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Review article

Nano-delivery system targeting to cancer stem cell cluster of differentiation biomarkers

Ahad Mokhtarzadeh[a,b], Soodabeh Hassanpour[b], Zahra Farajzadeh Vahid[c], Maryam Hejazi[d], Maryam Hashemi[e], Javad Ranjbari[f], Maryam Tabarzad[g,*], Saeed Noorolyai[b], Miguel de la Guardia[h,*]

[a] Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Department of Biochemistry, Higher Education Institute of Rab-Rashid, Tabriz, Iran
[c] Department of Biology, Faculty of Natural Sciences, University of Tabriz, Tabriz, Iran
[d] Zabol University of Medical Sciences, Zabol, Iran
[e] Nanotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[f] Department of Biotechnology, School of Advanced Technologies in Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[g] Protein Technology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[h] Department of Analytical Chemistry, University of Valencia, Dr. Moliner 50, 46100 Burjassot, Valencia, Spain

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ABSTRACT

Cancer stem cells (CSCs) are one of the most important origins of cancer progression and metastasis. CSCs have unique self-renewal properties and diverse cell membrane receptors that induced the resistance to the conventional chemotherapeutic agents. Therefore, the therapeutic removal of CSCs could result in the cancer cure with lack of recurrence and metastasis. In this regard, targeting CSCs in accordance to their specific biomarkers is a talented attitude in cancer therapy. Various CSCs surface biomarkers have been described, which some of them exhibited similarities on different cancer cell types, while the others are cancer specific and have just been reported on one or a few types of cancers. In this review, the importance of CSCs in cancer development and therapeutic response has been stated. Different CSCs cluster of differentiation (CD) biomarkers and their specific function and applications in the treatment of cancers have been discussed, Special attention has been made on targeted nano-delivery systems. In this regard, several examples have been illustrated concerning specific natural and artificial ligands against CSCs CD biomarkers that could be decorated on various nanoparticulated drug delivery systems to enhance therapeutic index of chemotherapeutic agents or anticancer gene therapy. The outlook of CSCs biomarkers discovery and therapeutic/diagnostic applications was discussed.

1. Introduction

Recently developed strategies for cancer diagnosis and treatment included encapsulation technology [1] and targeting of nanoparticles to the specific cancer cell surface biomarkers. Cancer stem cells (CSCs) were firstly reported in human leukemia [2]. CSCs or, in other terms, tumor-initiating cells (TICs) commonly refer to the neoplastic cells that possess stem cell-like properties, long life span, having elevated capacity to initiate new tumors and self-renewal ability [3]. The unique capability of repairing DNA damage in cancer stem cells is responsible for tumor re-growth after treatment, and induction of radio-resistant tumors [4]. According to the these features as well as the protective and self- renewal activity of multiple drug resistance (MDR) transporters, CSCs play cardinal role in cancer recurrence, metastasis and drug resistance [5]. Approximately 150 years ago, the finding of CSC theory was suggested that cancers had roots in “stem cells” or “germ cells”, as well newly approaches on the biological and methodological aspects of stem cells have been confirmed the cancer stem cell hypothesis [6].

CSCs have been reported in a wide range of cancers; such as brain tumors [7], leukemia [8], melanoma [9], lung [10], breast [11], colon [12], head and neck [13], ovarian [14], pancreatic [15], prostate [16], liver [17] and bone cancer [18].

There are two hypotheses about CSCs; the stochastic and the hierarchical model. Based on the stochastic model, it is assumed that each mature (somatic) cell owns the intrinsic ability to stochastically generate tumors due to the consecutive mutations during the time, arising from environmental factors and/or genomic instability [19]. In this model, sub clones of tumor cells from various microenvironments and

* Corresponding authors.
E-mail addresses: m_tabarzad@sbmu.ac.ir (M. Tabarzad), miguel.delaguardia@uv.es (M. de la Guardia).

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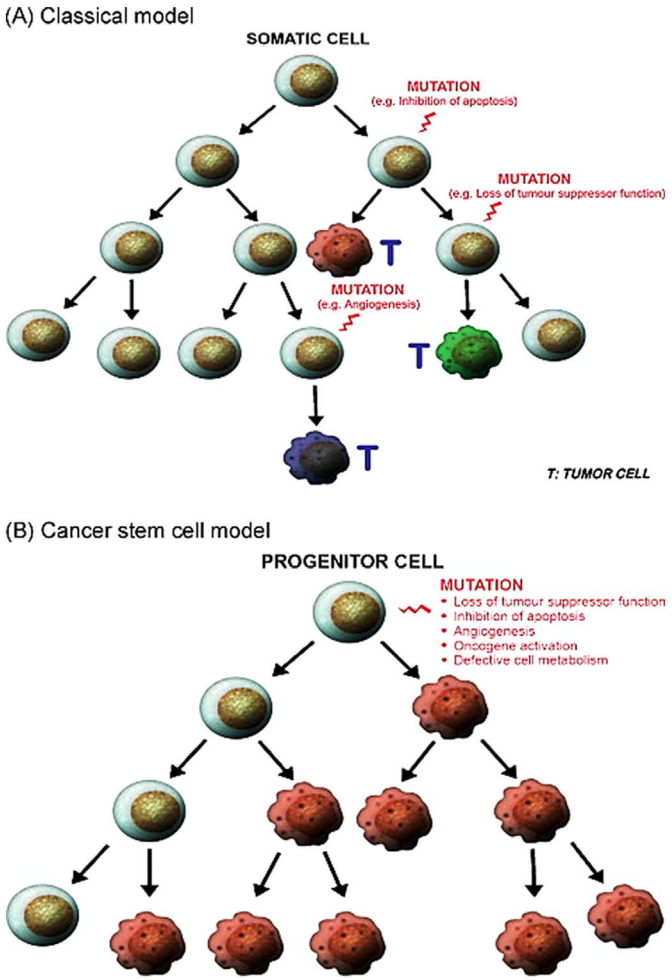

Fig. 1. Two models of cancer development and metastasis regarding CSCs role; (A) The stochastic model (B) The hierarchical cancer stem cell model. This figure was obtained with permission from Ref [24].

haphazard genetic alterations can cause tumor heterogeneity. This model indicates that eradication of all cancer cells is the prerequisite of efficient cancer cure [20]. On the contrary, according to the hierarchical model, the cancer cells of a tumor can give rise to the malignant cells through the stem cell natural processes of self-renewal and pervasive proliferation [21]. This model postulates the hierarchical arrangement of cancers with the CSCs at the top of the arranging [22].

An additional characteristic to be defined regarding CSCs, is the self-regeneration potential that related to a unique feature of daughter cells resulting from cell division and involving a stem cell–like phenotype and function, endowed with the capacity to produce a new stem cell with the same capability of proliferation as the parental cell [23]. However, the way through cancer stem cells regeneration can be two different ways and it still remains ambiguous and unclear what the exact mechanism is (See Fig. 1) [24].

It has been widely perceived that multiple mutations were the basic reason of emerging malignant cells. Since the complexities of cancer therapy, CSC model has triggered novel progresses in cancer treatment [25]. Currently, one of the most conventional challenges in chemotherapeutic medications is the selective delivery of nonselective cytotoxins with widespread activity against both, normal and malignant cells to tumors. These chemotherapeutics agents are applicable despite the fact that they may not commonly target CSCs, even if differentiated cancer cells are just killed [26]. CSCs with the exceeding expression of transporter proteins, involving in the efflux of regularly used chemotherapeutic agents, are expected to develop drug resistant forms [27]. The resistance of cancer tumors to anticancer chemotherapeutic agents is closely related to several intrinsic or acquired properties of CSCs, including their dormancy state, infrequently division, overexpression of anti apoptotic proteins, changed morphology, capacity of a CSCs for DNA repair, high expression of ATP-binding cassette (ABC) transporters and detoxifying enzymes. It has been reported that CSCs expressed several ABC transporters, such as ABCB1, ABCC1, and ABCG2, which was associated with drug resistance. It seems that after exposure to the chemotherapeutic drugs, only the CSCs that overexpressed the ABC transporters or have multi drug resistance (MDR) pumps can survive. These CSCs then divide and repopulate a tumor including stem cells accompanying with differentiated cells originated from the stem cells. It has been showed that ABCG2 transporter expressed in over 50% of all drug resistant cancerous cells. For example, ABCG2 (breast cancer-resistance protein [BCRP]) transporters overexpress in hematopoietic stem cells, while in the most progenitor and mature blood cells, the gene of this transporter is turned off. Studies showed that ABCG2 could transport mitoxantrone, doxorubicin, methotrexate, and topotecan out of the cells. ABCB1 (P-glycoprotein) is another transporter with high level expression in cancer cells, which encoded by the MDR1 gene and acts as an ATP dependent efflux pump for a variety of anticancer and antimicrobial drugs [28–30].

It should be noted that in the field of CSCs, the studies supported the bidirectional interaction between mesenchymal stem cells and the monocyte–macrophage lineage that could result in drug resistance in cancer therapy [31]. The process of epithelial–mesenchymal transition (EMT) significantly participates in the carcinogenesis and generation of cancer stem cells (CSCs) [32]. These two phenotypes expressed distinct biomarkers which could be applied for identification of tumor state and prognosis. It was evaluated in breast cancer and the results showed quiescent mesenchymal-like breast CSCs in the early stage of tumor invasion, characterized as $CD24^{-}CD44^{+}$, whereas proliferative epithelial-like breast CSCs expressed aldehyde dehydrogenase (ALDH) and characterized as $EPCAM^{+}CD49f^{+}ALDH^{+}$ cells, were located in the interior of hypoxic zones [33]. Similarly, it was confirmed that higher metastatic cells expressed higher levels of proliferative genes, such as MYC and CDK2 as well as MMP1 and CD24, compared to the low metastatic cells in human mammary cells [34] or breast CSCs with $CD44^{+}CD24^{-}$/loSSEA-3^{+} (stage-specific embryonic antigen 3 as an anti-apoptotic antigen) or $CD326^{hi}CD201^{hi}SSEA\text{-}3^{+}$ markers had higher tumorogenicity [35]. This type of transition could be induced by external stimuli, like the *Helicobacter pylori* infection in gastric cancer led to CSCs with higher expression of CD44 as the mesenchymal phenotype with higher tumorogenicity [36]. Therefore, according to the change of CSCs marker during various stage of tumor life, it seems to be essential to target alternative CSC biomarkers for efficient treatment of tumors.

Previous studies have shown that various specific surface biomarkers could be used for the discrimination of differentiated CSCs from other tumor cells and the normal stem cells [37]. Currently, the most established method in order to identify CSCs is fluorescence-activated cell sorting, which is based on the recognition of particular cell surface biomarkers or intracellular molecules [38]. In this review, we look over the remarkable attributes of CSCs' biomarkers as a crucial element in cancer studies. Biomarkers are used as specific biological indicators in biological fluids or cells with promising qualification and can eliminate or minimize the false positive or negative results of investigation and clinical approaches [39].

There is a boosting progress in the biomarkers' applications in drug development. Because of that, the classification of specific biomarkers is one of the most applicable approaches. Basically, two models for biomarkers classification were presented; first that based on pharmacokinetic/pharmacodynamics (PK\PD); which distinguished six types of biomarkers and the second one, proposed by Weickert and colleagues [40], paying attention to their general use for diagnostic and prognostic. Obviously, any biomarker could be in multiple classifications