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Nanotheranostics: A tactic for cancer stem cells prognosis and management

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ABSTRACT

Advances in cancer nanotechnology had led to the development of various theranostics (therapy and diagnosis) strategies, by incorporating multifunctional approaches for trafficking against deadly cancer disease. In metastatic relapsed cancers, cancer stem cells (CSCs) exhibits drug resistance towards several therapies leading to their increased self-renewal, proliferation and differentiation. Hence, designing an effective strategy by employing the use of smart nanotheranostics can eliminate CSCs with the ultimate goal of enhancing the survival of cancer patients and offering a quality life. This review compiles the recent nanotheranostics strategies that are being employed for diagnosis, imaging and therapy of CSCs for circumventing the chances of cancer recurrence.

1. Introduction

Cancer stem cells (CSCs) are a small subset of a population within the cancer cells, commonly termed as 'cancer-initiating cells', discovered in the late 1990s and have been majorly accountable for cancer recurrence owing to their distinguishing characteristics of self-renewal [1]. Leukemic stem cells (LSCs), a type of CSCs was first demonstrated in human acute myeloid leukemia (AML) by Bonnet and Dick [2]. A small subset of $CD34+/CD38^-$ LSC population within AML displayed two major characteristics of stem cells: self-renewal and differentiation. Later, the presence of CSCs was confirmed in many other solid cancers, making them a potential target of investigation in cancer therapy [3]. (see Table 1)

CSCs are remarkably known to exhibit the discrete property of being resistant to the existing chemo and radio-therapies coupled with its highly invasive and metastasized tumorigenicity potential [4]. Hence, CSCs have become the trending topic of translational cancer research in finding an appropriate effective therapeutic approach as the existing treatment destroys only cancer cells without eliminating CSCs due to their distinct drug-resistant mechanisms. Malignant tumors that are highly invasive and resistant to radiation are also found to be resistant to a variety of currently used drugs priming to disease recurrence due to CSCs [5]. According to the conventional view, cellular targets modification, reduced drug accumulation, and alteration lead to the progression of drug-resistant cancer cells and CSCs, alarming the need for repeated chemotherapeutic treatment. However, CSCs survive due to a variety of growth factors and cytokines present in the tumor microenvironment which in turn activates the CSCs survival pathways and promotes the transformation of cancerous cells into CSCs [6]. In recent times, an increased number of CSCs have been developing due to the irradiation of breast cancer cells demonstrating the transformation of cancer cells into CSCs [7]. It is also reported that treatment of gastric cell line with an anticancer drug such as 5-fluorouracil (FU) leads to the attainment of stem cell features such as stemness, tumorigenicity, self-renewal ability and resistance to drugs [8]. Similarly, investigators have demonstrated the existence of CSCs in many other cancer types like lung [9], prostate [10,11], pancreatic [12,13], colon [14,15], glioma [16], etc. CSCs in all these types of cancers exhibit an efflux pump bolting them away from the ionizing radiations and anticancer drugs effects [17].

Use of nanotechnology in cancer management is likely to overpower the burdensome challenges encountered *via* conventional methods thereby allowing the smart nanocarriers to direct precisely within the body [18]. Several such nanomedicines have been permitted for clinical use over the last decade with few of them tagged as the standard care of treatment towards a specified cancer type [17,19]. Based on the previously investigated accomplishments the use of nanotechnology in cancer diagnosis and therapy (cancer nanotheranostics), have been greatly enhanced for their efficacy in cancer management [20,21]. Nanotheranostics are most often used in monitoring the biodistribution

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Table 1
Nanomedicines for cancer stem cells management.

Nanoformulation	Target	Therapeutic/diagnostic/imaging molecule	*In vitro*/*In vivo* model	Therapy	Reference
Liposomes	Brain gliomas	Ursolic acids (UA)	C6 glioma cells and glioma stem cells	Chemotherapy	[135]
Liposomes	Breast cancer	All trans retinoic acid, vinorelbine	Human breast cancer-MCF-7 and MDA-MB-231 cells/ Brain cancer stem cells in NOD/SCID mice	Combination therapy	[89]
Liposomes (TriCurin)	Glioblastoma	Curcumin, epicatechin gallate, resveratrol	Glioblastoma and glioblastoma stem cells	Combination therapy	[90]
Chitosan oligosaccharide-g-stearic acid (CSOSA) polymeric micelles	Breast cancer	Doxorubicin	CSCs enriched mammospheres	Multi-cycle chemotherapy	[93]
Salinomycin-loaded DSPE-PEG-methotrexate nano-micelles	Head and neck squamous cell carcinoma	Salinomycin	HNSCC CSCs and HNSCC cells	Combination therapy	[92]
Zinc oxide nanoparticles	Cancer stem cells	Doxorubicin	CSCs	Combination therapy	[99]
Silver nanoparticles	Cancer	Cisplatin	Teratocarcinoma stem cells	Targeted therapy	[100]
Mesoporous silica nanoparticles (MSN)	Acute leukemia	Anthracycline daunorubicin	Leukemic stem cells (LSC)	Combination therapy	[101]
Nanodiamonds	Hepatic carcinoma	Epirubicin	In vitro and *in vivo* killing of hepatic cancer stem cells and hepatic cancer cells	Chemotherapy	[115]
Albumin-conjugated fluorescent nano diamonds	Cancer	Single-cell imaging and quantitative tracking of human stem/progenitor cells	Human placenta choriodecidual membrane-derived mesenchymal stem cells (pcMSCs) in miniature pigs	Background-free imaging and quantitative tracking of human MSCs in animal models	[114]
Fluorescent nano diamonds	Cancer	Biocompatibility and cellular uptake	Cancer cells (HeLa) and pre-adipocytes (3T3-L1)	Bio-medical applications	[136]
Single walled carbon nanotube and SWCNT-COOH	Osteosarcoma	TGFβ induces OS dedifferentiation and OSCs Viability	Osteosarcoma and OS stem cells	Targeted therapy	[137]
Single walled carbon nanotube	Cancer	Combretastatin A4 (CA4)	Hela Cells and cancer stem cells	Chemotherapy	[138]
Semiconductor nanocrystal QDs, MSCs labelled with QD	Breast cancer	Cell-mediated delivery of nanoparticles	Breast cancer cells and breast cancer stem cells (MDA-MB-231)	Targeted therapy	[121]
Gold nanoparticles	Cancer	Doxorubicin	KATO-III and Chago cancer cells	Chemotherapy, drug delivery	[139]
Chitosan nanoparticles	Hepatic carcinoma	Ginsenoside compound K (CK)	Hepatic carcinoma cells (HepG2)	Combined therapy	[140]
Poly (lactic-co-glycolic acid) nanoparticle	Childhood cancer that causes azoospermia	Cisplatin	Mouse malignant cell line (EL4) and SSCs	Targeted therapy	[105]
Polymer–lipid hybrid anti-HER2 nanoparticles	Breast cancer	Salinomycin	Breast cancer cells and breast CSCs	Targeted therapy	[141]
Chitosan nanoparticles	Breast cancer	Doxorubicin	CSCs and tumor reinitiating cancer stem like cells stem-like cells	Combination therapy	[104]
Oxidized carbon nano tube with polyethylene glycol	Hepatic carcinoma	Photon energy transformed to heat to extirpate cancer.	HeLa and HepG2 cell lines	Photothermal therapy (PTT)	[142]
Gold nanoparticles	Colorectal cancer	High-linear energy transfer (high LET) irradiation	Colorectal CSCs and colorectal cancer stem like cells	Radiation therapy	[143]

of nanomaterials within the animal models and in viewing its intracellular localization for studying the complete patient response. The development of nanotheranostics with the superior ability to target CSCs can be achieved by target-specific drug delivery. This review provides an overview of CSC drug resistance mechanisms and the loopholes associated with the current methodologies for tackling CSCs. The potential role of currently available nanotheranostics in targeting CSCs have been highlighted in detail.

2. Cancer stem cells (CSCs)

CSCs have been an important concern for tumorigenesis, metastasis, recurrence, and resistance to radiochemotherapy and hence elimination of CSCs is crucial for the prevention of cancer relapse [22]. Existing strategies aren't potent enough to detect and target the CSCs, posing a risk of disease relapse or increased recurrence in patients [23]. Thus, for CSCs eradication, a substantial amount of effort has been laid down for developing several strategies in targeting CSCs and in identifying disparate therapeutic compounds effective against CSCs within malignant tumors [24,25]. Targeting surface markers expressed on CSCs, altering the signalling pathways and changing the tumor microenvironment are few of the existing alluring therapeutic targets in CSCs management [26].

2.1. Stem cell surface markers

The unusual occurrence and activation of CSCs may alter at the concentration and localization of biomarkers at the tumor site [27]. Therefore, a feasible approach for early detection is by imaging the surface biomarkers of CSCs *via* the use of ligand or antibodies may help in rapid diagnosis. Some of these strategies are being successfully translated to clinics with most of them under pre-clinical evaluation [28,29]. One significant CSCs based marker strategy include targeting CD133 (Prominin 1), a cell surface glycoprotein with anti-CD133 therapy. The presence of CD133 on CSCs is seen amongst many solid cancers including glioma, lung and breast cancer correlating with poor clinical outcomes [30]. Zhang et al. had developed a fluorescent-based diagnosing system by utilizing 0–630 nM graphene oxide for detecting the CD133 positive CSCs in CT26 cells [31]. In another study, treatment of colorectal adenocarcinoma cell lines Caco-2 cells with paclitaxel drug loaded on polymeric nanoparticles (NP) in conjugation with CD133 antibody reduced the number of cells and colony formation. In addition to that, conjugated paclitaxel loaded NPs exhibited superior effectiveness when compared to free paclitaxel in breast cancer xenograft model [32]. Intraperitoneal injection of anti-CD133 and Pseudomonas exotoxin 38 fusion in ovarian cancer xenograft model evidenced the tumor regression in 4–6 weeks with cancer-free survivors for a long time [33]. Similarly, the reduced tumor in the sarcoma CSCs was due to the anti-proliferative activity of CD133 + cell therapy [34]. Pancreatic and hepatic CSCs expressing CD133 + cells displayed similar effective results with anti-CD133 + cell therapy. Current investigations reported the selective killing of CD133 + glioblastoma cells by the anti-CD133 conjugated with carbon nanotubes when combined with irradiation of near-infrared laser light [35]. These studies show that a combination of anti-CD133 with targeted drug delivery could possibly increase the efficacy of CD133 + antibody in abolishing the CSCs.

CD44, a transmembrane protein is overexpressed on different cancer cells such as prostate, ovary, pancreas, gastric, breast, colorectal, bladder, head and neck, hepatocellular, AML CSCs, etc. Thus, eradicating CSCs by targeting CD44 monoclonal antibody may prove to be a promising strategy for CSC therapy [36]. The LSCs that are highly expressed in AML can be neutralized by the use of anti-CD44 antibody. Lee et al. had investigated the use of anti CD44 with manganese ferrite nanoparticles (MFNPs) as a probe for visualizing by *in vivo* magnetic resonance imaging (MRI) in a gastric cancer mice model [37]. Muntimadugu et al., have shown that the combination of hyaluronic acid coated with salinomycin NPs and paclitaxel NPs exhibited increased cytotoxicity towards CD44 $^{+}$ cells. Adopting a combinational approach of utilizing an anticancer drug along with a CSC inhibitor is an encouraging strategy to repress the cancer relapse [38]. Similarly, triple-negative breast CSCs have been targeted by a pentameric nanocomplex (PNC) comprising of doxorubicin-loaded gold NPs coupled with thiolated hyaluronic acid and thiolated PEGylated CD44 aptamer. This nanocomplex effectively reduced the CSC self-renewal besides increasing the efficacy of doxorubicin and reducing its nontargeted toxicity issues [39]. In the recent decade, there are several antibodies used for the treatment of numerous solid and haematological cancer as approved by the FDA including anti-CD20 (Rituximab), anti-EGFR (cetuximab), anti-ER2 (trastuzumab), anti-VEGF-A (bevacizumab), etc.

2.2. Dysfunctional signalling pathways in cancer stem cells

Dysregulation in Notch, Wnt, Hh signalling pathways alters the genes required for the maintenance within tumor microenvironment affecting the CSCs [40]. The growth, metastasis, development of drug resistance and finally incurrence of cancer relapse are due to either mutation or abnormal activation of the genes within the signalling pathways. The conservative signalling pathways of multicellular organism linked to CSC survival and self-renewal is the Notch pathway [41]. Breast cancer, glioblastoma and various other cancer types evolve due to the dysregulation in Notch signalling [14,42–44]. The Notch protein inhibits tumor regrowth, reduces migration and invasion of cancer cells contributing to the drug resistance and therefore decrease in Notch expression could lead to enhanced drug sensitivity of cancer cells [45]. Recent clinical trials inhibiting the CSC growth targets the notch pathway with monoclonal antibody-based therapies like OMP-21 M18, OMP-52 M51, and OMP-59 R5 [46]. In addition, the metastasis property of CSCs are also directly linked with the Notch pathway. CSCs facilitates metastasis by resisting apoptosis and DNA damage induced by drugs. The epithelial-mesenchymal transition (EMT) is a crucial developmental phase that is activated during cancer invasion and metastasis in the process of cancer progression [47]. EMT is characterized by the conversion of epithelial cells into highly mobile migratory and invasive cells. This occurs with loss of E-cadherin markers and an increased level of N-cadherin expression signifying the hallmarks of EMT [48]. It is well known that EMT is also associated with CSCs characteristics. Thus, EMT inhibition can potentially suppress CSCs formation and can become an attractive strategy for cancer metastasis treatment [49]. A large body of investigations has been reported linking the Notch signalling with CSCs maintenance and also with EMT [50–52]. The maintenance of EMT and acquisition of CSC property attributes to the overexpression of Notch-2 and its ligand jagged 1 [53]. Invasion of CSCs into healthy organs is due to the EMT, where CSCs migrate from tumor lesions into the blood. Current treatment strategies target these signalling pathways for controlling stem cell survival, replication and differentiation. Either single or combination of notch inhibitors along with chemotherapy drugs has been established to treat cancer and its recurrence [54].

The predominant pathway crucial for embryogenesis and progression of cancer has been the Wnt pathway [55]. The proliferation and maintenance of normal healthy stem cells are due to the Wnt proteins which suffice the role of growth factors. The progression of different kinds of cancers like leukemia, colon, epidermal, breast and cutaneous carcinoma have been reported due to the mutation in Wnt/β-catenin pathway [56]. Furthermore, the transcription of ABCB1/MDR-1 in chronic myeloid leukemia (CML) is due to impediment in Wnt/β-catenin signalling [57]. The Wnt signalling pathway has been reported to enhance stem cell properties and confer resistance to current cancer therapeutics in glioblastoma [58]. Several studies have elucidated an effective inhibition of the drug resistance lung cancer cells by silencing the Wnt pathway using siRNA against β-catenin [59]. The maintenance of stemness such as self-renewal capacity and heterogenicity of breast

CSCs properties are developed by proliferating cell nuclear antigen-associated factor (PAF), linked with the Wnt pathway [60]. Malladi et al. investigated that the expression of SOX2 and SOX9 induces DKK1 (a natural Wnt inhibitor) for the transition of normal cells into the quiescent state. They also isolated latent competent cancer cells from lung and carcinoma cell lines which lower the innate immunity and expression of natural killer cells (NK) confirming the activation of cells to a quiescent state for a longer time [61].

Similarly, the development of various types of cancer such as basal cell carcinoma, breast, brain, and pancreatic tumors are due to the activation of the Sonic Hedgehog (Shh) signalling pathway [62]. Shh pathway reactivation, caused by the somatic mutation has been studied by several mechanisms in solid tumors. The association of Shh pathway and CSCs have been extensively studied. Li et al. had isolated cells from primary cultures of pancreatic adenocarcinomas expressing the CSC phenotype that is being 100 times more tumorigenic as compared to other cells [63]. This was studied by the development of xenografts in mice with impaired immune system and these cells relatively over-expressed Shh pathway in comparison with other tumor cells. It has also been observed that tamoxifen resistance in breast cancer cells (MCF-7 and **T47-D**) are regulated owing to the high expression of Shh signalling [64]. Similarly, colon and pancreatic CSCs shows sensitivity to the Shh pathway inhibitors. The destructive potential of several compounds in targeting different signalling pathways is efficient at the pre-clinical level and is currently at the level I and II stage of clinical trials [65].

2.3. Tumor microenvironment

Three major characteristics of tumor microenvironment facilitating the survival of CSCs are (1) secretion of cytokines causing chronic inflammation, (2) hypoxia and (3) proliferation and differentiation capacity that is regulated by perivascular niches. Inflammatory cytokines (IL-1β, IL-6, and IL-8) secretion promotes the development and maintenance of CSCs for their self-renewal, angiogenesis, and metastasis traits. This leads to the activation of Stat3/NF-κB pathways in stromal and cancer cells. The distinctive feature of niches is a hypoxic environment along with augmented angiogenesis in the tumor microenvironment including blood vessels. The possible pharmaceutical targets of eradicating the CSCs could be devising on strategy by attacking anyone of these key features of the tumor microenvironment [66].

Tumor hypoxia is one of the interesting techniques for targeting CSC niches. It plays a major role in the progression of cancer and hence it is very important to monitor the level of hypoxia in biosystems. The survival of CSCs mainly depends on the hypoxic region of the tumor microenvironment [67]. Hypoxic environment vents up the activation of hypoxia-inducible factor (HIF) pathway, upregulating HIF-1α which in turn affects tissues by intervening hypoxia-related several biological effects causing increased resistance towards radiation as well as chemotherapy [68]. Thus, for destructing and eliminating the soil of the CSCs population, detection of the hypoxic CSCs niche is highly essential. A two-photon fluorescent probe has been devised to monitor the hypoxic level by measuring the nitroreductase (NTR) level under *in vitro* 3D cultured-CSCs and *in vivo* tumor models. This system extends the excitation spectra in near-infrared (NIR) region assisting in deep tissue penetration for detecting hypoxic microenvironment under *in vivo* [69].

Moreover, the disruption of the CSC niche takes place by targeting the tumor vasculature. The substantial delay in growth and regression of tumor was studied at the pre-clinical level through *in vivo* studies by utilizing anti-angiogenic agents, however, the outcome of this has not been evaluated at the clinical level yet [70]. CD133 + stem cell-like subpopulation can differentiate into endothelial and tumor lineages in glioblastoma, a highly angiogenic form of malignancy [71]. In glioblastoma, the CSCs differentiates into pericytes and subsequent remodelling of the perivascular niche have been due to SDF1/CXCR4 axis and TGF-β of the endothelial cells [72]. In a mouse glioma model, a γ-secretase-regulated intracellular domain of CD44 promotes the expression in the perivascular niche. In case of bevacizumab-resistant glioblastoma, intercellular adhesion molecule 1 (ICAM-1) expression has been reported due to the hypoxia-induced activation of STAT3. The decrease in tumor size and inhibition in the invasion of macrophage at the site of tumor has been seen in the animal model due to the knockdown of ICAM in glioma stem cells [73].

3. Current challenges in CSCs management

Cancer stem cells are eradicated by currently available strategies and these were initially discovered to be originated in solid tumors and later found to be responsible for tumor development. Many cancer stem cell antigens are not specific to these tumors and are also expressed by normal stem cells. This poses the greatest challenge to effectively diagnose by a conventional method when tumors are heterogeneous and complex. Traditional strategies for cancer treatment such as chemo- and radiotherapy has several drawbacks as they induce local and systemic toxicity because the therapeutic molecules are not selective and affect the healthy tissues [74]. Additionally, unique characteristics of CSCs including slow proliferation rate, enhanced expression of surface efflux pumps, increased ability of DNA repairing and their ability to adapt to microenvironment characteristics like hypoxia and acidosis are have also been listed down as bottlenecks in cancer treatment and prevention [75].

Recently, several approaches have been conceptualized with the primary goal of destroying the CSCs and their niches. These comprise targeting specific surface markers, modulating the signalling pathways, inhibition of drug-efflux pumps, altering the microenvironment signals, etc for the induction of CSCs apoptosis and differentiation [76]. In this context, the use of nanomaterials provides sensitivity and specificity for eradicating CSCs [77]. Currently, some of these are successfully translated to the clinic, especially in combination with traditional therapies while few others are under evaluation [78].

4. Nanotheranostics for CSCs management

Nanotheranostics are increasingly used in the current molecular diagnostic methods for CSCs management. Several nanotechnological devices such as metallic nanoparticles, gold nanoparticles, quantum dots, etc are used for diagnostic applications [79–81]. Currently available nanotechnologies could overcome the disadvantages of existing molecular diagnosis and may provide acute care of diagnosis and therapy for CSCs. Identifying CSCs with traditional clinical imaging scanners were very challenging [82]. In this context, clinical diagnostic procedures using nanotechnology incorporated within the molecular diagnosis is a protagonist in nanomedicine and personalized medicine. The receptors, pores and the other components of the living cells that are nanoscaled are detected by nanoscale probes. It is proposed that nanotechnology can be used in improving PCR and non-PCR methods for quick diagnostics. The greatest advantage of using nanotechnology in molecular diagnostics is that a very small quantity of sample is required and the diagnostics methods include nanoscale materials to tag or label, which makes them faster and more sensitive. There are numerous nanomaterials that are being used for CSCs diagnostics. Similarly, nanomedicines for cancer therapy are commonly used to increase the stability, solubility, and permeability of the encapsulated drugs effectively with safety and efficacy [83]. NPs have discrete multifunctional characteristics accompanied by several physico-chemical properties. Higher concentration of therapeutic drug can be encapsulated to facilitate the release at the specific tumor site targeting CSCs over a period of time. Target selectivity is achieved due to the conjugation of specific ligands to the NPs surface. An enormous variety of NPs of different sizes, physicochemical features, and bifunctional compositions are available to sustain under *in vivo* conditions [84,85].

Numerous forms of nanotheranostics are being deployed for

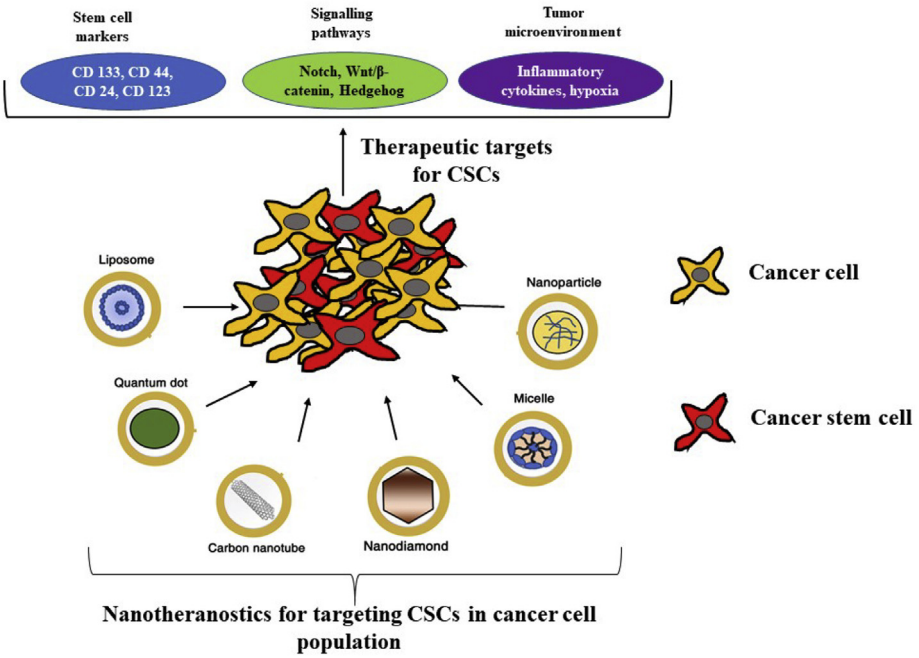

Fig. 1. Different therapeutic targets accessible within CSCs. Applications of different nanotheranostics for tackling CSCs within the cancer cell population.

destroying CSCs (Fig. 1). Clinically approved nanomedicine for cancer management includes doxil® (liposomal doxorubicin), abraxane® (albumin-bound paclitaxel) oncaspar® (PEG-L-asparaginase) and a few more. Doxil® has been the first US-FDA approved nanomedicine with the superior property of exhibiting longer circulation time, enhanced therapeutic efficacy and reduced cardiotoxicity. In the later section of this review, we would be discussing the significant nanotechnological approaches that can be employed for effective management against CSCs [86].

4.1. Liposomes

Liposomes are defined as small sphere-shaped artificial vesicles made up of different polymers aligned as an aqueous central core with one or multiple concentric layers of phospholipid on the periphery [87]. They are considered as a versatile tool in biology, biochemistry and in medicine due to their ability to incorporate hydrophilic, hydrophobic, and amphiphilic molecules. Despite all these, they could be easily controlled during their formulation. Targeted imaging and therapy for CD133 positive glioma stem cells have been achieved by an RNA aptamer and a lipoprotein receptor-related protein for dual targeting receptors loaded with survivin siRNA and paclitaxel to form dual modified cationic liposomes [88]. Liposomes have also been proved as an ideal nanocarrier for breast cancer stem cells. All-*trans*-retinoic acid (ATRA) stealth liposomes have been investigated for preventing the recurrence of breast cancer thereby acting as a co-therapy alongside with a cytotoxic agent. The relapse of breast cancer was prevented by ATRA stealth liposome by promoting BCSCs differentiation and arresting the cell cycle [89]. Similarly, Mukherjee et al., evidenced that the liposomal TriCurin (mixture of curcumin, epicatechin gallate, and resveratrol) triggered the p53-mediated mechanism for inhibiting the proliferation of mouse glioblastoma and glioblastoma stem cells leading to apoptosis under *in vitro* conditions [90].

4.2. Micelles

A micelle is defined as an aggregate of amphiphilic surfactant molecules dispersed in a liquid colloid. These are formed by the self-assembling of amphiphilic molecules in aqueous solution. The hydrophilic 'headgroups' remain facing the surrounding medium while the hydrophobic chains form the core of micelle minimizing the assembly contact with the water [91]. Micelles of varying size have remarkable characteristics including increased drug solubility, enhanced circulation time, low toxicity and high cellular penetration. Thus, these are revolving as a keystone in the future of therapeutics.

Cancer relapse, progression and diagnosis of hepatocellular carcinoma (HCC) is mainly due to the biomarker of cancer stem cells (CSCs) which is Epithelial cell adhesion molecule (EpCAM). Chemotherapy and photodynamic therapy are performed using an anti-EpCAM antibody grafted nanoparticle-based micelles loaded with an anticancer drug mitoxantrone (MX) and a photosensitizer for dual-modality magnetic resonance/upconversion luminescence (MR/UCL). These micelles are biocompatible and highly specific to HCC and possess higher magnetic/fluorescent properties *in vitro*. Zhu et al. have formulated PEGylated salinomycin and methotrexate loaded nanomicelles for targeting both head and neck squamous cell carcinoma (HNSCC) and cancer stem cells (CSCs). Experimentally they have shown that these nanomicelles exhibited increased cytotoxicity effect on both HNSCC CSCs and non-CSCs in comparison to methotrexate and salinomycin treatment alone. Furthermore, M-SAL-MTX has shown to exhibit enhanced tumor suppression property, thereby the micellar system offers an exciting approach for dealing with HNSCC by dealing with both HNSCC CSCs and HNSCC cells [92]. Meng et al. designed a nanovehicle composed of chitosan oligosaccharide-g-stearic acid (CSOSA) polymer towards the evaluation of tri-cycle chemotherapy in an animal tumor model. Investigation revealed that the CSOSA encapsulated doxorubicin (CSOSA/DOX) showed an enhanced antiproliferative effect in mammospheres enclosing a high number of CSCs as detected by acid phosphatase assay (APH). Moreover, animal studies showed that the CSOSA/DOX micelles inhibited the tumor development leading to a noticeable reduction in the number of CSCs thereby lowering the MDR activity [93].

4.3. Nanoparticles

Nanoparticles are colloidal particles with varying size of 10–1000 nm. They are made up of biocompatible and biodegradable polymeric matrix that can encapsulate or conjugate or adsorb the therapeutic agents of interest [74]. The nanoparticles provide a

sustained and controlled release of the drug by modulating the characteristics of polymer to attain the desired therapeutic concentration of drug at the target tissues for a particular time period consequently with optimal therapeutic efficacy. Subsequent release of the drug into the circulation causes the polymer matrix to break down into non-toxic molecules which are further excreted from the body [94].

Nanoparticles surface can be modified with the targeting moiety and are targeted to disease sites by offering a biochemical interaction with the surface receptors expressed on tumor cells. Moreover, these nanoparticles are able to deliver the drugs to the disease site by overcoming various biological barriers like blood retinal barrier, blood brain barrier, etc [20].

Nanoparticles have also shown to exhibit a potential role in diagnosing cancer [95] with some of them being assessed for clinical trials [96]. However, these nanodiagnostics are useful in limited situations [97]. These nanodiagnostics can be used for tumor imaging, locoregional imaging and also early detection of CSCs, circulating tumor cells (CTCs), etc. Whereas theranostic nanoparticles are multifunctional nanosystems that are designed for multipurpose use of diagnosis and therapeutic have potentially attracted a huge attention in the scientific field [98].

Zinc oxide nanoparticles (ZnO NPs) have shown to target various types of cancers including cancer stem cells with multifactorial abilities of inhibiting cell growth, overcoming drug resistance, prevention of cancer relapse and metastasis. Wang et al., showed the potential effects of Doxorubicin loaded ZnO NPs in decreasing the stemness of CSCs within the drug resistant breast cancer cells [99].

Silver nanoparticles (AgNPs) have been used for many biomedical applications owing to their distinguishing trait of attacking against most bacterial infection, inflammation, cancer, etc. Han et al., studied the mechanism of cytotoxicity induction and stem cell differentiation by utilizing the AgNPs in neurodegenerative diseases and cancer through several analytical techniques [100].

Similarly, Mandal et al. investigated the role of daunorubicin loaded anti-B220 functionalized mesoporous silica nanoparticles (MSNs) for the treatment of AML-LSC. Results demonstrated that functionalized antibody-tagged MSNs containing antileukemic drugs efficiently targets LSC *in vitro* and proficiently destroys the AML-LSCs at a lower concentration of daunorubicin than free drug. MSNs treatment lead to significantly delayed leukemic development under *in vivo* conditions in mice [101].

Platinum complex are known to exhibit selective toxicity on breast cancer stem cells [102]. Therefore, platinum nanoparticles with characteristic features of being nontoxic, thermally stable and thermoplasmonic property are profoundly used in cancer management. Combination of platinum nanoparticles along with doxorubicin have been shown to be effective on osteosarcoma cells, however they displayed higher toxicity as compared to the use of single counterparts [103].

4.3.1. Polymeric nanoparticles

Polymeric NPs are made up of either natural polymers like chitosan, gelatin, agarose, etc or synthetic polymers such as poly(ε-caprolactone) (PCL), poly (lactic-co-glycolic) acid (PLGA), polyvinyl alcohol (PVA), polyethylene glycol (PEG), etc [83]. These are more stable in nature that allows the release of the drugs for a longer period of time. In these polymeric structures drugs can be adsorbed on the surface or entrapped in the core of the polymeric matrix [74].

In this regard, Rao et al., have developed CD44 targeted chitosan decorated doxorubicin loaded polymeric nanoparticles. They have demonstrated the higher cytotoxic effect of these nanoparticles as compared to the free doxorubicin in CD44 positive breast cancer tumor cells. Further, these nanoparticles have shown greater tumor regression property in xenograft model [104].

Similarly, Shabani et al., have formulated folic acid conjugated cisplatin loaded PLGA NPs and have found that these nanoformulations have shown promising efficacy as a cisplatin carrier inducing higher apoptosis than the corresponding native drug in mouse malignant cells and spermatogonial stem cells [105].

4.3.2. Gold nanoparticles

Gold nanoparticles are widely known for its theranostic application in a myriad of diseases along with the plasmonic nanoparticles by holding a higher and adjustable surface plasmon resonance (SPR) at NIR region. Gold nanoparticles improve the temperature for photothermal therapy (PTT) and light-induced chemotherapy along with bioimaging ability. In comparison to surgical resection, thermoablative technology shows lesser morbidity without any evidence of damaging the healthy tissues. They also lowers the financial burden by reducing hospitalization time [106] meeting the technical needs in cancer therapy [107]. Liu et al. developed human induced pluripotent stem cells encapsulated gold nanorods@SiO2@CXCR4 (AuNRs-iPS) with photothermal therapeutic effects. This system displayed good optical properties along with their ability to migrate towards the targeted tumor. Additionally, iPS cells aids in the delivery of Au nanorods with prolonged retention and distribution at the tumor site in mice through photoacoustic tomography and two-photon luminescence evaluation [108].

4.3.3. Magnetic nanoparticles

The magnetic nanoparticles (MNPs) are biocompatible and are potentially used for biomedical purposes such as stem cell tracking, imaging, diagnosis and cancer therapy management. In recent times, MNPs are more likely to be used as nano vehicles for delivering the drug in targeted manner at the site of cancer and MRI traceability. Nanoparticles are retained inside the tumor site along with the externally applied magnetic field. The magnetic property of the iron oxide core enables targeted delivery due to the magnetic response. In addition to this, it is recognized that visible quantities of MNPs reach the site of cancer. Iron oxide nanoparticles (IONPs) is made up of iron oxide or magnetite core and is covered by an outer polymeric shell (dextran, starch, etc). Many investigators have used it for various biological applications like contrasting agents in MRI for theranostic purpose. The lower cost, biocompatibility and superparamagnetic characteristic of IONPs make them superior over other nanoformulations. The theranostic application is added along with surface modification of MNPs using several polymers, inorganic molecules, and ligands facilitating the application of IONPs-loaded biomolecules. Moreover, owing to its biocompatible property, IONPs can be easily degraded and metabolized into iron as hemoglobin in the biological system. MRI contrasting agents use several dextran-MNPs formulations that have been already approved for clinical trials [109]. Sun et al. investigated the theranostic ability of a peptide conjugated thermally cross-linking the superparamagnetic iron oxide nanoparticles (SPIONs) against breast cancer stem-like cells (BCSCs) [110].

4.4. Carbon-based nanomaterials

Mostly, carbon-based nanomaterials have unique optical, thermal, mechanical and chemical properties. These includes carbon nanotube, nanodiamond, graphene and its derivatives, etc. Recently, these are mostly used for theranostic purposes for biomedical applications including cancer management.

4.4.1. Carbon nanotube

Carbon Nanotube (CNT) is evolving as a promising nanomaterial with tremendous attraction due to their unique properties and are used in numerous biomedical applications. CNTs are tubular materials which have nanometre-sized diameter with axial symmetry providing them with specified characteristics of size stability, bigger surface area, ease for surface functionalization and aspect ratio [111]. CNTs are exploited specifically for cancer cell imaging, carriers, mediators and are also used as a nanocarrier for anti-cancer drugs and genes for treating

cancer.

Luis et al. prepared functionalized multi-walled CNTs (fMWCNT) and oxygen-doped MWCNTs (fCOxs) for investigating its cytotoxicity effects on rat derived mesenchymal stem cells (rMSC). Both fMWCNTs and fCOxs exhibited toxic effects on rMSCs *in vitro*, as shown by the change in cell morphology, slower cell proliferation, and altered cell cycle of MSCs. Cells exposed to fMWCNTs exhibited dramatic variations displaying severe embryotoxicity in chicken embryos whereas fCOxs exerted cardio embryotoxicity along with discrete teratogenicity. Time of contact played a significant role in cell transformation and the toxicity of embryos. Exposing rMSC to fMWCNTs once was not sufficient to alter cells rapidly but the acquaintance of fMWCNTs for two continuous weeks led to transformation along with cardio embryotoxicity effects [112].

4.4.2. Nanodiamonds

Nanodiamonds (NDs) are carbon-based diamond nanoparticles having a large surface area, optical transparency, chemical inertness, hardness and lower toxicity for their use in medical therapeutics. NDs are used as biomarkers, biolabeling and as a fluorescent probe for tracking a single particle in a heterogeneous environment. Additionally, NDs are used in the drug delivery applications for treating cancer where the surface is modified by attaching a targeting moiety for the biological/medical applications and in bio-imaging by interacting with biological objects. It is assumed that ND based drug delivery system offers a promising treatment against the resistant and aggressive diseases [113].

A derivative of ND i.e. Fluorescent nanodiamond (FND) is modified with carboxyl and another functional group. Long Jyun et al. studied the stability of albumin conjugated fluorescent ND specific for tracking mesenchymal stem cells (derived from human placenta choriodecidual membrane) in miniature pigs [114]. Wang et al. showed a promising approach of nanomedicine to overcome chemoresistance in hepatic cancer stem cells by the delivery of epirubicin *via* ND. The ND complex helps in enhanced endocytosis and increased retention within the tumor cell. Hence, ND mediating drug delivery is a promising strategy to overcome drug resistance in CSCs thereby enhancing their treatment against cancer cells [115].

4.4.3. Graphene based nanomaterials

Graphene is a nanocarbon materials which possess brilliant optical and chemical properties [116]. Graphene derived materials such as graphene oxide, reduced graphene oxide, etc have mostly used for many biotechnological applications such as nanoprobes, biosensors, imaging and others [117].

Recently, Toomeh et al., have studied the selective enhanced cytotoxicity effect of radiotherapy in combination with graphene oxide nanoflakes in cancer stem cells that lowers the risk of cancer recurrence [118].

Choi et al., have synthesized a nanocomposite consisting of reduced graphene oxide and silver nanoparticle. They demonstrated the significant toxicity of these nanocomposites towards ovarian cancer and cancer stem cells [119].

4.5. Quantum dots

Quantum dots (QDs) are semiconducting nanomaterials that emit light. The destined characteristics of quantum dots include photophysical properties, broad excitation, and narrow photoluminescence (PL) emission spectra. The important applications of the quantum dots include a cell imaging probe and a tumor-targeting agent. It is reported that unique characteristics of QD includes the brightness and photostability of long-term tissue imaging for *in vivo* cell tracking. QDs have been used as an *in vivo* tracker for tracking the MSCs in regenerative and cancer therapies [120].

Dominyka et al. demonstrated the delivery of semiconductor nanocrystal QDs labelled MSCs under *in vitro* conditions for specific targeted delivery into a human xenograft model [121]. Mahdi et al. modified the surface chemistry of QDs to hydrophilic polymers for attaining colloidal characteristics. Colloidal quantum dots are found to be essential in diagnostics, imaging and stem cell tracking [122].

4.6. Nanobiosensors

Nanobiosensors are found to be latent in the detection of cancer as they have high sensitivity and specificity. They are made by the combination of nano along with biological materials as a carrier system. These nano-scaled materials are useful to detect a minimum quantity of any physical/chemical/biological substances [123]. The diagnosis and therapy of cancer is simultaneously performed by the nanobiosensors with the integration of therapeutic agents. The imaging and therapeutic efficacies are progressed by the use of polymers for delivering nanobiosensors and therapeutic agents. These polymers are very important during the delivery process for enhancing the stability and biocompatibility of the nano biosensors. Nano biosensors are pH-sensitive allowing them to selectively target pathological areas, activate imaging signals and controls the release of loaded substances. The relevant information is conveyed in the form of signals through signal detecting methods. These signals depend on the principle that antibody or the bioligand recognizes the cancer cell which is associated with the intracellular or surface biomarker. The signal transduction mechanism and bio-recognition elements are the basis for diversified nano biosensors varieties [124].

Zheng et al. detected general cancer biomarker with the optical fiber nano biosensor allowing the nanoscale tip to sense telomerase at the single-cell level. The sensitive viable single cell detection is performed by inserting the nanotip restrained with particular antibody into MCF-7 cell lines that assists in detecting telomerase directly along with the performance of *in vitro* enzymatic sandwich immunoassay [125].

5. Delivery strategies of nanotheranostics into CSCs

Traditional therapeutic drugs are inefficient, non-specific and have broader side effects during their course of treatment. Hence it is necessary to develop strategies for extending the retention time, stability and solubility of drugs into the target cells or tissues. Under such circumstances, nanotechnology serves as a powerful tool where a variety of nanomedicines are being formulated to target specific cells with reduced side effects. The therapeutic effects of a variety of nanoparticles against cancer cells are being investigated through clinical trials [126].

5.1. Targeted delivery

Drugs are extremely potent when they are successfully delivered at the target site at an effective concentration while overcoming the physical and biological barriers like mucosal and blood-brain barriers. For example, in the case of delivering the drug through a systemic route, the drug should pass through many biological routes including bloodstream, blood vessels, extracellular matrix, tumor cell membrane and must evade from endosomal degradation to reach its target site. Under such circumstances, nanocarriers play a pivotal role in enabling the drug to reach the target cells either through passive or active targeting and possess several advantages over traditional therapy [74] (Fig. 2).

5.1.1. Passive targeting

Passive targeting is one of the most commonly used approaches for targeting tumors. They occur owing to the leaky vasculature (gaps between cells ranges from 600 to 800 nm) and due to poor lymphatic drainage in tumors. Due to this reason macromolecules such as nanoparticles can enter and accumulate at the tumor site conveniently allowing the subsequent release of the therapeutic molecule at the site. It

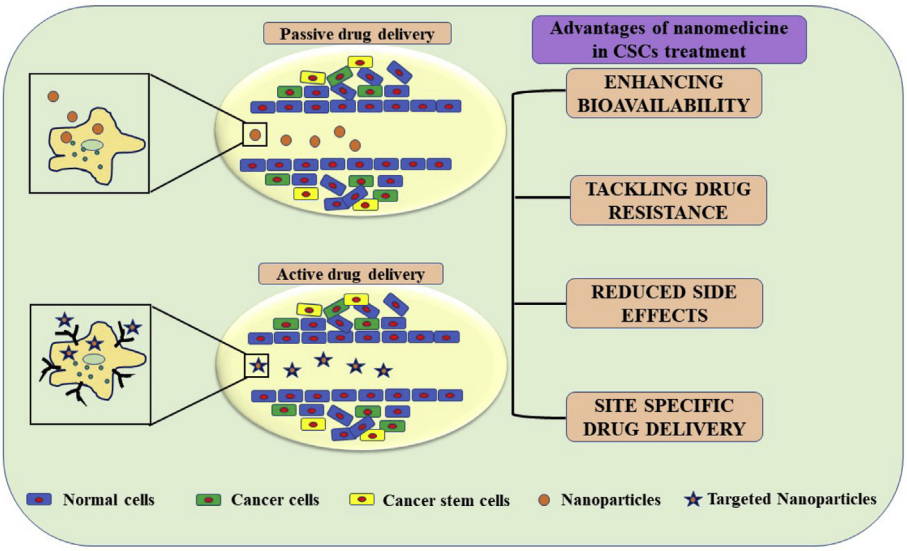

Fig. 2. Delivery mode of nanomedicines for targeted drug delivery and their advantages over traditional therapy. Nanomedicines are actively used in the drug delivery system where drugs are targeted in an active and passive way. Passive targeting is attained by the extended circulation of the drug in the blood and selective 'leaking' of nanomedicines in the typical low-quality tumor blood vessels. Active targeting is achieved by ligand-receptor recognition that makes the nanomedicines accumulate in the tumor tissue. Delivery of nanomedicines to the target cells aids in cancer treatment.

is noteworthy to know that nanoparticles escape from the reticuloendothelial system (RES) clearance and have a long circulation time in plasma. The limitation in this targeting is due to difference in the diffusion of the anticancer drug into the target as tumor vessels permeability varies, while some drugs are permeable and some are unable to diffuse [127].

5.1.2. Active targeting

Active targeting refers to the binding of the drug-loaded cargo-carrier moiety with the target receptor or antigens. This kind of targeting refers to the endocytic delivery model, making them more successful than passive targeting. The increase in the uptake of drugs and enhancement of its accumulation at the tumor proximity is extremely enhanced due to the active entry of drugs leading to the elimination of the CSCs. The surface modification of nanomedicine with targeting ligands/antibodies can also enable active targeting. Nanomedicine binds to the target cells through ligand-receptor interactions, where the bound nanomedicine can be internalized before the drug is released and the nanomedicine is recognized [128]. This is achieved by combining ligands/antibodies to corresponding CSC markers such as CD44, CD133. AML stem cells that express C-type lectin-like molecule-1 (CLL1) could be potentially eradicated by targeted micelles coated with CLL1-targeting peptides [129].

6. Nanotheranostics for CSCs diagnosis, imaging and therapy

Nanotechnology has a crucial significance in cancer prevention, diagnosis, imaging and therapy. This nanotheranostics helps in delivering multiple diagnostic and therapeutic payloads at the target site by crossing different biological barriers. Diagnosis, imaging and selective therapy for tumor has been combined in a multifunctional integrated system providing different methods to approach cancer.

Gold nanostars (GNSs) are investigated to be a developing nanomaterial for their use in nanomedicine, including Raman scattering, imaging and therapy. Yet there are some studies where they used gold nanoparticles as theranostic agents for gastric cancer stem cells (GCSCs) imaging and therapy. PEG-modified GNS nanoprobes functionalized with CD44v6 monoclonal antibody was developed against $CD44^{+}$ GCSCs. These targeted nanothernostics have been used for imaging and photothermal therapy of GCSCs. CD44v6-GNS successfully targets GCSCs and has a wide application in targeted imaging and therapy preventing the recurrence of gastric cancer [130]. Thus, nanotheranostics can be the smart nanoshuttles to deliver the therapeutic molecules at the target sites for diagnosis and therapy (theranostics) with enhanced clinical value and lesser toxicity.

7. Advantage of nanotheranostics for CSCs management

The resistance properties of CSCs have refracted disease curing by current therapeutics and under this scenario, nanotechnology-based tactics provide a ray of light with promising outcomes. Nanotechnology-based therapeutics possess six major advantages over currently used cancer therapeutics in targeting CSCs. (i) The therapeutic index of the formulated drug owing to sustained and controlled delivery manner can be significantly increased by the use of nanomedicines (ii) CSCs can be easily targeted by surface modification with specific ligands conjugated nanomedicines (iii) High transportation efficiency could be achieved with nanomedicines by endocytosis process to deliver the drug across cell membrane (iv) Nanomedicine escapes from the intracellular autophagy (v) Nanomedicine protects the drug from the degradative microenvironment and finally (vi) multifunctional nanoformulations can display synergistic interactions with more than one drug for targeting cancer cells and CSCs [85].

7.1. Enhancing the bioavailability of theranostic agents specific to CSCs

A wide understanding of the CSC has been achieved from extensive research, however, the delivery of anti-CSC agents needs to be explored with effective improvement. Most importantly, the current therapeutics are limited revolving their use to poor solubility, less stability, high toxicity, improper cellular uptake, and increased toxicity. In this context, nanoparticles play a vital role in carrying therapeutic molecules to the disease site with improved activity and bioavailability. Nanoparticles get passively accumulated by the EPR mechanism at the tumor site. Additionally, these nanoparticles can be designed with CSCs specific surface receptors for the enhanced accumulation of nanoparticles in the tumor site offering new prospects for CSCs treatment. Such a rationally designed nanoparticle enables the penetration of drugs into hypoxic microenvironment niches of the tumor which are far away from vasculature for the traditional chemotherapeutics, making nanotechnology a new prospect for CSCs treatment [131].

7.2. Tackling the drug resistance of CSCs

A number of studies have shown that rationally designed nanomedicines provide a strategy for surmounting the ATP pump-mediated drug resistance in CSCs. Studies have reported that drugs in the form of nanoconjugates or encapsulated within the nanoparticle could be

evaded to capture from ABC efflux systems present in CSCs. Moreover, the incorporation of MDR inhibitor in combination with the anticancer drug in a single nanoformulation helps in a significant increase of intracellular accumulation of the drug due to the avoidance of the efflux pump mechanism thereby enhancing the cytotoxic effects of the drug [84].

7.3. Reducing side effects to other normal cells

Genome-wide screening techniques have been a powerful tool in the identification of many CSCs markers and signalling pathways. Unfortunately, some of these markers are found to be displayed by healthy cells by which drugs could have undesirable side effects causing toxicity to healthy stem cells or progenitor cells. Hence it is essential to establish the molecular dissimilarities of CSCs and the other stem cells that are present in the tissue for efficiently targeting specific delivery approaches. The effect of the chemotherapeutic agents on cells other than stem cells residing in the healthy tissues is decreased by the use of NPs [132].

8. Future perspectives

Although nanomedicines provide various benefits, special attention focussing on the safety and toxicological issues in CSCs treatment require much attention. Specific care has to be taken to eliminate CSCs while protecting normal stem cells simultaneously. Molecular studies have been done in order to eliminate CSCs effectively towards the development of new drugs. Moreover, the therapeutic strategy can be improved by targeting the pathways or markers which are unregulated in CSCs only. Furthermore, the possible toxicity of nanomedicine on human health should be investigated deeply. The use of biodegradable polymers in nanomedicine applications can solve the toxicity issues up to a considerable extent. Numerous biodegradable polymers such as PCL, PLA, PLGA, are FDA approved for commercial use. However, they hold some disadvantages of being hydrophobic, possessing high mechanical strength and exhibiting slower degradation rate leading to the slow release of the drug posing various hindrance in meeting the therapeutic needs and may also induce deterioration of the encapsulated agents [83]. Additionally, the conjugation of any hydrophilic moiety to these polymeric nanoparticle surface is not an easy task and requires the need for an amphiphilic linker molecule. In this regard, investigators are attaching hydrophilic polymers with these hydrophobic nanoparticles in order to conjugate hydrophilic targeting moiety [133]. Though several nanomedicines have been developed and applied for targeting CSCs effectively, nanotechnology is still at infancy stage with continuing efforts needed for developing nanomedicines with improved properties in delivering therapeutic agents towards CSCs effectively without any toxicological profiles [134].

Several nanomedicines have reached the clinics successfully for efficient targeting of CSCs. However, the safety profile of nanomaterials is still questionable to determine the level of toxicities in the tumor environment/microenvironment. The nanotechnological approach may aid in overcoming several obstacles of drugs by delivering at the tumor site with increased concentration. Recognizing the potential risks associated with these new developments through meticulous nanotoxicology evaluation might have a crucial role to circumvent such risks and avoid varying side effects. Many more constant efforts and coordination from multidisciplinary aspects may be essential for the understanding of CSCs characteristics and to formulate an effective nanotheranostic system.

Executive summary

- Cancer stem cells are the major reason for cancer recurrence. These are remarkably known to exhibit the discrete property of being resistant to the existing chemo and radio-therapies coupled with its highly invasive and metastasized tumorigenicity potential.
- In this context, numerous forms of nanotheranostics are being deployed for destroying and to achieve simultaneous imaging and therapy of CSCs for cancer management.

Declaration of competing interest

None to declare.

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