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Review Article

Breast Cancer Stem Cells Eradication: A Newer Approach towards the Treatment of Breast Cancer

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ABSTRACT

Cancer is one of the major public health problems around worldwide, and the number of cancer cases increases every year and it was expected to reach 17.1 million by the year of 2020. Stem cells are known as the primal cells found in all multi-cellular organisms. They have the ability to renew themselves through mitotic cell division and can differentiate into a variety range of specialized cell types. Stem cell transplants are mainly used to replace bone marrow that has been destroyed by cancer or destroyed by the chemo and radiation therapy which is used to treat the cancer. Breast cancer remains the most common malignancy among women around the worldwide and more over, it is believed that cancer targeted therapies particularly stem cell targeted therapy are superior to current treatments such as traditional chemotherapy or radiotherapy inorder to overcome recurrence, metastasis and chemo-resistance. This review article details about the stem cells, normal human breast and stem cells application in treatment of breast cancer.

Keywords: Breast cancer stem cells, cancer stem cells, Aldehyde dehydrogenase

INTRODUCTION

The term cancer defines a group of diseases that can be characterized by the uncontrolled cellular growth, cellular invasion into adjacent tissues, and it has the ability to metastasize if left untreated during early stages. These cellular abnormalities arise from the accumulated genetic modifications, either through variations in the genetic sequence or from the modifications to gene activation- or DNA-related proteins that do not affect the genetic sequence itself. [1,2] Breast cancer exist as the worldwide most common malignancy among women, with an increase in incidence from 10.9 to 20 million new cases per year by the year of 2020, and it has the annual mortality rate ranges from 6.6 to more than 10 million. [3-5] Development in recent innovations in breast cancer screening methods and treatment strategies such as chemotherapy and radiotherapy leads to a significant elimination of primary tumour size, thereby increasing chances of survival for breast cancer patients. [6] Stem cells are defined as cells that have the ability to perpetuate themselves through self renewal and to generate mature cells of a particular tissue through differentiation. Stem cells from a variety of organs can be used for different therapies in the future, but hematopoietic stem cells have the vital role in the bone marrow transplantation that has already been used widely in the field of therapeutics. [7] Cancer Stem Cells (CSCs) have the functional and biological heterogeneity within the tumor and support the conservation of the tumor cell population. The contribution of CSCs to tumor maintenance and heterogeneity is

summarized in two main principal theories: according to the hierarchical CSC model, only a small number of tumor cells are capable of self-renewing and differentiation, while providing the tumor with all differentiated nontumorigenic progeny, thus maintaining the tumor hierarchy. [8-10] Breast cancer stem cells (BCSCs) can be characterized as CD44(+)/CD24. This was the first identification of a CSC population in solid tumors. [11] Stem cells play a vital role in breast cancer that comes from epidemiology data on breast cancer incidence following radiation exposure. [12] Cancer stem cells can be defined as cells in the tumour growth with a tumour initiating potential. Normal stem cells are characterised by three properties: 1. Capability of self-renewal; 2. strict control on stem cell numbers; 3. Ability to divide and differentiate to generate all functional elements of that particular tissue. Compared to normal stem cells, the cancer stem cells are believed to have no control on the cell numbers. Cancer stem cells form very small numbers in whole tumour growth and they are said to be responsible for the growth of the tumour cells.

ORGIN OF BREAST CANCER STEM CELLS

Current experimental evidence had suggested different theories about the origin of BCSCs, in which stem cells, progenitor cells or differentiated cells can be a potential model for the formation of BCSC. The concept of BCSCs arising from either mammary stem cells or progenitor cells seems more plausible among various hypotheses. [12] Most supporting evidence shows similar phenotypic features and cell surface markers which are related to those specific cells originate from the same lineage in the differentiation hierarchy. Recent research identified that the CD44+CD24 cell marker expressed on mammary progenitor cells resemble the CD44+CD24 Lineage found on BCSCs. [13] The population of BCSCs also showed specific properties highly familiar to normal mammary stem cells or partially differentiated mammary progenitor cells. [14] They are characterised with its ability to undergo self-renewal, differentiation, tumour initiating ability, invasion and resistance to conventional therapy which lead to generation of more cancer stem cells (CSCs) and heterogeneity of malignancy. [15] Other than that, due to the long-lived nature of stem cells, normal stem cells tend to persist in tissue for a longer period as compared with other differentiated cells, which continuously undergo cellular turnover. Therefore, stem cells are more likely to acquire multiple genetic alterations which are crucial for oncogenic transformation.[16] Exposure to environ-mental damaging factors including chemotherapy and radiotherapy lead to genetics and heterotypic variations of non-malignant somatic cells and hence causing de novo generation of CSC in which those cells undergo dedifferentiation to regain its stem-like properties, which then cause enrichment of BCSCs. [17] Newly developed evidence also found that microenvironment stimuli can trigger malignant transformation of differentiated cells into BCSCs. [18]

BIOMARKERS FOR ISOLATIONG BREAST CANCER STEMCELLS

Identification of biomarkers is a critical step in defining BCSCs. The study of molecular signatures contributes to the characterization and isolation of BCSC subpopulations. A better understanding of stem cell markers expressed in breast cancer provide a better insight onto BCSC biology, and thus enable the discovery of new therapeutic targets. The most common biomarkers used to identify the BCSC phenotype are CD44, CD24, and ALDH1. [19]

CD44

CD44 is a transmembrane glycoprotein present on the cell surface which plays an important role in adhesion, intracellular signalling, enhancing cell proliferation, tumour angiogenesis, differentiation, modulating migration and invasive properties in breast cancer. [20,21]

CD44 shows strong expression in BCSCs as well as numerous human cancers. CD44 acts to retain tumourigenicity and multipotency of the population. [22] Another study showed that CD44 interacts with hyaluronic acid to promote cell invasiveness and metastasis. [23] Also, inhibition of CD44 expression decreases anti-tumour drug resistance. [22]

CD24

CD24 is known as a cell surface glycoprotein which promotes adhesion properties and enhances tumour metastasis and proliferation. [24] In contrast, a study proved that upregulation of CD24 was capable to inhibit stemness in breast cancer cells. [25] CD24 was found to express in a wide variety of cancers but expression of CD24 was not associated with aggressive breast cancer subpopulation. [26] This marker was considered a poor prognostic tool for identifying breast cancer when evaluated independently. [27]

ALDH1

Aldehyde dehydrogenase (ALDH) is a form of detoxifying enzyme that catalyses oxidation of intracellular aldehydes and mediates conversion of retinol to retinoic acids, which then act as a cell proliferation modulator. [28] ALDH was found to mark both normal and cancerous mammary cells as assessed by the ADELFLUOR assays technique, and exhibit functional role in cell proliferation, differentiation and self-protection. [29]

GENES INVOLVED IN BREAST CARCINOGENESIS

Sl.NO	Breast cancer susceptible genes	Presumed function of genes
1	BRCA1	Guardian of genome integrity
2	BRCA2	Guardian of genome integrity
3	TP53 (Tumor protein 53)	Protection against replication of damaged DNA
4	PTEN (Phosphate and tensin homologue)	Suppresses cell cycle progression and induction of apoptosis
5	NAT1(N-acetyl trasferase 1)	Detoxification of arylamines
6	NAT2(N-acetyl transferase 2)	Detoxification of arylamines
7	GSTM1(Glutathione S transferase M1)	Detoxification of a wide range of xenobiotics, including environmental carcinogens, chemotherapeutic agents, and reactive oxygen species
8	GSTP1(Glutathione S transferase P1)	Detoxification of numerous chemicals including chemotherapy agents and catechol oestrogens
9	GSTT1(Glutathione S transferase T1)	Detoxification of a wide range of xenobiotics, including environmental carcinogens, chemotherapeutic agents, and reactive oxygen species
10	Estrogen receptor gene	Binding and transfer of oestrogens to the nuclei, ER modulates transcription of a number of growth factors
11	Progesterone receptor gene	Binding and transfer of progesterone to the nuclei, PR modulates transcription of a number of growth factors
12	Androgen receptor gene	Binding and transfer of oestrogens to the nuclei, AR modulates transcription of a number of growth factors
13	COMT (Catechol-O-methyltransferase)	Conjugation and inactivation of catechol oestrogens
14	Tumor necrosis factor alpha	Central mediator in the inflammatory response and immunological activities to tumour cells
15	UGT1A1 (Uridine diphospho glucuronosyltransferase 1A1 gene)	Phase II drugs metabolism and maintain intracellular steady state levels of oestrogen
16	HSP70 (Heat shock protein 70 gene)	Molecular chaperones, regulation of structure, Subcellular localisation, and turnover of cell proteins
17	VDR (Vitamin D receptor gene)	Cell differentiation

TREATMENT TARGETING BREAST CANCER STEM CELLS

One of the main objectives of breast cancer treatment is the eradication of BCSCs, which showed resistance to conventional chemotherapy and that causes tumor recurrence. Failure of conventional chemotherapy to eradicate the BCSC subpopulation results in BCSC enriched residual tumors, which display a more mesenchymal and aggressive phenotype. [30] Thus, simultaneous targeting of CSCs and non-CSCs leads to a great assurance towards the development of more efficient therapeutic practices. Indeed, combined chemotherapy and BCSC targeting therapy is currently being examined on a clinical basis. [31] The fact that CSCs showed phenotypic similarities with normal stem cells, however, it raises the question of

selective targeting of cancer versus normal stem cells. CSCs could be differentiated from their normal structure and function because they carry cancer-specific glycans. These are mainly originated from altered glycosylation of normal stem cell glycoproteins during their malignant transformation and are introduced as CSC specific glycans. [32] The targeting of BCSCs involves the destruction of BCSC survival signaling pathways induction of differentiation with the use of small inhibitors such as salinomycin, histone deacetylase inhibitors, all trans retinoic acid, and small RNA lentivirus particles, targeting of CSC metabolic pathways, and the use of microRNAs. [33] Cancer immunotherapy, drugs involved in the treatment of noncancer diseases, and nanotechnology. [34] Nanodrugs can easily accumulate within the tumor sites due to their increased vascular permeability. Biodegradable polymeric micelles combined with paclitaxel and functionalized with anti-CD44 antibodies have been used in breast cancer cell lines. [35] In order to evaluate the effectiveness of nanomedicines on the CSC subpopulation, an in vitro fluorescent CSC model was developed that allows the visualization and post treatment evaluation of biological performance of CSCs. [36] Although targeting BCSCs shows a great assurance in the treatment of breast cancer and is widely tested on a basic research level, it is indirectly proportional to limited number of clinical trials evaluating the effect of treatment on the expression of BCSC biomarkers are in progress. [37] Ongoing clinical trials evaluating the effect of Hedgehog, CXCR1/2, EGFR/HER2, AKT, and angiogenesis inhibitors on the CSC subpopulation of breast cancer patients in addition to the clinical testing of novel CSC vaccines will provide further insight on their clinical applicability and efficacy. [38] The use of antibiotics for the targeting of CSCs is a novel approach in the field of breast cancer. [39] Intriguingly, the authors propose the treatment of cancer as an infectious disease and highlight the role of antibiotics in the prevention of the disease relapse, based on the fact that many of these drugs are nontoxic to normal cells, thus reducing the side effects of anticancer therapy. [40] One of these antibiotics is doxycycline which is a member of the tetracycline class, which is having an excellent pharmacokinetics. [41] It has also been showed that doxycycline treatment significantly reduced the expression of many main protein targets functionally associated with mitochondrial metabolism, glycolysis, [42] protein synthesis, and the DNA damage response as well as inflammation and protein degradation, in human breast cancer cells. [43] In particularly, DNA-PK, an enzyme thought to confer resistance in cancer cells, was down regulated by doxycycline. [44] Doxycycline is relatively attractive as a new anticancer agent with low toxic side effects. [45] It has a long half-life systemically and has been commonly used for the long-term treatment of patients with urinary tract infections, prostatitis, or acne, for extended duration of time. [46] Doxycycline enhances the culturing efficiency, survival, and self-renewal of human pluripotent stem cells. [47] Precisely, through the direct activation of the PI3K-AKT intracellular pathway, it dramatically enhances the expandability of human embryonic stem and induced pluripotent stem cells. [48] Combination therapy targeting both BCSCs and breast cancer cells via the co-delivery of salinomycin and doxorubicin displayed a twofold in vivo breast tumor suppression compared to single drug therapy. [49] Recently, the establishment of ex vivo cultures of CTCs from the blood of breast cancer patients has enabled the examination of drug sensitivity of cultured cells, revealing new potential therapeutic targets, activation of specific signaling pathways, [50] and constituted the basis for the future design of novel individualized therapeutic strategies. [51]

STEMCELL THERAPY IN PATIENTS WITH BREAST CANCER

Systematic delivery of drug or gene therapy has promising future but is currently limited by various factors such as immune detection, non-specific accumulation in normal tissues and poor permeation. [52] The effects of many anticancer agents are limited due to either their toxicities or their short half lives such as interferon β, which shows anti-proliferative and pro-apoptotic activities in vitro, but has shown restricted effects on human malignancies in vivo. One proposed solution for these would be the cell-based carriers that may target the desired site. [53] The recent concept of use of stem cells as delivery vehicles came from the fact that the tumours, similar to the wounds, send out chemo-attractants such as the vascular endothelial growth factor (VEGF) to recruit Mesenchymal Stem Cells to form the supporting stroma of the tumour, and pericytes for angiogenesis. [54] MSC transduced with an adenoviral expression vector carrying interferon-β gene has been demonstrated to increase the production of interferon-β at the local site. [55] However this in vivo function of MSC depends partly on signals from the target tissue microenvironment. The use of the endothelial progenitor cells as the delivery vehicles for gene therapy because of their attraction towards the site of angiogenesis rather than the quiescent vasculature. [56] It may be possible to deliver immune activating cytokines and other secreted proteins to brain and breast tumours though the stem cells. [57]Although current treatments can shrink the size of the tumour, these effects are transient and usually do not improve patient's survival outcomes. For tumours in which the cancer stem cells play role, three possibilities exist. First, the mutation of normal stem cells or progenitor cells into cancer stem cells can lead to the development of the primary tumour. [58] Second, during chemotherapy, most of the primary tumour cells may be destroyed but if cancer stem cells are not eradicated, they become refractory cancer stem cells and may lead to recurrence of tumour. Third, the cancer stem cells may immigrate to distal sites from the primary tumour and cause metastasis. [59] Theoretically, identification of the cancer stem cells may allow the development of treatment modalities that target the cancer stem cells rather than rapidly dividing cells in the cancer. [60] This may cure the cancer as the remaining cells in the cancer growth have limited proliferative capability. Although the origin of the cancer stem cells is yet to be defined, the concept of the cancer stem cells may allow new treatment options in the possible cure of the cancer. [61]

ADVERSE EFFECTS AND CLINICAL LIMITATIONS

One of the major factors on the use of pathotropic stem cells for the treatment of cancer is their ability to secrete signalling molecules that could modify the tumor microenvironment and contribute to tumor invasiveness, growth, and angiogenesis. [62] Pro-neoplastic properties of normal stem cells within a non regulated tumor microenvironment should be taken into consideration before the development of any therapeutic strategy. [63] Moreover, the route of administration and cell concentration must be determined for an accurate therapeutic result. Due to the above limitations, clinical trials analyze the effect of normal stem cell-mediated therapy for the specific treatment of breast cancer are rather lacking. [64]

CONCLUSION

The cancer stem cell hypothesis is a new paradigm that could have a major impact on the treatment of disease by suggesting a new target for cancer therapy. Mammary stem cell biology needs to be understood in the context of both mammary development and as potential sources of the BCSCs. Transformed mammary stem cells have been identified as a potential source of breast cancer, tumour relapse, and tumour metastases; as such, they have gained prominence as potential targets for immunotherapy of cancer. Current treatments of cancer have shown efficacy in

removing the bulk of differentiated cancer cells while failing to eliminate the cancer stem cells responsible for tumour relapse. Future therapies will need to effectively target the cancer stem cells to induce clinically significant remission of disease. Target antigens for BCSCs need to be further defined so that effective targeting of the BCSC compartment can be realised which spares normal stem cell niches but disrupts the cancer stem cell niche. New treatments typically will not be fully optimal by themselves and will need to be further developed and placed into combination therapy with existing treatments. Therapies targeting BCSCs might be employed after debulking of the differentiated tumour tissue. This would allow immune surveillance to more efficiently eliminate the few remaining cancer stem cells. Targeting BCSCs might be an attractive approach to treat breast cancer metastasis and relapse and could lead to significant increases in clinical remissions and quality of life for breast cancer patients when used in a multimodal treatment regimen.

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