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Breast Cancer Stem Cells: Understanding and Opportunities for Therapeutics

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Introduction

Cancer stem cells (CSCs) are defined as rare immortal cell population within a tumor that can self-renew and give rise to several different cell types that establish the tumor and contribute to cancer therapy resistance. CSC follows asymmetric cell division that generates un-identical cell types during embryogenesis which ultimately helps these cells to maintain the homeostasis. The CSCs contribute to the development of tumor heterogeneity that is recognized by the existence of the diverse cell population within the tumor which poses a serious challenge for diagnosis and therapy. Breast cancer is one of the most heterogeneous tumors due to the high degree of diversity between and within tumors and a leading cause of cancer-related deaths in the women worldwide. Breast cancer stem cells (BCSCs) have been implicated in therapy resistance that significantly influences the overall clinical outcome of the breast cancer. The BCSCs phenotypes of tumors found to be unresponsive to chemotherapy and paclitaxel treatment. Interestingly these drugs induce the BCSCs phenotype in breast cancer cells *in vitro*. In addition, BCSCs escape chemotherapy and promote drug resistance by accumulate mutation, and accelerate self-renewal process after drug delivery[1]. Moreover, enhanced expression of CD44+/CD24-, a CSC marker were detected in primary tumors after chemotherapy[2]. Further, resistance to endocrine therapy was associated with elevated BCSCs[3]. In addition, the BCSCs were demonstrated to be resistance to radiotherapy in animal model[4]. Altogether, this evidence suggests that BCSC promotes therapy resistance, thus targeting this cancer cell population can be an effective therapeutic strategy for breast cancer treatment.

The BCSC demonstrated resistant to conventional therapies attributed to elevated membrane transport, ROS scavenging systems, altered mechanisms of DNA repair, and the ability to detoxify cytotoxic drugs. Altered expression of transcription factors, tumor suppressor and downstream signaling pathway genes further contribute to the amplification and maintenance of a state of stemness. In addition, extensive cross-talk between BCSCs and their surrounding micro¬environments significantly influence CSC function. Understanding of the molecular mechanisms that is responsible for resistance phenotype by enhanced drug efflux transporters, DNA repair machinery, and antiapoptotic proteins expression can be beneficial to target these populations. Several signaling pathways such as Wnt, Notch, NF-kB, Hedgehog, and EGFR have been implicated in the activity of malignant stem cell. Further, the role of microRNAs (miRNAs) such as let-7, miR-200, miR-183, miR-214, miR-221-222 and miR-142, and their clusters are determined to be differentially expressed in BCSCs and non-tumorigenic cancer cells[5]. These miRNAs are implicated in targeting the genes and pathways crucial for apoptosis, stem cell maintenance, self-renewal, and epithelial-to-mesenchymal transition. Thus, understanding the role of miRNAs in the induction of BCSCs is important to effectively counter breast cancer. Several therapeutic agents have been developed to eliminate or inhibit the BCSCs including disulfiram[6], curcumin[7], salinomycin[8], chloroquine[9], and siRNA[10]. Further, several nanocarriers based delivery system is also employed to target the BCSCs. However, only limited success has been achieved in the in vivo conditions. To advance anti-BCSCs targeted therapy, a better understanding of BCSCs microenvironment is crucial. Moreover, identification of genetic and-/or molecular markers that are more specific to BCSCs may help to optimize the BCSCs targeting strategies.

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