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Molecular imaging in tracking cancer stem cells: A review

Hamed Ghaffari[1], Mohammad Reza Atashzar*[2], Hamid Abdollahi*[3]

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Abstract

Cancer stem cells (CSCs) have critical roles in tumor development, progression, and recurrence. They are responsible for current cancer treatment failure and remain questionable for the design and development of new therapeutic strategies. With this issue, medical imaging provides several clues for finding biological mechanisms and strategies to treat CSCs. This review aims to summarize current molecular imaging approaches for detecting CSCs. In addition, some promising issues for CSCs finding and explaining biological mechanisms have been addressed. Among the molecular imaging approaches, modalities including Magnetic resonance imaging (MRI) and positron emission tomography (PET) have the greatest roles and several new approaches such as optical imaging are in progress.

Keywords: Cancer stem cells, Molecular imaging, MRI, PET, Optical imaging

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Introduction

Despite recent advances in cancer treatment, cancer remains one of the most common leading causes of death worldwide (1, 2). Nowadays, although cancer is diagnosed and treated at earlier stages, some residual cancer cells, potentially resistant cells still exit after treatment and the same cells contribute to cancer recurrence. On the other hand, residual cancer cells are one possible cause of therapeutic failure (3, 4). These residual cells exhibit stem-like properties known as the cancer stem cells (CSCs), also called tumor-initiating cells (TICs) (3, 4). CSCs are considered a major challenging concept in the field of cancer therapy (4). Elimination of CSCs population, as a small subpopulation of cells within tumors, is essential to achieve stable, long-lasting remission, and cure of cancer (5).

In recent decades, many studies have been conducted on CSC theory to clarify understanding and eradication of CSCs (3-7). Of note, in-vivo understanding of the complex behavior of CSCs still remains largely a mystery. One of the novel and promising strategies that will revolutionize our understanding of CSCs theory is imaging technologies. Recent advances in preclinical and clinical imaging modalities have been provided new opportunities to locate the CSCs, and also evaluate the tumor biological

Corresponding author: Dr Mohammad Reza Atashzar, atashzar@sums.ac.ir
Dr Hamid Abdollahi, H_Abdollahi@kmu.ac.ir

1. Department of Medical Physics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
2. Department of Immunology, School of Medicine, Fasa University of Medical Sciences, Fasa, Iran
3. Department of Radiologic Sciences and Medical Physics, School of Allied Medicine, Kerman University of Medical Sciences, Kerman, Iran

↑What is "already known" in this topic:
Cancer stem cells (CSCs) are considered a major challenging concept in the field of cancer therapy. One of the novel and promising strategies that will revolutionize our understanding of CSCs theory is imaging technologies, providing new opportunities to locate the CSCs, and also evaluate the tumor biological processes involving CSCs.

→What this article adds:
This study aimed to provide an overview of current molecular imaging approaches for detecting CSCs. In vivo CSCs imaging can provide opportunities to investigate therapeutic response or metastatic CSCs, tumor propagation and plasticity of CSCs at high resolution. To date, there is no best imaging modality to track CSCs in vivo.

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processes involving CSCs. Accordingly, the aim of this review was to summarize recent studies on imaging techniques that have been utilized to monitor and visualize CSCs.

Cancer stem cells properties

CSCs are a rare subpopulation of tumor cells possessing similar characteristics as normal stem cells (6, 7). As suggested by recent studies, CSCs can self-renew and have the pluripotent capacity (8). There are several unique characteristics for CSCs, including self-renewal ability, capability to develop into multiple lineages, potential to proliferate extensively, being rare subpopulation of cells, radioresistance, chemoresistance, and promoting invasion and metastatic activity (4, 6, 9, 10).

Initially, CSCs were discovered in hematological cancer (11). In 1994, it proved that the $CD34^{+}/CD38^{-}$ (as cell surface markers) cells from acute myeloid leukemia (AML) patients can induce hematopoietic malignancy in NOD/SCID mice (11). Subsequently, studies have identified CSCs in a variety of solid tumors, including breast cancer, brain cancer, colon cancer, pancreas cancer, lung cancer, ovarian cancer, prostate cancer, melanoma, and glioblastoma (7, 12-18).

Distinct and specific cell surface biomarker phenotypes have used to isolate and distinguish CSCs from other cancer cells and normal stem cells. Nowadays, fluorescence-activated cell sorting (FACS) based on cell surface biomarkers or intracellular molecules is known as the main method for identifying CSCs (6). There are various CSCs markers such as CD44, CD24, CD90, CD133, epithelial-specific antigen (ESA), and aldehyde dehydrogenase1 (ALDH1) that express in a specific cancer type (6, 7, 12, 13, 19), as shown in Figure 1.

CSCs are resistant to traditional radiotherapy and chemotherapy (4). Radioresistance mechanisms of CSCs can be attributed to activation of DNA repair, overexpression of reactive oxygen species (ROS) scavenger proteins, activation of cell cycle checkpoint proteins, activation of anti-apoptotic pathways, and protection by microenvironmental niche (4, 20). Recently, Ghaffari and colleagues have reviewed new physical approaches to eradicate CSCs (4).

Molecular imaging

Molecular imaging (MI) is a novel promising noninvasive strategy that can provide the ability of quantitative measurement and visualization of the function of biological and cellular processes in vivo (21, 22). In contrast to anatomical imaging that is useful for disease or cancer diagnosis, surgical guidance/follow-up, and treatment monitoring, MI can improve specificity of cancer screening and early diagnosis and personalized treatment without invasive biopsies or surgical procedures (21). MI permits real-time tracking and monitoring of biological, physiological, and pathological processes in vivo. Cancer biomarker-based MI is an effective strategy for cancer diagnosis.

There are several preclinical and clinical MI approaches such as positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), ultrasound, and optical imaging (OI) (21). Table 1 summarizes the pros and cons of MI modalities. Currently, PET, SPECT, MRI, and ultrasound have clinical use, whereas OI modalities such as bioluminescence imaging (BLI), intravital microscopy, fluorescence-mediated tomography (FMT) do not have clinical use, and are in progress.

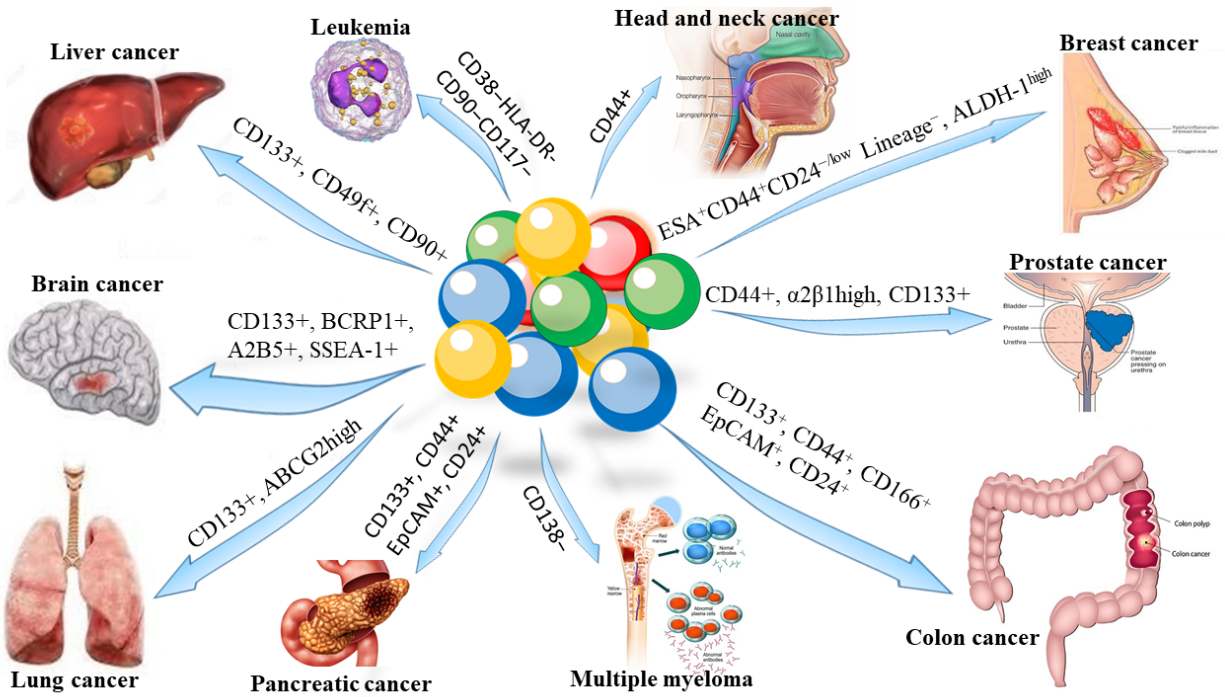

Fig. 1. Surface biomarkers of cancer stem cells (CSCs)

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Table 1. General characteristics of molecular imaging modalities

Imaging modality	Type of signal	Quantitative	Spatial resolution	Penetration depth	Common Contrast agents/ Readout	Real-time imaging	Whole-body imaging	Data acquisition time	Cost
Nuclear medicine (SPECT and PET)	Gamma-ray	Yes	0.3-2mm	No limit	PET: ^{18}F, ^{68}Ga, ^{64}Cu, etc. SPECT: ^{99m}Tc, ^{123}I, etc.	No	Yes	Min	High
MRI	Radiofrequency waves	Yes	50-250µm	No limit	Gd^{3+}, SPIO, USPIO, etc.	No	Yes	Min to Hrs	High
Ultrasound	High-frequency sound waves (>20KHz)	Yes	30-500µm	Several cm	Contrast Microbubbles	Yes	No	Sec to Min	Low
Optical	Visible light or near infrared	No, except FMT	1-5mm	≤ 1 cm	Fluorescent molecules & dyes, Light absorbing nano-particles	Yes	No	Sec to Min	Low

FMT: Fluorescence-mediated tomography; SPIO: Superparamagnetic iron oxide; USPIO: Ultra-small superparamagnetic iron oxide

Cancer stem cells imaging

CSCs imaging is a new approach that can identify the mechanisms of resistance of CSCs to treatment, response to therapy, and predict the outcome of therapy, as well as prognosis. On the other hand, MI can explore CSCs biology (23). Various imaging modalities have been investigated for in vivo imaging of CSCs such as PET, SPECT, MRI, and OI modalities, including BLI, FMT, and near-infrared (NIR) fluorescence reflectance imaging, and have shown interesting results for in vivo imaging of CSCs. Taken all together, in vivo imaging of CSCs results in applying a more personalized treatment planning regimen. The specificity and sensitivity of molecular probes targeting genes or proteins that have a great role in cancer growth and progression can be key factors that determine the accuracy of cancer prediction.

To our knowledge, there are few studies conducted to track CSCs with MI modalities, as shown in Table 2. The application of the MI in CSCs is discussed in the following. Table 2 outlines MI in tracking and monitoring CSCs.

Positron Emission Tomography

PET imaging is a high sensitive modality compared with other traditional imaging techniques. It also provides noninvasive, real-time tracking in vivo, as well as quantitative data (21). PET with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) analysis is considered as a promising and emerging clinical tool for cancer diagnosis and staging, as well as monitoring of response to treatment (24). Few studies have been evaluated the application of PET for CSCs imaging, as observable in Table 2. CD133, a membrane protein, is considered as a CSCs marker in a wide variety of tumors. A recent study by Jin et al. has examined the potential of in vivo radionuclide imaging of CSCs using Iodine-125 (^{125}I)- labeled ANC9C5, anti-CD133 antibody in human colon carcinoma HCT116 xenograft–bearing mice model. Data from their study revealed that the expression of CD133 was reflected by biodistribution and intratumoral distribution of ^{125}I- labeled ANC9C5. Radioiodinated anti-CD133 monoclonal antibody (mAb) ANC9C5 in comparison with the control antibody showed nearly a 2-fold higher tumor uptake. In addition, intratumoral distribution of ^{125}I- labeled ANC9C5 and expression of CD133 had a good overlap on autoradiography. As a consequence of that study, radio-immuno-targeting of CSCs using PET is possible (25). In another study, AC133 (an epitope of the second extracellular loop of CD133) was detected by PET imaging (26). Gaedicke et al. developed clinically relevant tracers that can provide highly sensitive and high-resolution monitoring of $AC133^+$ glioblastoma CSCs in both subcutaneous and intracerebral xenograft tumors using PET and NIR fluorescence molecular tomography (FMT). MicroPET with ^{64}Cu-NOTA-AC133 mAb can clearly image s.c. xenografts containing $AC133^+$ CSCs, and can also obtain accurate and high-resolution images of small brain tumor lesions (2-3 mm in size) (26).

Recently, keratin 19 (K19) is identified as a novel hepatocellular carcinoma (HCC)-CSC marker (27). Since ^{18}F-FDG-PET is an effective imaging modality for predicting postoperative outcome in HCC, it can be utilized to track $K19^+$ CSCs in HCC. For these purposes, the expression of K19 and glucose transporter-1 (GLUT1) was examined in human HCC surgical specimens. A significant correlation was found between the expression of K19 and GLUT1 expression and FDG accumulation in HCC patients. ^{18}F-FDG uptake in $K19^+$ HCC cells was significantly higher than in $K19^-$ cells. Furthermore, K19 regulates the accumulation of ^{18}F-FDG through TGFβ/Smad signaling pathways, including Sp1 and downstream target GLUT1. Data indicate the ^{18}F-FDG-PET is a novel approach for identifying K19 expression in HCC tissues (27).

^{64}Cu-diacetyl-bis (N^4-methylthiosemicarbazone) (^{64}Cu-ATSM) is also reported to be an imaging agent for PET, which can target hypoxic tumors. ^{64}Cu-ATSM has a high accumulation in regions of $CD133^+$ high expression, and can then kill such regions by radiation. As a result, it can reduce the percentage of $CD133^+$ cells. Taken together, ^{64}Cu-ATSM not only is PET imaging agent, but it also is a potential agent for internal radiotherapy (28).

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Table 2. A summary of recent studies on tracking various cancer stem cells (CSCs) by molecular imaging modalities

Molecular imaging technique	Imaging agent	Biomarker	Type of cancer	Reference
PET	^{125}I	CD133	Colon	[25]
	^{64}Cu-NOTA	AC133	Brain	[26]
	^{18}F-FDG	K19	Hepatocelluar carcinoma	[27]
	^{64}Cu-ATSM	CD133	Colon	[28]
MRI	Ferritin heavy chain	$CD44^+/CD24^-$	Breast	[38]
	HA-MNCs	CD44	Breast	[42]
	APT_{EDB}-TCL-SPIONs	EDB-FN	Breast	[43]
	Dox@APT_{EDB}-TCL-SPIONs	EDB-FN	Breast	[44]
NIR-FMT	Antibody AC133.1	CD133	CD133-overexpressing glioblastoma	[48]
NIR-FMT	Antibody AC133	CD133	Orthotopic glioblastoma model	[26]
Intravital microscopy	Yellow fluorescent protein	CD133	Human glioblastoma	[49]
NIR-fluorescence Imaging	NIRSHs	CD44	Gastric	[52]
BLI	Optical bifusion reporter genes	CD44	Breast	[53]
Fluorescence imaging	Fluorescent protein (ZsGreen)	26S proteasome	Human glioma and breast	[54]
MRI/SPECT/NIR-fluorescence imaging	CD44 antibody conjugated SWCNTs tagged with SPIONs and either Gallium-67 or Vivotag-S750 fluorophores	CD44	Breast	[57]
MRI/ fluorescence imaging	Fe3O4@PEI@Cy5.5@PEG@HCBP-1 NPs	$HCBP\text{-}1^+$	Lung	[58]
MRI/ fluorescence imaging	Anti-CD133 mAb-nano-MSN	CD133	Glioblastoma	[59]

PET: Positron emission modality; MRI: Magnetic resonance imaging; NIR-FMT: Near-infrared fluorescence-mediated tomography; BLI: Bioluminescence imaging; SPECT: Single positron emission computed tomography; Cu-ATSM: Copper labeled diacetyl-bis(N^4-methylthiosemicarbazone); ^{18}F-FDG: ^{18}F-fluorodeoxyglucose; HA-MNCs: Hyaluronan-modified magnetic nanoclusters; APT_{EDB}-TCL-SPIONs: Extra domain B of fibronectin--specific peptide-conjugated thermally cross-linked Superparamagnetic iron oxide nanoparticles; Dox@APT_{EDB}-TCL-SPIONs: Doxorubicin (Dox)-loaded APT_{EDB}-TCL-SPIONs; NIRSHs: NIR-sensitive supramolecular hydrogels; SWCNTs: Single-walled carbon nanotubes

Magnetic Resonance Imaging

Without question, nowadays, MRI is an important clinical tool in disease or cancer diagnosis. MRI as a noninvasive imaging modality, has high spatial resolution, and uses non-ionizing radiation (21, 29, 30). MRI can provide morphological and pathophysiological information in living subjects (29). Recent advances in new MR methods resulted in using MRI in the field of MI that evaluates specific cellular or subcellular events. Owing to the ability of MRI with contrast agents (CAs) for labeling cells, dynamic assessment of cell migration into target tissues is provided (31). MRI is capable to detect single cells in both stem cell studies and cancer cell tracking studies (32). Ultra-small superparamagnetic iron oxide (USPIO) and superparamagnetic iron oxide (SPIO) are two most important MR labels that are currently used to track cells (30). Contrast with conventional paramagnetic gadolinium-based CAs, USPIO and SPIO have low toxicity, sub-nanomolar-range detection limits, and higher contrast enhancement (33, 34).

With regard to CSCs imaging, several groups of researchers have been investigated the feasibility of detecting CSCs with MRI. As demonstrated in studies, SPIO can successfully detect and track glioblastoma CSCs in vitro (35). In vivo tracking and imaging cells of interest using MRI are performed by two approaches. In the first method, CA is utilized as a labeling or targeting agent. As reported in several studies, SPIO nanoparticles (SPIONs) have been recently employed as CAs for tracking and imaging various cells owing to their high relaxivity (31, 36). SPIONs functionalized with targeting ligands, such as monoclonal antibodies, peptides and nucleotide conjugation are recognized as useful CAs for molecular imaging (37). When SPIONs are placed in the magnetic field, T2 signal intensities significantly reduced (38). However, it should be noted that MRI signal intensity change is determined by the amount of USPIO and SPIO. Therefore, using SPIONs is not suitable for the long-term imaging of cells because the CAs become diluted by cell proliferation (38). On the other hand, SPIONs distribute to CSCs daughter cells, and also these nanoparticles can be absorbed by macrophages. Therefore, above-mentioned mechanisms can reduce the sensitivity and specificity of the signal (39). To overcome these limitations, recently, Choi et al. used the MRI reporter gene ferritin to noninvasively track breast CSCs (BCSCs). The overexpression of ferritin resulted in increasing of cell iron uptake, producing low signal intensities in MRI during cell division (38). MRI can be used for studying dynamic processes, such as the migration and invasion of cells over an extended period. Furthermore, this can provide temporal and spatial information for anti-cancer treatment effects on a specific cell population. The number of cancer cells in deep tissues can be quantified by calculating R2* (=1/T2*) values from T2* mapping of MRI images (40, 41). In Choi et al. study, BCSCs transduced with ferritin heavy chain (FTH) and enhanced green fluorescence protein (EGFP) dual reporter genes were transplanted into NOD/SCID mice to permit noninvasive monitoring BCSC-derived populations during tumor growth and to show tumor responses after docetaxel chemotherapy. Both in vitro and in vivo studies have showed a significant difference in MRI signal intensities (R2* values) between BCSCs and FTH-BCSCs. As revealed in histological analysis, areas showing high R2* values in docetaxel-treated FTH-BCSC tumors by MRI contained $EGFP^+/FTH^+$ viable cell populations with high percentages of $CD44^+/CD24^-$ cells. In the light of these results, ferritin-based MRI can be used as a noninvasive method to monitor viable cell populations in tumors after chemotherapy (38).

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In addition, Lim et al. have introduced hyaluronan-modified magnetic nanoclusters (HA-MNCs) as another labeling technique targeting CSCs for in vitro and in vivo studying of CD44-overexpressing breast cancer using MRI. CD44, a cell surface glycoprotein, is a major surface receptor for HA, an immune-neutral polysaccharide. Signal intensity on the T2-weighted MR images of cells treated with HA-MNCs was significantly reduced, demonstrating as an effective MR CA. HA-MNCs have good biocompatibility and excellent capability for targeted diagnosis of CD44-overexpressing breast cancer (42).

It has been demonstrated that extra domain B of fibronectin (EDB-FN) can be utilized as a putative biomarker of BCSCs (43). Previous study by Sun et al. showed the feasibility of detecting BCSCs with MRI using EDB-FN-specific peptide (APT_{EDB})-conjugated thermally cross-linked (APT_{EDB}-TCL)-SPIONs (43). In another study by same group, theranostic ability of doxorubicin (Dox)-loaded APT_{EDB}-TCL-SPIONs (Dox@APT_{EDB}-TCL-SPIONs) in a BCSC xenograft mouse model was evaluated. The results indicated that Dox@APT_{EDB}-TCL-SPIONs can selectively target BCSCs in vivo. Moreover, Dox@APT_{EDB}-TCL-SPIONs can detect BCSCs within tumors by targeting EDB-FN-expressing cells (44).

Optical imaging

Optical imaging (OI) is a new and highly versatile modality for noninvasive in vivo MI, and plays a vital role in molecular and cellular imaging (21). OI techniques are cheap in comparison with other imaging modalities. The most important concerns in imaging CSCs using OI can be attributed to choosing reporter signal and imaging modalities because CSCs constitute only a small percentage of population of tumor cells (45).

Bioluminescence signal emitted from cells although has low sensitivity and specificity, it can identify tumor growth, regression, and metastases (45). BLI can monitor molecular and physiological processes in real time such as cell survival and gene expression (46). In order to obtain an optical signal from subpopulation of cells it needs to select a reporter signal. Luciferase reporter plasmid is known as one of the main specific reporter signal, and is high sensitive to measure biologic activity in growing tumor (47).

Currently, fluorescence imaging is considered as the best OI technique for imaging CSCs. Due to sensitive detectors and the intensity and stability of fluorescence signal, imaging of fluorescent cells in vivo at high resolutions has been provided. The application of multiple fluorophores at the same time can be a useful method for imaging biological features of CSCs. There are several factors that should be considered in choosing OI devices for studying CSCs, including penetration depth in biological tissue, imaging time points, and using multispectral unmixing (45). Recently, several studies have been investigated imaging CSCs using OI, as summarized in Table 2. Tsurumi et al. using near-infrared fluorescence molecular tomography (NIR-FMT) indicated that the feasibility of non-invasive antibody-based in vivo imaging of tumor-associated CD133 (AC133) on mouse subcutaneous xenograft models. In addition, CD133 antibody-based tumor targeting was effective. A low signal to noise ratio was found in cells expressing CD133 at endogenous levels (48). In another study, it has demonstrated that in vivo CD133 imaging using fluorescence labelled-mAb can also be utilized to an orthotopic glioblastoma model. The Alexa 680-labeled AC133 mAb revealed a remarkable high in vivo fluorescence signal in the tumor region in comparison with the Alexa 680-labeled isotype control antibody (26).

Intravital microscopy is an optical imaging technique that can visualize CSCs with a proper resolution. In addition, it has several benefits such as deeper penetration, minimal image distortion, signal quantification, and three-dimensional image reconstruction (49, 50). According to this, Lathia et al. showed that CSCs growth can be seen in vivo through lentivirus-transduced fluorescence-labeled CSCs ($CD133^+$ cells) (49). Moreover, intravital microscopy may be used to investigate CSCs plasticity (51).

A novel NIR-sensitive molecular imaging probe based on hydrogel complexes has recently developed that can visualize CD44-expressing gastric CSCs. NIR-sensitive supramolecular hydrogels (NIRSHs, Cy5.5- conjugated polyethyleneimine/hyaluronic acid polyplexes) were fabricated by polyplexing in an aqueous medium, and showed good water-stability, biocompatibility, and specificity to CD44 (52).

Application of reporter genes is another technique for studying CSCs in vivo. Dual-function bioluminescence imaging-fluorescent reporter constructs (Luc2 fused with eGFP coding sequence) in BCSCs were recently applied. Luc2 sequence was used for whole body tracking by bioluminescence imaging (BLI) while EGFP was employed for intravital imaging and ex vivo analysis. With BLI, as few as 10 $CD44^+$ cells of stably labeled BCSCs could be tracked in vivo, that provides studies of early tumor growth and spontaneous metastasis (53). In addition to surface protein markers, in vivo tracking of CSCs can also performed by proteasome activity (54). A recent study has found a reduction of 26S proteasome activity in CSCs. According to this, in vivo CSCs tracking in human glioma and breast cancer was provided. Human glioma and breast cancer cells were engineered to stably express ZsGreen-ornithine decarboxylase, a fluorescence fusion protein that accumulates in cells in the absence of 26S proteasome activity. In vivo tracking of ZsGreen positive cells was successfully performed by fluorescence imaging. The results of the study suggested that reduced 26S proteasome activity can be a property of CSCs (54).

Multimodal imaging

As stated earlier, there are several MI techniques such as MRI, PET, and OI. Each imaging modality has its own strengths and limitations. The main goal of multimodality imaging is to combine best characteristics of separate imaging modalities. Recently, several studies have developed multimodality imaging probe for studying CSCs. FDG-PET/CT is known as a standard clinical practice and main diagnostic tool to distinguish cancer cells from normal cells (55). Studies have been shown that patients with

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ovarian clear cell carcinoma (CCC) have a low mean maximal standardized uptake value of FDG in comparison with patients with serous adenocarcinoma or endometrioid adenocarcinoma in FDG-PET/CT, reflecting glutaminolysis of its CSC-like properties (55).

The ability of NPs as CAs or carriers to efficiently intensify signals in various imaging modalities has demonstrated. Accordingly, incorporation of NPs in multimodality imaging techniques have been investigated, and multimodality nanoprobes were developed (56). Regarding the role of multimodality imaging in tracking CSCs, CD44 antibody-conjugated single-walled carbon nanotubes (SWCNTs) were recently developed as a biocompatible multimodality nanoprobes. CD44 antibody-conjugated SWCNTs and their conjugation with various imaging tracers i.e., SPION, Gallium-67 or Vivotag-S750 NIR fluorophores allowed noninvasive tracking and monitoring of BCSCs using MRI, SPECT, and NIR-fluorescence imaging (57).

Zhou et al. synthesized a multifunctional peptide-fluorescent-magnetic nanocomposites (Fe3O4@PEI@Cy5.5@PEG@HCBP-1 NPs) to recognize the lung CSCs specifically, and enrich the HCBP-1 positive CSCs from H460 tumor xenografts effectively (58). Their results showed that this agent can be used for fluorescent and MR imaging of lung CSCs in tumor xenografts. A novel smart immunomagnetic nanosensor (anti-CD133 mAb-conjugated nanoscale magnetic sensor (mAb-nano-MSN)) is introduced for MI of the targeted glioblastoma CSCs. This fabricated immunomagnetic nanosensor can be monitored real-time in the targeted glioblastoma CSCs as a fluorescence nanoprobe and distinguished CAs for MRI (59).

Conclusion and future perspectives

In vivo monitoring and tracking of CSCs can result in achieving novel therapeutic approaches, improving radiation oncology outcomes. In vivo CSCs imaging can provide opportunities to investigate therapeutic response or metastatic CSCs, tumor propagation and plasticity of CSCs at high resolution. To date, there is no best imaging modality to track CSCs in vivo. However, PET and MRI currently are useful modality for investigating therapeutic response or metastatic CSCs, and also OI techniques can be suitable modality for evaluating tumor propagation and plasticity of CSCs. CSCs is known as an important cause of local recurrences and distant metastases, thus in vivo imaging of CSCs can be a useful tool to detect these events at the early steps.

Currently, PET, MRI, and OI are promising MI modalities that can be used for clinical application of CSCs detection. Advances in CSC-specific tracers, CAs, and imaging modalities with high resolution will result in improving MI for CSCs detection.

Conflict of Interests

The authors declare that they have no competing interests.

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