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Cancer stem cell in breast cancer therapeutic resistance

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ABSTRACT

Development of therapeutic resistance and metastasis is a major challenge with current breast cancer (BC) therapy. Mounting evidence suggests that a subpopulation of cancer stem cells (CSCs) contribute to the cancer therapeutic resistance and metastasis, leading to the recurrence and death in patients. Breast cancer stem cells (BCSCs) are not only a consequence of mutations that overactivate the self-renewal ability of normal stem cells or committed progenitors but also a result of the de-differentiation of cancer cells induced by somatic mutations or microenvironmental components under treatment. Eradication of BCSCs may bring hope and relief to patients whose lives are threatened by recurrent BCs. Therefore, a better understanding of the generation, regulatory mechanisms, and identification of CSCs in BC therapeutic resistance and metastasis will be imperative for developing BCSC-targeted strategies. Here we summarize the latest studies about cell surface markers and signalling pathways that sustain the stemness of BCSC and discuss the associations of mechanisms behind these traits with phenotype and behavior changes in BCSCs. More importantly, their implications for future study are also evaluated and potential BCSC-targeted strategies are proposed to break through the limitation of current therapies.

Introduction

Breast cancer (BC) is one of the most common cancers responsible for approximately 30% of new female cancer cases and ranked as the 2nd cause of cancer-related deaths in annual statistics [1]. The treatment options for BC, including breast-conserving surgery or mastectomy, radiotherapy (RT), chemotherapy (CT), hormone therapy (HT), and other novel therapies, are decided based on the individual features of clinico-pathology. For instance, mastectomy and adjuvant RT are utilized for many early BCs with curative intent. Conventional anticancer drugs can be employed as a single agent or in combinations to minimize the recurrence risk. For women with estrogen receptor positive (ER^+) or human epidermal growth receptor positive ($HER2^+$) tumors, tamoxifen or trastuzumab respectively contribute to the substantial improvements in long-term survival rate. These therapeutic options are considered as a milestone in dealing with BC.

However, many BC patients still experienced relapse in a few years and the long-term mortality remains high. The 15-year BC mortality fluctuated between 41.3% and 49.5% regardless of post-mastectomy radiation [2], indicating current therapies blend BC treatment with high degrees of uncertainty in spite of widely applied neoadjuvant therapies. BC is normally treated based on its intrinsic subtypes, which can only partially explain the biology and response to treatment. The failure of treatment to deal with intractable cancer cells has raised a question of whether there is a special population of cells in tumor heterogeneity which exhibit resistant phenotypes that favor the micrometastasis and have the potential to cause recurrence.

For the past few years, cancer stem cell (CSC) model was proposed and has received increasing interest. Collective work has revealed that tumor regeneration could be initiated by these CSCs. They are capable of self-renewal, recapitulating the heterogeneity of original tumors, and differentiating into the whole bulk of a new tumor in immunocompromised mice. Fractional irradiation caused lower level of reactive oxygen species (ROS) in breast cancer stem cells (BCSCs) compared to highly differentiated tumor cells, suggestive of a radioresistant phenotype [3]. Treating BCSCs with a multidrug CT not only increased the expressions of markers in pre-existing BCSCs but also promoted CSC-dependent non-stem cancer cells-to-CSC conversion [4]. As a result, targeting BCSCs seems to be an efficient adjuvant way to improve disease prognosis.

In this review, we summarize the latest studies about cell surface markers and signaling pathways that sustain the stemness of BCSC and

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discuss the associations of mechanisms behind these traits with BCSC generation, regulation, and transition. More importantly, their implications for future study are evaluated and potential BCSC-targeted strategies are proposed to break through the restriction of current therapies. We believe that the further exploration in this field of research will help researchers effectively identify and target BCSCs in tumors and eventually help doctors and patients achieve an improved response to BC therapy.

Is CSC the culprit of BC therapeutic failure?

The existence of CSCs was first evidenced by Bonnet and Dick [5] in human acute myeloid leukemia. These cells were similar to normal hematopoietic stem cells and can hierarchically differentiate into leukemic clone. The hierarchy resembles the differentiation process of hematopoietic progenitor cells and puts forward the necessity of targeting CSCs in cancer treatment. Based on research findings, a consensus definition of CSC was proposed by American Association for Cancer Research in 2006, and that is 'a cell within a tumor that possess the capacity to self-renew and to cause the heterogeneous lineages of cancer cells that comprise a tumor' [6]. Newly presented evidence suggested that BCSCs may be not only a consequence of mutations that overactivate the self-renewal ability of normal mammary stem cells or committed progenitors but also a result of the de-differentiation of cancer cells induced by somatic mutations or microenvironmental components under treatment (Fig. 1) [7]. The most relevant mutant genes that may give rise to BCSCs are listed in Table 1. Under conventional treatments that kill rapidly proliferative cancer cells, CSCs remain self-renewal and contribute to the risk of tumor recurrence. Of note, the model of colony evolution also suggests that CSCs may be not the same as the initial tumorigenic cells. There might be some variations occurring in the stemness-related genetic features of CSCs during disease progress, leading to the phenotypic and functional switches [6]. The so-called tumor-initiating feature of CSCs can therefore be only used to refer to their ability to cause a tumor in xenografts but not to address the cell-of-origin.

BCSCs were first identified and isolated by Al-Hajj [19] from a patient-derived xenograft (PDX) model in 2003. The tumorigenic subpopulation of cells displayed the surface marker of $CD44^+CD24^{-/low}$ and lack of lineage markers. In next few years, they were sequentially detected in early disseminated or peripheral circulating BC cells from patients' bone marrow and thus considered to be associated with BC recurrence and distant metastasis [20]. The presence of undifferentiated $CD44^+CD24^{-/low}$ tumor cells after CT was unfavorable in patients with invasive ductal carcinoma, and the increased proportion of $CD44^+CD24^{-/low}$ cells in tumor mass was strongly associated with lymphatic metastasis [21]. These studies provided clear evidence for the existence of BCSCs and highlighted the critical role of CSCs in BC relapse and metastasis. However, $CD44^+CD24^{-/low}$ cells are not a universal marker. In MDA-MB-231 and MDA-MB-361 cell lines, most cells display $CD44^+CD24^{-/low}$ phenotypes, but only 5% and 12% of which have tumorigenic ability, respectively [22]. Also, the correlation between the increased proportion of BCSCs in tumor tissues and poor prognosis became more significant when aldehyde dehydrogenase 1 (ALDH1) was employed in combination [23]. Such phenomenon may be due to the distribution disparity of CSC markers among different tumor subtypes [24], and, as a result, more BCSC markers are required to be found and used in combinations for a specific and efficient identification of BCSCs from different cell lines, tumor tissues, or even progression stages. The putative CSC phenotypes identified in BCs so far and their sources are showed in Table 2. Their functional contributions to BC therapeutic resistance and progression will be further discussed in the next section.

In chemoresistant or radioresistant BC cell lines and human tissues, the proportion of BCSCs was significantly increased [3]. CSCs are the root of cancer development and characterized by the common features of mammary stem cell, including quiescence, self-renewal, and differentiation potential. The self-renewal ability gives BCSC a survival advantage by efficiently repairing the DNA damage, while the differentiation potential confers BCSC a tumorigenic ability. Microenvironmental components, including exosomes, chemokines, and extracellular matrix, also play an essential role in maintaining the phenotypes through interacting with BCSC surface markers [26,30,43]. The action closely links the changeable stem-like properties to the diverse tumor microenvironments via intracellular signaling. Compared with non-CSCs, the overactivation of several transcriptional factors and signaling pathways, such as SRY (sex determining region Y)-box 2 (SOX2), Sonic Hedgehog (Hh) pathway, Notch pathway, and Wnt/β-catenin pathway, that are related to embryonic stem cell growth and differentiation can explain the stemness of BCSCs [44–47].

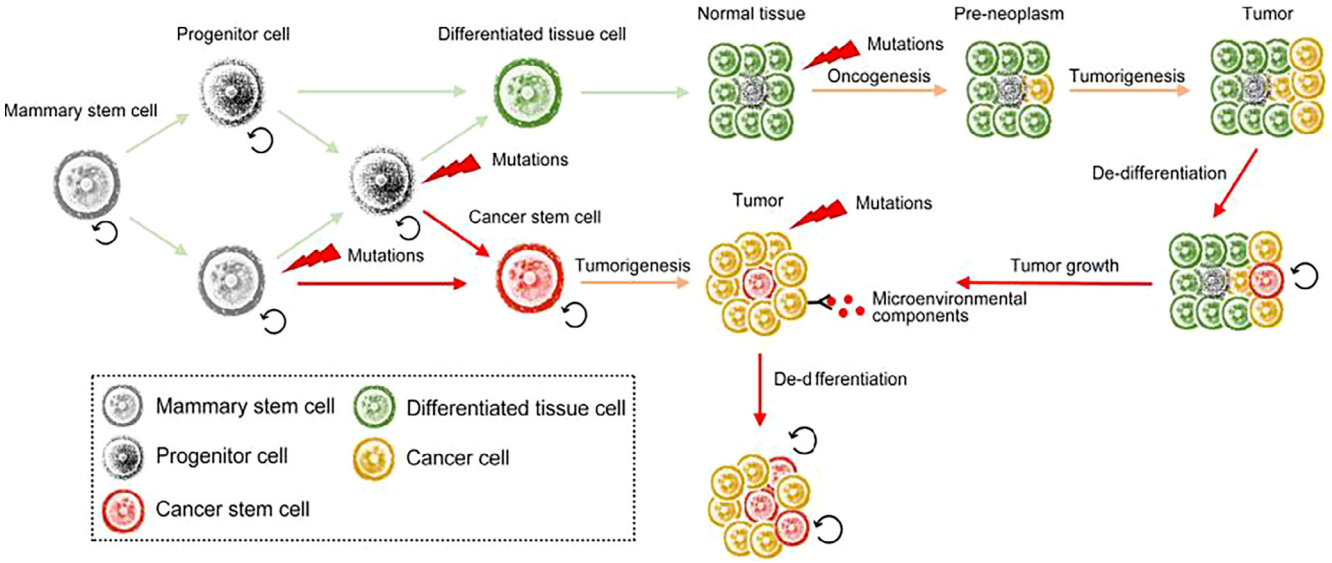

Fig. 1. Generation of BCSCs. The oncogenic mutations on mammary stem cells and progenitors can give rise to BCSCs [7]. These cells differentiate into BC cells and lead to the tumorigenesis which follows the hierarchical model. Furthermore, BC cells have the potential to de-differentiate into BCSCs due to the cellular genetic/epigenetic mutations (colony evolution) or different microenvironmental components. These two factors along with hierarchical model also collectively contribute to the breast tumor heterogeneity [8].