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REVIEW PAPER

Cancer stem cells (CSCs): the blockage of metastatic and stemness properties by metal nanoparticles

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ABSTRACT

Cancer stem cells (CSCs) are comprised of hierarchically-organized subpopulations of cells with distinguished phenotypes and tumorigenic capabilities that concrete to metastasis and cancer recurrence. According to related studies, their presence stands as the main reason of cancer associated fatalities. The fundamental feature of these cells is their ability to provide resistance towards conventional treatments or facilitate escaping routes, which include the overexpression of multifunctional ATP-binding cassette (ABC) efflux transporter gene family, metabolism reprogramming, and activation of survivance pathways . Conventional therapies are mainly capable of annihilating cancer cells, while lacking the ability to remove vital CSCs. The recurrence of tumors can be impeded through the targeting of CSCs by different therapies. Nanoparticles with unique properties have emerged as a promising approach for combating stem cancer cells. Therefore, the exertion of nanoparticles, especially metal nanoparticles- based drug delivery systems in cancer imaging and remedial treatment, can surpass the obstacles of conventional treatments. Therefore, the possibility of achieving nonspecific toxicities through the administration of lower but more accurate targeted doses can be provided by the production of theranostic metal nanoparticles and the incorporation of payload drugs into metal nanoparticles carriers, which requires a particular focus on the significance of biomarker targeting for remedial purposes and the unique contrast-enhancing features of theranostic metal nanoparticles for facilitating image-guided delivery. Despite the benefits of using nanoparticles for treating cancer stem cells, yet it is necessary to surpass the numerous challenges and further conduct comprehensive researches.

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INTRODUCTION

According to the strong proofs on the heterogeneous form of most of the malignant cancers, it is affirmed that they contain a populace of cancer stem cells (CSCs) and differentiated cancer cells. Generally, the Heterogeneity of applied cancer stems are recruited to the tumor from various cell types, as well as genetic and/or epigenetic dissimilarities among the cancer cells. In conformity to the discovered proofs in regards to cancer cells, the represented plasticity by tumors is indicative of two classifications of tumor cell population that include CSCs and non-CSCs. There are numerous arguments on the topic of resemblances and diversities among normal tissue stem cells and cancer stem cells (CSCs). The significant traits of normal stem cells and CSCs throughout the quiescent stage are known to be self-renewal and maintenance. Considering the lack of a complete

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comprehension on the origination of CSCs, yet the related data are indicative of their emanation from normal stem, progenitor cells, or possibly other cancer cells. Known as tumor-initiating cells, CSCs are abled to exhibit self-renewal, proliferation, and differentiation proficiency in novel cancer cells. In comparison to non-stem cancer cells, cancer stem cells contain various functionalities and phenotypic traits . According to studies, apparently CSCs are the basis of every villainous that are hidden far from the surface of tumor tissues, while eluding the drugs and anticipating for the proper time to devastate the organ [1-8]. The statues of metastasis, drug resistance, tumor progression, and tumor recurrence condition rely on the functionality of these cells [9-11]. CSCs contain some vital qualities that can significantly affect the process of metastasis and tumor recurrence, which include multidrug-resistant, the overexpression of multifunctional ATP-binding cassette (ABC) efflux transporter gene family as a similar phenotypic property, metabolism reprogramming, and activation of survival pathways. Different elements such as tumor microenvironment, which is consisted of numerous varieties of proteins that contain growth factors and cytokines, can activate CSC survival pathways and possibly fill the functionality of chemo- or radiotherapy for improving the stemness feature through the aid of transforming cancer cells into CSCs. Moreover, the inducement of local and distant metastasis is usually initiated by CSCs through the epithelial-mesenchymal transition (EMT) program (EMT is a property of embryogenesis). In cancers, EMT is implicated throughout the development of tumors into a metastatic phenotype, which is marked by the inactivation of epithelial properties and the upregulation of mesenchymal features. [6, 12-25]. Next to their numerous embryonic or tissue stem cell traits, different cellular signaling pathways are involved in the management of CSC cellular physiology throughout their tumor microenvironment. The arrangement of these signaling routes, which include Notch, Wnt, and Hedgehog, has a substantial functionality in regularizing self-renewal, proliferation, and differentiation traits of stem cells. The mutation or abnormal activation of these pathways' genes can disturb their regulation. There are researches that confirmed the potential of these three pathways in inducing tumorigenesis, driving tumor progression and facilitating epithelial to mesenchymal transition in malignant cells, causing the growth of CSC, forcing metastasis, maintaining the stemness of stem cells, and initiating drug-resistant behaviors in the course of cancer treatment [26-29]. CSCs are considered as the cause of tumor resistance due to their innate resistance to standard therapies such as chemo- and radiotherapy. In this regard, the available treatments can be enhanced and the obstacle of cancer drug resistance can be surpassed in longterm through the application of novel therapeutic strategies with the ability to target CSCs markers. As a result, it is crucial for clinical implications to develop new methods for improving the sensitivity of CSC markers. Nanotechnology provides the possibility of performing targeted and effective drug delivery to desired locations, as well as decreasing the rate of induced side effects on normal cells, facilitating the production of personal medicine, providing simultaneous diagnosis and treatment, and creating a suitable platform to overcome the existing obstacles. The potential of several nanomaterials, such as liposomes, nanoemulsion, polymeric micelles, and metal nanoparticles , in functioning as the carriers of therapeutic agents were examined for the treatment of CSCs [30-32]. A large number of research has been conducted on the exertion of metal nanoparticles throughout CSCs therapies. Choi et al. reported the application of Graphene Oxide – Silver Nanocomposite for improving the Cytotoxic and Apoptotic Potential of Salinomycin in Human Ovarian Cancer Stem Cells (OvCSCs). Their results displayed the inducement of a notable toxicity in both ovarian cancer cells and OvCSCs. Apparently, the applied nanocomposite showed toxicity towards OvCSCs and decreased the cell viability through the mediation of generated reactive oxygen species, causing the leakage of lactate dehydrogenase, decreasing the potential of mitochondrial membrane, and improving the expression of apoptotic genes, which leads to the inducement of mitochondrial dysfunction and possibly initiates the occurrence of apoptosis [33]. In the work of Hembram and colleagues, Quinacrine Based Gold Hybrid was applied in Nanoparticles, CSCs model SCC-9 oral cancer cells, to achieve QAuNP, which displayed a satisfying anti-CSC growth potential in opposition to SCC-9-cancer stem like, while down-regulating the agents of CSC marker. The observance of an extended G2 / M population and apoptosis to SCC-9-CSC like cells were considered as the signs of S-phase arrest and the generated re-replication that occurred

as a result of QAuNP lengthened exposure. In general, a irreversible replication fork movement was caused by the QAuNP treatment. Additionally, MRE-11 may have caused a degradation in the stalled replication fork that ultimately leads to the occurrence of apoptosis and CSCs annihilation [34]. In the current review, next to presenting the highlights of recent major progresses in metal nano particle-based techniques in regards to CSC-specific markers and/or related signalling pathways, we also explored the application prospects and discussed the related issues, approaches, and challenges.

CSC ISOLATION AND CHARACTERIZATION

There are similarities and differences between the functionality and phenotypic properties of normal tissue stem cells and cancer stem cells (CSCs), which resulted in the expansion of various assays for isolating and distinguishing the CSCs. Certain substantial features, including self-renewal and lineage capacity, can facilitate the recognition of CSCs [35-38]. Moreover, they can be also distinguished through more specific qualities that include phenotypic surface markers similar to CD34+/CD38− in leukemia cells, CD44+/CD24− in solid tumors, CD133+ in other tumors, and EpCAM. In the form of a transmembrane protein, there are reports on the overexpression of CD44 on varying cancer cells, which include breast, prostate, gastric, pancreas, ovary, colorectal, bladder, hepatocellular, head and neck, and leukemia CSCs. The existing glycosaminoglycan (hyaluronic acid) in extracellular matrix forms a binding with this protein to facilitate the attachment of CSC, as well as contribute to the proliferation and migration of stem cells. Known as a cell surface glycoprotein, the major expression of CD133 (Prominin-1) can be observed on certain types of CSCs of solid tumors that are implicated in glioma, lung, and breast cancer. In addition, reports are indicative of its highly expression on the CSCs of various cancers throughout varying tissue origins that augmented drug resistance. CD24 is a 27-amino-acid single-chain protein that can form a binding to the extracellular matrix and is widely exerted as a cancer stem cell marker. Its overexpression has been observed in numerous cancer cases including nasopharyngeal carcinoma, ovarian cancer, and pancreatic cancer. The hallmark of haematopoietic stem cells is known to be CD34 transmembrane protein. The population of CD34 cell within bone marrow is composed of haematopoietic stem cells and progenitor cells, while being capable of functioning throughout reconstruction progresses in humans and certain primates. According to related reports, CD34 can maintain the self-renewal, bipotency, and tumorigenicity properties of CSCs. In the form of a I trans-membrane glycoprotein, EpCAM is composed of 314 amino acids of extracellular, trans-membrane, and cytoplasmic domains . This protein can function in various roles such as cell-cell adhesion migration, proliferation, cell cycle metabolism, cell signaling, cell differentiation, metastasis, regeneration, and organogenesis [39-46]. CSCs can be chiefly isolated through the exertion of (fluorescence-activated cell sorting) technique. This uncomplicated procedure involves fluorescent activated cell sorting and is exerted for the purification and isolation of CSC. FACS is contingent on the expression of various particular cell surface markers including CD24, CD34, CD44, and CD133, EpCAM [47-50] . One of the standard methods for isolating CSC is MACS (magnetic-activated cell sorting), which is build upon the implication of specific stem cell markers and can provide the isolation of high-quality cells from a heterogeneous population cell. In this technology, the cell surface markers are initially tagged with monoclonal antibody (mAb) or magnetic microbeads to perform a complete isolation. Then, positive selection is conducted to remove the unmarked cells and sequester the marked cells, as well as to impressively isolate the objective cells from a cell suspension [51-54]. CFU(colony-forming unit assay) is recognized as a quantitative and high-throughput procedure, which is reported to be analogous for in vivo transplantation. The utilization of CFU assay helps to examine the pattern of CSC proliferation and differentiation through their quality of producing colonies within a semisolid medium. A peculiar number of input cells are required to create these colonies in order to provide vital data on the proliferation and differentiation potential of CSCs. Briefly, in a non-adhesive manner, CSCs are cultured within a serum-free medium that had been supplied with growth factors for the purpose of developing into tumorspheres. As the cancer cells are subjected to anoikis (a suspension-induced apoptosis) throughout the arranged conditions, CSCs have the ability to remain alive and produce tumorspheres on the colony basis. The ability of this technique in isolating highly pure CFU can facilitate the achievement of accurate cellular

and molecular characterization of existing cell populations [55-57]. An overexpressed situation of drug can efflux transporters, particularly BCRP or ABCG2, and consequently function as the basis of CSCs isolation. For instance, the cell populations with the ability to efflux Hoechst 33342 dye can maintain the properties of CSC throughout different types of cancer,; considering these facts, this procedure stands as the most popular route for isolating CSCs [19, 58-61].

COMMON TREATMENTS IN CANCER STEM CELL THERAPY

Due to the many disadvantages and restrictions of the common therapeutic tactics for cancer, including chemo- and radiotherapy, the applied treatments are often defeated and result in the recurrence of cancer in patients. The available treatments are incapable of particularly targeting CSCs and consequently cause toxicity in normal tissues, which heightens the risk of illness recurrence in patients[62-64]. Recently, a number of developed approaches with the particular goal of eliminating CSCs and varying their niche were studied due to the significance of CSC omission for deflecting cancer recurrence. The effectiveness of a therapy relies on its ability in targeting both CSCs and non-CSCs. Current researches attempted to consecrate the multiple modern remedial approaches for extinguishing CSCs. The alterations in signaling pathways (Notch, Wnt, and Hedgehog) and surface marker differences are alluring remedial purposes for CSC therapy. The securing of EMT and acquisition of CSC phenotype, which assists the metastasis potential of CSS, are the factors of establishing the direct link of signaling pathways. The focus of many studies was centered on the surface marker differences and dysregulation of signaling pathways in CSCs in order to discover enhanced techniques to successfully treat cancer patients. According to related researches, the application of surface markers as significant targets can be considered for therapies, which include CD133 ,CD44,CD24 and etc . The selected ligands or antibodies are applied as the surface markers in order to be implicated in chemotherapy, radiotherapy, and surgery . As a very significant factor, the enhancement of monoclonal antibody is emphasized in the process of targeting CSCs [13, 26, 65-78] . Moreover, some studies reported the certain CSC remedial targets with a higher potential such as ABC transporter-binding protein and microenvironment niche. Next to the expression of high levels of ABC transporter proteins in CSCs, these proteins can facilitate the preserving of CSCs from therapeutic agents. Therefore, the downregulation of these proteins can stand as a applicable method for conquering the inducement of drug resistance to common Traditional cancer therapies and prevent the occurrence of recurred conditions. Tumors are composed of cancer cells and intricate organs that contain a large number of other recruited cells, which may be in correlation to the transformed cells. Tumors microenvironment (TME) is consisted of interplays that exist among cancer and non-transformed cells. The tumor microenvironment (The cells of the immune system, Proteins, peptides, growth factors, cytokines, the lymphatics, endothelial cells, extracellular matrix,the tumor vasculature, pericytes, fibroblasts, and adipocytes and etc) aids to defend the CSCs from outside toxic agents [79-90]. In addition, next to CSC survival and chemo-resistance, tumor angiogenesis is a vital factor that is triggered by VEGF. According to many studies, targeting VEGF with certain antibodies, such as bevacizumab, can normalize the tumor vasculature and cause a decrease in tumor stem cell number [91-94] . Generally, the current treatments in Cancer Stem Cell Therapy that are build on various targeting methods (Table 1) include tumor microenvironment, surface marker expression, deregulated signal cascades, and ABC transporters, which facilitate the prevention of relapsed conditions.

Abbreviations in this table are defined as the following: TRXT :Tarextumab, McAb: monoclonal antibody , PTX: paclitaxel, FAP :fibroblast activation protein, Smo: smoothened, Hh: Hedgehog, LGR5: encoding an R-spondin (RSPO) receptor, FZD: Frizzled, CS : Chondroitin sulfate[is founded in extracellular matrix], VEGF : Vascular endothelial growth factor, EpCAM : epithelial cellular adhesion molecule, small-molecule porcupine inhibitors (Signaling pathwayWNT: ETC-159, WNT-C59 and WNT974), tankyrase inhibitors (Signaling pathwayWNT: AZ1366, G007-LK, NVP-TNKS656 and XAV939),CD44: Cluster of differentiation 44, CD24: Cluster of Differentiation 24, CD34: Cluster of Differentiation34, miRNAs: microRNAs , ABCB1: P-glycoprotein/P-gp; multidrug resistance 1/MDR1,ABCC5: multidrug resistance protein 5, ABCG2: ATP-binding cassette sub-family G member 2, MDR : multidrug resistant, ABCA2:ATP

Table 1. Elimination of CSCs based on different targeting approaches

The current therapies to target CSCs	Drug		Target site	References
Deregulated signal pathways	Notch	MK-0752	Notch1	[95]
		Tocilizumab	Notch3	[96]
		RO4929097	Notch1	[8]
		Demcizumab (OMP-21 M18)	Notch 1	[97]
		WC75, WC629	Notch1	[98]
		OMP-52M51 (brontictuzumab)	Notch1	[99]
		N3_E10	Notch3	[100]
		N1_E6	Notch1	[101]
		N2_B6, N2_b9	Notch2	[100]
		256A-13	Notch3	[102]
		(Roche) PF-03084014	Notch1	[103]
		OMP-59R5, TRXT + paclitaxel + Gemcitabine	Notch 2/3	[104]
		nab-paclitaxel+ gemcitabine	Notch3	[105]
		RO4929097+ capecitabine	Notch1	[106]
		RO4929097 +gemcitabine	Notch1	[107]
		RO4929097 + temsirolimus	Notch-3	[107]
	WNT	OMP-54F28 (FZD8-Fc)	WNT	[108]
		miR-574-5p	WNT	[109]
		OMP-18R5 (Vantictumab)	WNT	[110]
		anti-LGR5 antibody-drug conjugate (ADC)[(mAb-mc-vc-PAB-MMAE)]	WNT	[111]
		anti-PTK7 ADC (PF-06647020)	WNT	[112]
		anti-ROR1 mAb (cirmtuzumab)	WNT	[113]
		anti-RSPO3mAb (rosmantuzumab)	WNT	[114]
		ETC-159	WNT	[108]
		WNT-C59	WNT	[115]
		WNT974	WNT	[116]
		AZ1366	WNT	[117]
		Av65	WNT	[118]
		G007-LK	WNT	[119]
		Sulindac	WNT	[120]
		NVP-TNKS656	WNT	[121]
		XAV939	WNT	[122]
		BC2059	β-catenin	[123]
		CWP232228	β-catenin	[124]
		ICG-001	β-catenin	[125]
		PRI-724	β-catenin	[126]
		Thiazolidinedione	β-catenin	[127]
		PNU-74654	β-catenin	[128]
		NSAIDs	β-catenin	[129]
		GANT61	Gli 1/2	[130]
		Femara® (letrozole)	Gli 1	[131]
		NVP-LDE225	Gli 1, Smo ,Ptch1	[132]

Continued Table 1. Elimination of CSCs based on different targeting approaches

The current therapies to target CSCs	Drug		Target site	References
	Hedgehog	NVPBEZ235	Gli 1/ Gli2, Ptch1/Ptch2	[133]
		IPI–92666	Smo	[134]
		GDC-0449128 (Cur-61414)	Smo	[134]
		BMS–833923129	Smo	[134]
		Robotnikinin64	Smo	[134]
		PF–04449913	Smo	[135]
		HPI 1–465	Gli1, Gli2	[136]
Tumor microenvironment		PF-06647020	WNT	[137]
		Hu5F9-G4	anti -CD47	[138]
		IO3D9	anti -CS	[139]
		IO3H10	anti -CS	[140]
		IO3H12	anti -CS	[141]
		GD3G7	anti -CS	[142]
		TRC105+ bevacizumab	anti -VEGF	[143]
		mAb FAP5-DM1	Anti- fibroblast	[144]
		αFAP-PE38	Anti -fibroblasts	[145]
		ab28244	Anti-FAP	[146]
		RIP140	Anti-Adipocytes	[147]
CD markers		H90	anti-CD44	[148]
		H460-16-2	anti-CD44	[149]
		Bivatuzumab (BIWA-4)	anti-CD44	[150]
		ING1	anti-EpCAM	[151]
		MT201	anti-EpCAM	[152]
		Catumaxomab	anti-EpCAM	[153]
		Selumetinib (AZD6244; ARRY-142886)	anti-CD44/CD24	[154]
		LabVision	anti-CD44/CD24	[155]
		SN3b	Anti-CD24	[156]
		Neomarkers	anti-CD44/CD24	[157]
		Fremont	anti-CD44/CD24	[158]
		VFF18	anti-CD44	[159]
		Millipore	anti-CD44	[160]
		Billerica	anti-CD44	[161]
		VFF-327v3	anti-CD44	[162]
		156-3C11	anti-CD44	[163]
		AC133	anti-CD133	[164]
		AC141	anti-CD133	[165]
		293C3	anti-CD133	[166]
		CMab-43	anti-CD133	[167]

Continued Table 1. Elimination of CSCs based on different targeting approaches

The current therapies to target CSCs	Drug	Target site	References
	C2E1	anti-CD133	[168]
	293C3	anti-CD133	[169]
	BXP-21	anti-CD34	[170]
	581 (PE)	anti-CD34	[171]
	QBEnd10	anti-CD34	[172]
	My10	anti-CD34	[173]
	FITC-518	anti-CD34	[174]
	AC136	anti-CD34	[175]
	8G12	anti-CD34	[176]
	5B12	anti-CD34	[177]
	4C8	anti-CD34	[178]
	Nilotinib	anti - CD34/CD38	[179]
	Ebiosciences	anti-CD38	[180]
	HIT2	anti-CD38	[181]
	miR-205	ABCA2 /ABCA5	[182]
	miR-200c	ABCG5 /MDR1	[183]
	miRNA-451	ABCB1	[184]
	miR-27a	ABCB1	[185]
	miR-137	ABCB1	[186]
	miR-145	ABCB1	[187]
	miR-298	ABCB1	[188]
	miR-331-5p	ABCB1	[189]
	miR-451	ABCB1	[190]
	miR-1253	ABCB1	[191]
	miR-138	ABCB1	[192]
	miR-296	ABCB1	[193]
	miR-491-3P	Caco-2 / ABCB1	[194]
	miR-9	ABCB1	[195]
	MiR-223	ABCB1	[196]
	MicroRNA-873	ABCB1	[197]
	miR-212 and miR-328	ABCB1 /ABCG2	[198]
	miR-34b/miR-892a	ABCB1/ABCB4	[199]
	miR-491-3p	ABCB1	[200]
	miR-508-5p	ABCB1	[201]

-binding cassette transporters A2, ABCA5:ATP -binding cassette transporters A5 , ABCB5: ATP-binding cassette sub-family B member 5, ABCC5: Multidrug resistance-associated protein 5, ABCG5: ATP-binding cassette sub-family G member 5, ABCB4 : ATP Binding Cassette Subfamily B Member 4.

METAL NANOPARTICLES-BASED DELIVERY SYSTEM FOR CANCER STEM CELL THERAPY

Currently, there are several effective therapeutic agents available in clinics for cancer patients that generally include surgery, chemo- or radiotherapy drugs, therapeutic nucleic acids, targeted monoclonal antibodies, small molecular inhibitors, and their combinations. These treatments are mainly capable of annihilating the cancer cells and can not remove the CSCs that exist throughout the population of tumor cell, which effectively getaway by applying certain resistance processes. According to the recent concept of CSC, the recurring condition is fundamentally assisted by the innate and earned resistance technique from the existing CSCs population in cancer cell mass. The potency of CSC in eluding the regular therapeutic orders is caused by their slow-cycling phenotype, the upregulated expression of efflux pumps (ABC), antiapoptotic proteins, competent DNA response, and repair machinery. Apparently, the therapeutic potential of these agents faced a reduction in clinical trials as a result of varying restrictions such as very weak stability, weak water solubility, lenient biodistribution, terse circulation time, or off-target impacts. Moreover, CSCs can inhabit throughout low oxygen regions (Hypoxia) away from vascularized area and consequently hinder the effectiveness of remedial agents delivery [202-222] . The results of some studies indicated the feasible functionality of chemo- or radiotherapy in augmenting the stemness feature through the conversion of cancer cells into CSCs. According to recent reports, the irradiation of breast cancer cells can result in augmenting a portion of CSCs population, while other discoveries pointed out the ability of some noncancerous cells in gaining the phenotype feature of CSC. Furthermore, traditional viewpoints claim that cancer cells initiate the progress of a small cancer cell population with drug resistance behaviors as a result of repeated chemotherapeutic remedy, which can lead to the inactivation of drugs, changing drug targets, and decreased drug aggregation within the cancer cells. The performed investigations on the monoclonal antibodies that are exerted for targeting CSC marker inculcated their potency in impeding the progress of tumors. In fact, there are many successful studies on CSC targeting antibodies that were permeated to propel on to the clinical trial stage. Nevertheless, a great number of antibodies lacked the sufficient efficacy for treating patients and caused the recurrence of tumors due to the drug-resistant behavior of cancer cells [223-227] . This survival ability of CSC result in illness recurrence with the creation of more malignant and highly invasive tumors that display resistance to chemo- and radiotherapy. In this regard, the remedy of tumors with conventional methods ends up in the increment of CSC fraction that cause the tumor cells survival and induce metastasis at distant positions. Generally, a complete treatment requires the annihilation of CSC along with the removal of non-CSCs. Therefore, tumor-recurrence conditions can be ruled out by targeting CSCS with diverse remedial modalities. According to previous data, the solo targeted elimination of CSC can not thoroughly cure a cancer disease due to the plasticity and heterogeneity of cancer cells that evert their phenotype into CSCs. Considerably, it is necessary to focus on the enhancement of modern remedial procedures capable of performing the simultaneous elimination of both multiple drug-resistant CSCs and bulk malignant tumor cells. Therefore, nanomedicine-assisted drug delivery systems succeeded in attaining the interest of many for conquering these obstacles . Nanotechnology has made different considerable developments throughout biomedical science such as the design of nanoparticle-based drug delivery systems, including liposomes, dendrimers, metal oxide nanoparticles, polymeric nanomicelles, and carbon nanotubes that attained the attention of many researchers. The loading of nano-medicines with high payload of single or multiple drugs requires control over their size and surface feature. Therefore, the enhancement of pharmacokinetic and pharmacodynamic features of nanomedicines became possible through the reduction of their side effects on normal cells. The amazing potential of nanomedicine-based procedures was conformed due to providing a multipronged route of selectivity and more profound bioavailability. Moreover, the optimization of biocompatibility and pharmacokinetic features of these nanodrug carriers is achieved by modifying the surface of

nanoparticles. The previously mentioned restrictions can be hopefully resolved through the distinct qualities of nanomedicines, which include having control over size, tunable surface features, surface-to-volume ratios, interesting surface functional groups for bioconjugation, reduced rate of nonspecific biological distribution, and fewer side effects [18, 227-245] . The simple passage of nanomedicines through blood capillaries for contacting the target site is facilitated by their smaller size (~200 nm). Various multifunctional nanoparticles formed their cancer therapeutic usages in available settings under the specific goal of targeting CSC. In recent years, some novel procedures were formulated to successfully target CSS, such as the design of nanoparticles that implicate a targeting ligand particularly for CSC that accommodate an anticancer drug molecule for omitting the combined CSS with a chemosensitizer to conquer drug resistance (such as an ABC transporter inhibitor) and an imaging agent to assist the tumor. Such combination procedures may be capable of performing a more impressive anti-tumor impact along with a reduced rate of side effects, while simplifying the accurate recognition of primary tumor localization and its metastases as well. The most significant benefit of nanocarriers is their ability to conduct the simultaneous delivery of multiple drugs . The exertion of varying kinds of nanomaterials, such as polymeric nanoparticles, metal-based nanoparticles, carbon nanotube, magnetic nanoparticles, and liposome, were considered for preparing targeted nano-drug carriers in order to target CSC by the application of chemo-drugs, antibiotics, nucleic acids, peptides, and proteins. The mentioned remedial agent modalities are capable of targeting downstream cellular signaling pathways, CSC survival-associated genes, cell surface markers, and metabolic pathways [246-249]. The interest of many has been invested in designing and developing a multifunctional and stimuli-responsive metal nanoparticles -based drug delivery system in regards to the diagnosis and therapy of cancer stem cells. Considering the quick progress of nanomedicine, the unique physical and chemical features of metal nanoparticles (gold, iron, silver, copper, tetanium,cobalt, nickel), including their high surface areas ,size, shape and surface construction, as well as their distinct optical , electronic , chemical and photoelectrochemical qualities ,size-dependent physicochemical features and etc, outshined the other options as a theranostic tool in biomedical implementations such as diagnostic imaging, drug delivery , gene therapy, novel therapeutics, magnetic resonance imaging , cell mechanics , hyperthermia , tumor advancement, in vivo tracking of stem cells, and cell detachment [234, 250-260]. The constructed Surface-functionalized metal nanoparticles by the utilization of engineered surface ligands provided useful approaches for the application of metal nanoparticles-based drug delivery systems in cancer imaging and remedial treatment for the objective of surpassing the difficulties of conventional treatments. The design and development of stimuli-responsive ligands were incorporated with the engineering of multiple physicochemical properties into metal nanoparticles for enhancing the efficiency of metal nanoparticles-based delivery system (Fig. 1). As a result , the production of theranostic metal nanoparticles and incorporation of payload drugs into metal nanoparticles carriers can offer a chance of achieving nonspecific toxicities through the application of lower but more accurate targeted doses, which required a particular focus on the significance of biomarker targeting in regards to remedial purposes along with the distinct contrast-amplifying features of theranostic metal nanoparticles that provide image-guided delivery [261-269] . Recently, researchers attempted to formulate several metal nanoparticles -based drug delivery system for CSC therapy (Table 2).

Abbreviations in this table are defined as the following: Glu-NP: Glucose-installed nanoparticle, siRNA :small interfering RNA, AuNPs: Au nanoparticle, PEG: Poly (ethylene glycol), HA: Hyaluronic acid, DOX :doxorubicin , G5- PAMAM: fifth-generation polyamidoamine dendrimer, Fe3O4@SiNPs:core/shell construction that the silica shell encapsulating Fe3O4 nanoparticles as the magnetic core, HSPI: heat shock protein inhibitor, CD20: Cluster of Differentiation 20, SPIONPs: super-paramagnetic iron oxide nanoparticles, aptamer CSC1:aptamers selected against DU145 prostate cancer cells, aptamer CSC13:subpopulation of prostate cancer stem cells, PDC:polydiallyldimethylammonium chloride, ABCG2: ATP-binding cassette sub-family G member 2, PTX: paclitaxel, EGFR: epidermal growth factor receptor, Dtxl:docetaxel, PLGA :poly(D,L-lactic-co-glycolic acid), PAH: poly(allylamine hydrochloride).

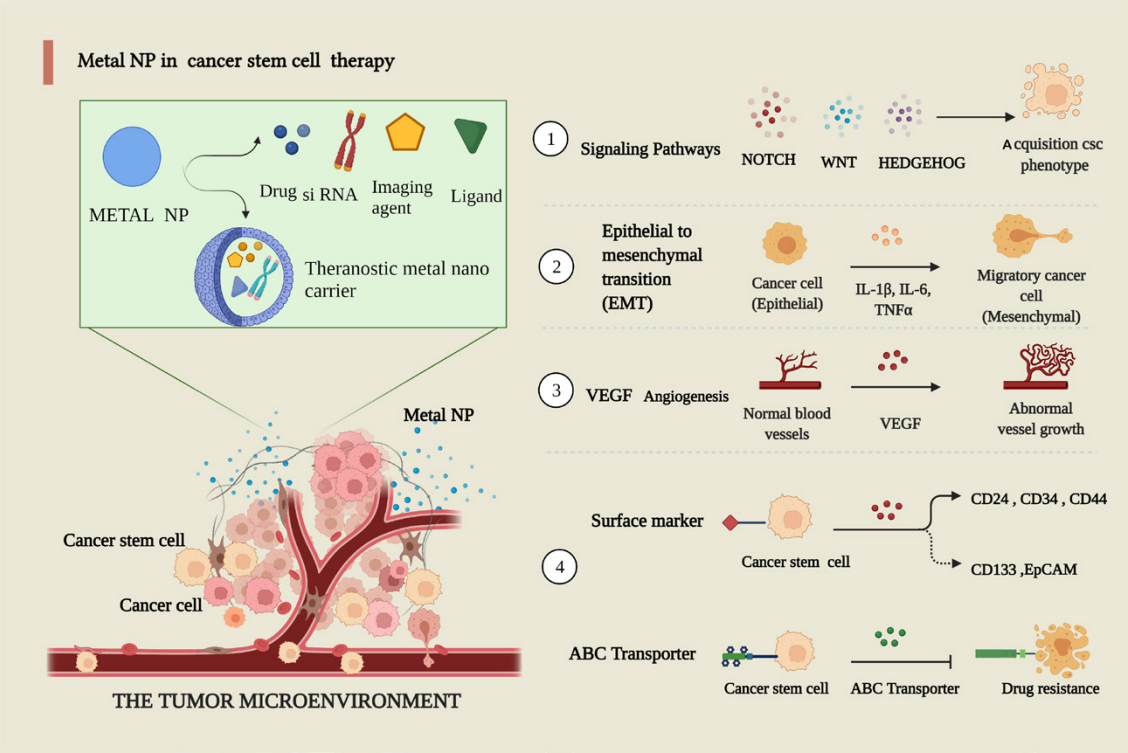

Fig. 1. Metal nanoparticles (iron, silver, copper, titanium, cobalt, nickel and gold) are used as theranostic agents for drug delivery systems in cancer imaging and therapy to overcome the obstacles of conventional treatment.

CHALLENGES OF TARGETED BIO-CONJUGATED NANOPARTICLE CANCER STEM CELL THERAPY

The promising stance of targeted nanoparticles design for CSC therapy is due to the ability of nanoparticles in enhancing the drug concentration in CSCs for the occurrence of omission throughout the tumor mass. In this regard, the remedial effectiveness of anti-CSC drugs for clinical trials can be increased by synthesizing targeted nanoparticles, which would also decrease the required time of treatment and result in achieving better outcomes from the patients; nevertheless, the form and optimizing process of impressive nanodrug carriers needs further investigations [294-297] .In recent years, next to the outshining progress in assessing the design of Targeted Nanoparticle bioconjugates to function as effective chemotherapeutic agents, however, the achievement of applicable and impressive cancer treatment is predicted to be very distant. The conjugation of nanoparticles (NPs) with different ligands can lead to the production of very selective products in binding to the target, which would consequently enhance their efficacy and lower the induced toxicity. It is necessary to consider the challenges that rely on different parameters which determine the success and effectiveness of these products [100, 298, 299] . One of the most substantial obstacles is the existence of an interplay among the nature and size of NP and ligand. The traffic of NP throughout the body is controlled by their size as a significant parameter. Next to the befitting ability of small NPs in passively targeting tumors, however, they can be easily cleared by kidneys which is quiet problematic. On the other hand, the availability of larger NPs is restricted by their size which is considered as a disadvantage [300-304] . Another challenge that needs to be addressed is the modification of targeting moiety that is required to obtain a higher therapeutic efficacy and leads to the inducement of several issues such as expanded complexity, regulatory barriers, and extra cost. In addition, numerous questions were generated by the performed practices in regards to nanoparticle targeting and drug aggregation throughout the appointed tumor and CSC subpopulation. Considering this

Table 2. Metal nanoparticles-based delivery system for Cancer Stem Cell Therapy

Nano metal carriers	Ligand	Drug	The role of metal nanoparticles	Application	References
AuNPs	DNA	-	Radiosensitizer	Glioma stem cells	[270]
Glu-NP	Au nanoparticle	siRNA	Ligand-mediated targetability	Glucose ligand to the glucose transporter 1(GLUT1)overexpressed on the CSC surface in breast cancer	[271]
AuNPs	AS1411 aptamer	-	Sensitize cancer cells and enhance the absorbed dose	Breast cancer stem cells	[272]
AuNPs	-	-	Sensitize pancreatic cancer cells to gemcitabine	Reduced cancer cell stemness in pancreatic cancer	[273]
PEG-coated gold nanoparticles (GNP)	-	-	Sensitize solid tumors to cold plasma	Blocking the PI3K/AKT-driven signaling axis - Suppress cellular transformation by inhibiting growth and EMT - Decreased CSC population	[274]
Hollow gold nanosphere (HAuNS)	Aptamer (selectively destroyed the CD30-expressing lymphoma cells)	Doxorubicin (DOX)	Carrier of the drug	The Apt-HAuNS-Dox was capable of selectively annihilating lymphoma tumor cells	[275]
G5- PAMAM-Au	HA	Recombinant methioninase (rMETase) [pcDNA-rMETase]	Enhances the therapeutic effect of HA-G5 PAMAM-METase	Inhibits gastric tumor growth via targeting CD44+ gastric cancer cells	[276]
Gold nanoparticles (GNPs)	Peptide CBP4	-	Imaging agent	Diagnosis of brain glioma stem cell marker CD133	[277]
GNP-Corona	-	Suberoylanilide hydroxamic acid (SAHA) Vorinostat+ PKF118-310	Carrier of the drug	induced Reduction in The MCF7 breast cancer stem cells	[278]
Ag NPs	-	-	Anti-cancer agent	inducement of Toxicity and differentiation effects of AgNPs in teratocarcinoma stem cells	[279]
Ag NPs	-	-	Anti-cancer agent	Cytotoxic Potential of Silver Nanoparticles in Human Ovarian Cancer Cells and Ovarian Cancer Stem Cells	[280]
A platelet–cancer stem cell (CSC) hybrid membrane-coated iron oxide magnetic nanoparticle (MN)	-	-	- Imaging agent(MRI contrast) -Photothermal therapy agent	Enhanced antitumor efficacy in the complex tumor microenvironment of Head and Neck Squamous Cell Carcinoma	[281]

Table 2. Metal nanoparticles-based delivery system for Cancer Stem Cell Therapy

Nano metal carriers	Ligand	Drug	The role of metal nanoparticles	Application	References
Fe3O4@SiNPs	Anti-CD20	HSPI	Thermo-therapeutic agent	Targeted destruction of cancer stem cells using multifunctional magnetic nanoparticles that enable combined hyperthermia and chemotherapy	[282]
SPIONPs	Anti -CD44	-	-Hyperthermia agent	CD44-Targeted Magnetic Nanoparticles destroyed Head And Neck Squamous Cell Carcinoma Stem Cells	[283]
Magnetic nanoparticles		Neuropilin-1 (NRP-1)	-Diagnosis and Therapy agent	- Diagnosis and therapy of gliomas	[284]
Iron oxide nanoparticles	Anti -CD44	Gemcitabine	- Nano Carrier	-Multi functionalized iron oxide nanoparticles for selective drug delivery to CD44-positive cancer cells in Breast Cancer	[285]
Macrophages	-	NP-Fe2O3	- Imaging agent - Improvement of the radiotherapeutic effect	-Improved effects of radiotherapy on tumor cells (non-CSCs, CSCs)when they were at the vicinity of laden macrophages	[286]
Gold nanorods (AuNRs)	Aptamer CSC1+ Aptamer CSC13	-	-Photothermal therapy agent	-Aptamer-Conjugated Nanorods for Targeted Photothermal Therapy of Prostate Cancer Stem Cells	[287]
PEG-AuNPs	Acid-labile hydrazone	Doxorubicin	-Nano Carrier	-Deliver chemotherapeutics to both cell populations (i.e., CSCs and non-CSCs cells) in breast cancer	[288]
PDC-AuNPs	-	Salinomycin (SA)	-Hyperthermia agent - Carrier of the drug	- Synergistic inhibition of BCSCs via hyperthermia and SA treatment	[277]
Fe3O4 NPs	ABCG2 mAb	ABCG2 mAb +PTX	- Carrier of the drug	-Inhibiting ABC transporters by antibody and targeting of CSCs by PTX-loaded magnetic NPs	[289]
Iron-oxide NPs	Cetuximab/EGFR and EGFRvIII	Cetuximab	- Carrier of the drug - Imaging agent(MRI contrast)	-Inhibit tumor growth (stem-like cells and tumor non-stem cells)and increase survival rate of GBM xenografts	[290]
Core-shell: Core:PLGA+ SPIONs Shell: PAH +PEG	Single-chain prostate stem cell antigen antibody(PSA)	Dtxl	- Carrier of the drug - Imaging agent(MRI contrast)	-Nanoparticles provided a negative MRI contrast enhancement and tumor growth inhibition in PC3M xenograft mice models agents in Prostate stem cell	[291]
SPIO NPs	-	-	-Hyperthermia agent	-Effective CSC eradication by magnetic hyperthermia in A549 and MDA-MB-231tumor cells	[292]
AuNPs	Anti-EGFR (C225)	Gemcitabine	- Carrier of the drug	-The nanoconjugates containing gemcitabine -C225 can specifically reach the metastatic tumor cells both in vitro and in vivo with enhanced efficacy in Pancreatic Adenocarcinoma	[293]

scheme, it is assumed by a substantial paradox that the appending of targeting moiety onto the surface of nanoparticles concedes with the stealth quality of nanoparticles, while intensifying their clearance by reticuloendothelial system from host body. The benefit of nanoparticles high avidity is recognizes as one of their conundrums, however, this quality causes a reduction in the infiltration ability of targeted nanoparticles into the tumor core. As another major challenge, observations were indicative of the existence of some CSC populations in the necrotic region of tumors, which is quiet difficult to be reached by targeted nanocarriers. Overall, the treatment of cancers that implicate accessible CSCs such as leukemia diseases can benefit from the application of targeted nanocarriers. Since a large number of CSC markers are utilized throughout the enhancement of targeted nanocarriers, the inducement of unwanted toxicity is expected due to their reported expression on normal stem cells; consequently, the discovery of highly CSC-specific ligands remains as a ambitious and difficult assignment [305-312]. Another major challenge related to CSC is to succeed in the particular targeting of slow-cycling cancer stem cells as one of the fundamental causes of recurrence condition. Moreover, there are other confrontations such as therapeutics targeting brain-related cancers that are limited by the blood-brain barrier, which makes it very difficult for targeting NP-bioconjugated to reach such tumors[3, 313, 314] . Furthermore, the high surface area and free surface energy of NPs stand as a crucial obstacle that requires attention since they can impact the obtained colloidal stability. There are inquiries for the exertion of surfactants, polymers, and proteins to cause improvement in the colloidal stability . Nevertheless, it is of outmost importance to discover a method for the oral delivery of bio-conjugated NPs by crossing the intravenous route and completing the procedure, which would benefit a tremendous number of patients [315-320] . Another fundamental challenge that has concerned many is related to the adverse biological impacts of NPs at cellular, tissue, organ, and organism levels due to the possibility of resulting in the inducement of nanotoxicity. Certain biophysical properties, including size and surface features, can influence these products in vivo distribution, and consequently affect the signaling pathways and biological functionalities. different researches reported the negative effect of varying NPs on the liver, kidney, and skin through the upregulation of inflammatory pathway[321-324], Some studies indicated the potential ability of nanoparticles in heightening the rate of epigenetic alterations, which implicate histone posttranslational modifications and DNA methylation [325, 326].

CONCLUSION

cancer stem cells (CSCs) are known to contain different mechanisms for escaping conventional treatments, which leads to tumor recurrence and relapse. Moreover, the therapeutic efficacy of conventional agents faced a reduction as a result of different limitations such as weaker stability, weak water solubility, lenient biodistribution, terse circulation time, or off-target effects. A complete treatment requires the omitting of CSCs without destroying non-CSCs. Therefore, it is essential to develop modern remedial procedures with the ability to perform the simultaneous elimination of both multiple drug-resistant CSCs and bulk malignant tumor cells. The potential capabilities of nanomedicine can overcome the resulting therapies from conventional methods. nanomedicine proved to be a promising tool for conquering aforementioned limitations due to containing specific properties, which include controllable size, tunable surface features, surface-to-volume ratios, appealing surface functional groups for bioconjugation, less nonspecific Biological distribution, and the lowest rate of side effects .The design and development of a multifunctional and stimuli-responsive metal nanoparticles -based drug delivery system with distinct physical and chemical qualities can be efficient throughout the treatment of cancer and the elimination of multiple drug-resistant CSCs and bulk malignant tumor cells. The form and development of stimuli-responsive ligands were incorporated with the engineering of multiple physicochemical properties into metal nanoparticles in order to improve the efficiency of metal nanoparticles-based delivery systems. As a result , the theranostic metal nanoparticles with the incorporation of loading drugs into metal nanoparticles carriers and contrast agent imaging may offer the possibility of achieving nonspecific toxicities through the administration of lower but more accurate targeted doses. Despite the efforts and advances in targeted bio-conjugated nanoparticle cancer stem cell therapy, there are still many challenges in this area that require solutions and till then, the achievement of an effective and

impressive cancer treatment is predicted to be very distant.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest

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