fig. 1. CSCs resistance to treatment can be obtained by, expression of ABC drug pumps, increased expression of anti-apoptotic proteins, resistance to DNA damaging agents, and slow cycle kinetics.

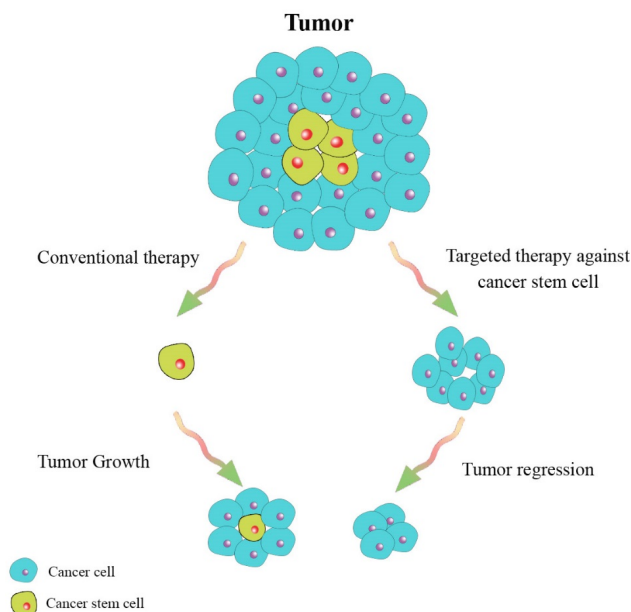


Fig. 2. A schematic illustration showing targeted therapy against cancer stem cells and tumors bulk.

medicine includes six areas including 1) detection of molecular changes in diseases; 2) diagnosis and imaging; 3) drug delivery; 4) combined therapeutic and diagnostic applications; 5) report of therapeutic agent efficacy; and 6) nanotechnology applications in scientific discovery and basic research (56). A variety of nanostructures from organic and inorganic materials have been recently used for cancer therapy and diagnosis in passive or active tumor targeting. A novel formulation of nanovesicles, liposomes, polymeric micelles, dendrimers, and polymeric nanoparticles can enter into the solid tumor site through the porous structure of a tumor vascular system, and then, selectively deliver the therapeutic agents (57, 58). Nanomaterials with proper targeting ligands could bind to antigens or receptors on the target cells. However, this powerful technology leads to a decreased toxicity in non-targeted cells, and therefore, the distribution of nanomaterials will be increased in the target cells (59). Some of the nanomaterials shown in Table 2 (60-73) such as semiconducting nanoparticles or quantum dots (QDs), colloidal nanoparticles, dendrimers, magnetic nanoparticles (MNPs), carbon-based nanomaterials (CBNs), and liposomal nanoparticles systems have been constructed for utilization in therapeutic applications. Quantum dots (QDs) are semiconducting nanoparticles with the diameter ranging from 2~10 nm, narrow emission and broad absorption profile, high photostability, long fluorescence lifespan, ability to be conjugated with proteins (74). Also, QDs have the potential of applications in molecular and cellular labelling, cell tracking, drug delivery and also, cancer detection and therapy (75, 76). Dendrimers are

highly branched synthetic polymers (about 1.5~13.5 nm) (77, 78) that have attracted considerable attention because of their hyper-branched structure, monodispersity, functional surface groups, and symmetrical conformation (79).

Furthermore, they have various types of core molecules, such as ethylenediamine, cysteamine, diaminobutane, carbohydrate, calixarene, etc. and functional surface groups like amino, carboxyl, hydroxyl that give the opportunity to modify their surfaces with biomolecules (80). Polyamidoamines (PAMAMs) are the most widely studied dendrimer because of the polycationic properties that can have interaction with charged molecules (81). Gold nanoparticles (GNPs), with diameter size of 0.8 to 200 nm have been used for imaging, targeting, drug delivery, and therapy applications. Biological molecules can be readily attached to the surfaces of the GNPs. Binding of molecules including biotin, peptides or oligonucleotides enhances cell penetration efficiency of the nanoparticles. Surface plasmon resonance of GNPs is used to many applications such as hyperthermia (82). Superparamagnetic NPs (SPIONs) are small synthetic particles of iron oxides with a core size of 0~10 nm. They show new magnetization behaviour totally like standard paramagnetic materials, but with, high field irreversibility, high saturation field, additional anisotropy contributions or shifted loops after field cooling (83, 84). Also, after eliminating the magnetic field, they do not show magnetic interactions (85). The SPIONs well-dispersed in a liquid and especially in water have drastically increased their biological and medical applications in recent years. Applications of SPIONs are diagnosis, therapy, and drug delivery system; Moreover, recent systems are

Table 2. Various nanomaterials for therapeutic applications

Nanomaterial	Ligand	Target	References
Quantum dot	HER2/neusiRNA	SKBR3	(60)
Quantum dot/Chitosan	DNA aptamer	A2780/AD	(61)
Quantum dot	HER2; RNase A	MGC-803	(62)
PAMAM	Tf and Tm	glioma Dual-targeting	(63)
PAMAM	Biotin	HeLa	(64)
SPIONs- $\alpha v \beta 3$	Anti αv antibody RGD peptides	$\alpha v \beta 3$ Integrin Breast cancer	(65)
SPIONs-PEG-Ab	Monoclonal Ab A7	Colorectal carcinoma	(66)
Gold nanoparticle	Folic acid	Ovarian cancer	(67)
Gold nanoparticle	Bombesinpeptides	Human prostate cancer cells	(68)
Gold nanoparticle	Transferrin	Hs578T (breast cancer) and a nonmalignant cell lines (3T3)	(69)
MWCNT	Folate (biologically active targeting) and iron (magnetically passive) targeting	HeLa	(70)
SWCNT	Hyaluronic acid Salinomycin	cancer stem cells (CSCs) Gastric	(71)
Graphene oxide	Rituxan (CD201 antibody)	CEM.NK T-cell and Raji B-cell	(72)
Nanoliposome	Anti-HER2	HER2- overexpressing breast cancer	(73)

used on stem cell differentiating/tracking (85, 86). Carbon-based nanomaterials (CBNs) are one of the most widely used tools in the fields of biomedicine, biotechnology, environment, and electronics (87, 88). CBNs with excellent physical, mechanical, electronic, and biological properties are engineered by using graphite, in different types of graphene, fullerene, and single- or multi-walled CNTs (89). Besides, modification of CBNs with biomaterials have been utilized in imaging, delivery systems, targeted therapy, tissue scaffold reinforcements, and bio-detection systems (90). Liposomes, as the most clinically established nano-scaled platforms, are merely formed from phospholipids and cholesterol by a self-assembling method in aqueous media in a variable size distribution from 20~1000 nm (91). The most application of liposomes is in drug delivery systems in which encapsulated drugs could be protected and directly delivered to the cells within lipid bilayers (92). Fig. 3 demonstrates the various nanomaterial that targeted cancer stem cells.

Targeting Cancer Stem Cells with Nanomaterials

The CSCs are believed to drive tumor growth and be highly resistant to conventional therapies (e.g. chemotherapy and radiotherapy) and lead to disease relapse and the formation of metastases. Therefore, there is consid-

erable interest in the use of nano-sized materials for CSC-directed anti-cancer therapies. The surface of nanoparticles has been designed to accurately and effectively target the CSCs (93). Identification of the CSC is possible by some markers, e.g. ALDH, CD44, CD90, and CD133, and specific signaling pathways, i.e. Notch, Hedgehog and transforming growth factor- β (TGF- β) (94, 95) to improve the treatment strategies and therapeutic outcomes (96).

Aldehyde Dehydrogenases (ALDH) marker

Aldehyde Dehydrogenases (ALDH) is a functional marker of the CSCs and also, the scavenger of reactive oxygen species (ROS) (97-99). Studies have been demonstrated that ALDH activity of converting retinol to retinoic acid increases in many cancers (100, 101), such as cervical cancer (102), non-small cell lung cancer (103), melanoma (104), and also is considered as a specific marker of BCSCs in breast cancer (105). Disulfiram (DS), is a specific inhibitor of the ALDH that have cytotoxic effects on a wide range of cancer cell lines including colon, breast and brain ones (106-112). However, its clinical application is limited due to very short half-life in the bloodstream. A study revealed that encapsulation of the by poly (lactic-co-glycolic) acid (PLGA) nanoparticles (DS-PLGA) causes longer circulating time in the blood-

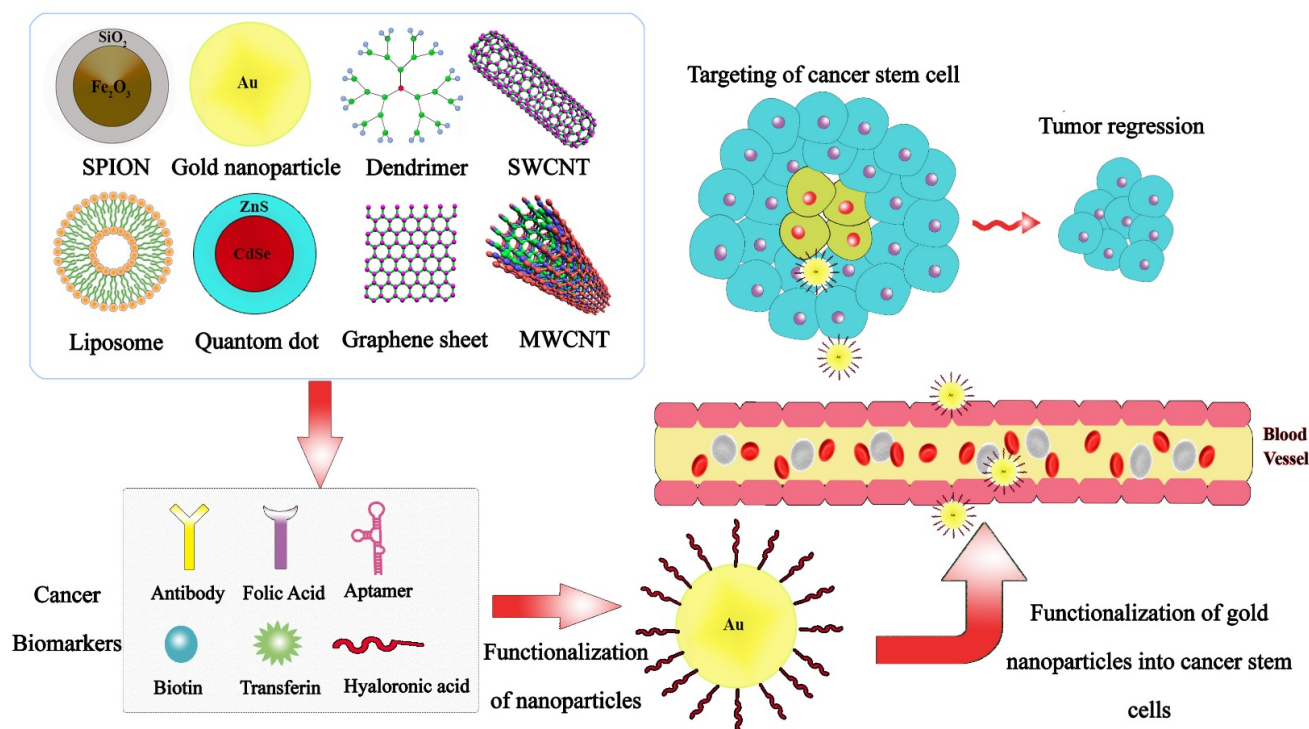


Fig. 3. The schematic representation of targeting cancer stem cell via functionalized nanomaterial.

stream, and also, DS-PLGA/Cu combination manifests very likely synergistic cytotoxicity effect with 5-FU and sorafenib. Finally, the results suggest that nano-based controlled delivery system would make DS fast translation into liver cancer cells (97).

CD44 factor

CD44 factor is one of the most popular and familiar surface biomarkers associated with cancer stem cells (113). Clinical studies have demonstrated the CD44 as one of the most critical proteins in tumor genesis, growth, metastasis, and chemo-resistant processes in a variety of tumors in colon, breast, head and neck, and pancreatic cancers (26, 114, 115). Antibody-based cancer treatments, over-expressing CD44, represents the dominant anti-CSC approach specifically in BCSCs (116). In a study, active targeting and drug delivery to the breast and colon cancer cell lines was evaluated by biodegradable poly[D, L-lactide co-glycolide)-co-PEG] (PDLGA-co-PEG) polymeric micelles loaded with paclitaxel (PTX) and functionalized with anti-CD44 antibodies. Evidence has shown that active-targeted PLGA-co-PEG-PTX micelles increase the intracellular concentration of PTX, and therefore, the effectiveness of drug delivery to the CSC (117). Arabi et al. (118) have demonstrated the selective drug delivery potential of liposomal doxorubicin functionalized with anti-CD44 and increased circulation time, biodistribution and therapeutic efficacies of CD44-Doxil compared to the non-targeted liposomal formulation and free drug. Magnetic NPs (MNPs) with anti-CD44 antibody have also shown the potential selective treatment of CD44 positive cancers such as pancreatic and breast cancers cell lines (119).

CD133 Marker

As mentioned before, the CSCs can be identified by detection of the CD133 expression as a stem cell marker and also, is explicitly regarded as a marker in osteosarcoma. The potential of CD133 targeting for drug delivery to the CSCs in osteosarcoma has been examined previously. It is illustrated in a study that Poly (lactic-co-glycolic acid) nanoparticles conjugated with CD133 aptamers would deliver salinomycin specifically and efficiently to the CD133⁺ CSCs in osteosarcoma and kill them (120). In another new form of drug nanocarrier, mesoporous silica nanoparticles (MSNs) have been used to deliver both antitumor drugs and siRNA into CD133⁺ cancer cells. This formulation significantly improved the efficacy of therapeutic drugs in laryngeal cancer cells (121). Curcumin and some other

natural chemopreventive agents have recently been shown to inhibit the CSCs, but with low bioavailability.

Furthermore, various nanotechnology-based formulations of curcumin have been recently evaluated as well. Preparation of the nanoscale drug delivery systems has been considered as an innovative approach to overcome the bioavailability and stability issues. For instance, it has been shown that a polymeric nanoparticle (made by mixing N-isopropylacrylamide, vinylpyrrolidone, and acrylic acid in a molar ratio of 60 : 20 : 20) encapsulating curcumin, named “nanocurcumin”, can inhibit brain tumor cell growth and deplete CD133⁺ stem-like cells (122, 123).

Notch Signaling Pathway

Another major pathway involved in the CSC regulation is Notch signaling pathway that controls cell-fate determination during development and maintains adult tissue homeostasis (124). This pathway could lead to the development of many cancers including melanoma, medulloblastoma, rhabdomyosarcoma, basal cell carcinoma, breast, lung, liver, pancreas, and prostate cancers (125). Fan et al. (126) examined the effects of Notch pathway inhibition on the growth and xenograft formation of medulloblastoma. They found that Notch blockade results in the growth of tumor cells and tumor-forming capacity, due to the depletion of stem-like cells. Clinical application of Notch inhibitors, γ -secretase inhibitors (GSIs), is restricted by severe side effects. Imagable mesoporous silica nanoparticles (MSNPs) have been developed as vehicles for targeted delivery of GSIs to block Notch signaling. GSI-loaded on biocompatible and biodegradable MSNPs enhanced therapeutic efficacy in tumor reduction and regulation of Notch driven stem cell fates (127). Specific functionalization of nanoparticles could be used to enhance targetability to specific cell populations. Mamaeva et al. (128) have demonstrated that breast CSCs display enhanced glucose uptake compared to normal breast cancer cells. This specific feature of the breast CSCs has been utilized to design functionalized mesoporous silica nanoparticles (MSNs). The MSNs were functionalized with glucose analogues to deliver Notch signaling inhibitors to the CSCs efficiently. The results have demonstrated a reduction in the CSC pool and suppression of tumor growth *in vitro* and *in vivo*.

CD 90

CD90 is glycosylphosphatidylinositol (GPI) anchored glycoprotein that is expressed in leukocytes, bone mar-

row-derived mesenchymal stem cells, hepatic stem/progenitor cells (HSPCs) and also, is identified in murine breast CSCs. Studies have shown that CD90⁺ cells have tumorigenicity and metastatic potential (129). 90% of blood samples from liver cancer patients contained CD45⁻/CD90⁺ markers (25). Bakalova et al. (130) have utilized CD90 as a valid therapeutic target. They have shown that photosensitizer trifluoperazine loaded in anti-CD90 antibody-mediated water-soluble CdSe core nanocrystals could be delivered directly to the CD90⁺ leukemia CSCs where it could cause leukemia CSCs sensitivity to UV irradiation and apoptotic cell death.

Hedgehog (Hh) Signaling Pathway

It is known that the Hh pathway helps in controlling cell growth and morphogenesis. The components of the Hh signal transduction pathway can control embryonic development and also, is expressed in postnatal and adult tissues. These components have assigned roles in the maintenance of stem cells and tissue repair (131). At least three Hh gene homologs have been identified in human: Sonic Hh (SHh), Desert Hh (Dhh), and Indian Hh (Ihh), among which SHh is the most widely used one (132). Hh ligand can bind to the 12-transmembrane receptor Patched 1, which relieves seven-pass transmembrane receptor named Smoothed (Smo) from repression and allows downstream activation of the pathway through the translocation of GLI, where it acts as a transcription factor to the nucleus with the mediation of SUFU and KIF17. High expression and aberrant activation of Hh ligands present in the majority of human cancers including brain tumors, melanomas, leukemia's, gastrointestinal, malignancies of the breast, ovary, prostate and, pancreas cancers (133). Therefore, targeting the Hh signaling pathway may provide a practical therapeutic approach in the treatment of various cancers. GLI inhibition through PLGA-PEG nanoparticles (NanoHHI) has illustrated tumor growth inhibition and antimetastatic effects in hepatocellular carcinoma (HCC) models (134, 135). In another study, the effects of anthothecol-encapsulated PLGA-nanoparticles (Antho-NPs) have been examined on the behaviour of pancreatic cancer stem cells (CSCs). They have discovered that Antho-NPs inhibited the CSC proliferation and induced apoptosis by disrupting GLI-DNA binding and also, it acts as GLI inhibitor. Using PLGA nanoparticles offers many benefits of appropriate stability in physiological environments, entering to a cancerous sphere without any auxiliary reagents, loss of toxicity towards human pancreatic normal cells and PLGA-NPs could cross the blood-

barrier (136).

Transforming Growth Factor- β (TGF- β)

TGF- β signaling is an important prognostic marker in various types of cancers including breast (137), colon (138), liver (139), lung (140) and ovary tumors (141). Also, its potential role in the CSCs has been recently reported in breast (142), colon (143), liver (144), and lung (145), cancers. Thus, selective targeting of TGF- β signaling would significantly improve therapeutic efficiency in tumor models (146). For breast cancer treatment, polyethyleneimine/polyethylene glycol-conjugated MSNPs were developed to load LY364947 as a TGF- β inhibitor (146). These polymeric nanoparticles and inhibition of TNF- β signaling pathway have been used in the delivery of siRNA to the breast CSCs. Nanoparticles could be accumulated in tumors that in turn, increases siRNA concentrations in tumor tissues and notably, lower the proportions of the CSCs (147). Gold NPs (AuNPs) with much application in therapeutic and diagnostic agents could selectively deactivate the TGF- β signaling pathway. Tsai et al. have found that AuNPs could attenuate the immunosuppressive function of TGF- β_1 signaling pathway and also, increase the number and frequency of tumor-infiltrating T lymphocytes (148).

Prospects

The cancer treatment needs the improvement of approaches which can efficiently eliminate cancer and amend the application of this novel drug-delivery modality (nanomedicines) (149, 150). Recently, researchers have been interested in the nanotechnology-based drug because these drugs are most useful for developing anti-cancer therapies and CSCs targeting. There is some clinically approved nanomedicine include Pegylated liposome (Doxil), Albumin-bound paclitaxel particles (Abraxane), Iron oxide nanoparticles (NanoTherm), PEG-1 Asparaginase (Oncaspar), Methoxy-PEG-poly (d,l-lactide)- paclitaxel micelle (GeneXol -PM) and SMANCS (Zinostatin) (151). Considering these issues that mentioned the nanotechnology-based anticancer drug helps treat and prevent various types of cancers because these drugs have excellent diffusion capacity, selective killing of tumor cells or CSCs. Also, CSC-targeting with nanomaterials is in the early stages because these studies have done in vitro and in vitro phase only. So a vast amount of detail in vitro, in vivo and other relevant information, is essential that these nanomedicine products have a clinical practice. The other important issues are the

safety, effective dosages and side effects of nanomaterials used in drug delivery systems which should be given special attention (152).

Finally, the most important thing is that the treatment of cancer using nanotechnology is helpful approaches for cancer patients because most of them suffer from chemotherapy and radiotherapy. Moreover, CSCs targeting with nanomaterial may present a novel method for reducing the costs on the public health care system.

Conclusions

The basic cause of cancer is a group of dividing cells with high power and high resistance to the drugs that they called Cancer Stem Cells (CSCs). CSCs were identified and characterized in the 1990s, in the blood of people with leukemia that seemed to have a vital role in cancer. CSCs are markedly resistant to conventional cancer treatments, such as chemotherapy and radiation. Therefore, understanding tumor biology is critical for the development of successful therapies. Identifying and selectively targeting markers and signaling pathways of CSCs are new therapeutic strategies for cancer treatment. The current success in the fight against CSCs has been reported in studies that using nanotechnology-based therapeutics with using different surface markers and biochemical assays for identification. Based on nanomedicine studies mentioned in our review, it is shown that nanomedicine in the treatment of CSCs can provide additional benefits for cancer patients with fewer drugs side effects such as, increasing their cellular uptake, prolonging systemic circulation, improving biodistribution profiles, and resolving problems of poor stability and solubility. This review has shown bright prospects of cancer treatment by nanomaterials, and specifically nanoparticles with increased therapeutic potency in drug delivery, CSC specificity and fewer side effects.

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Potential Conflict of Interest

The authors have no conflicting financial interest.

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