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Targeting breast cancer initiating cells: Advances in breast cancer research and therapy

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A B S T R A C T

Over the past 10 years there have been significant advances in our understanding of breast cancer and the important roles that breast cancer initiating cells (CICs) play in the development and resistance of breast cancer. Breast CICs endowed with self-renewing and tumor-initiating capacities are believed to be responsible for the relapses which often occur after various breast cancer therapies. In this review, we will summarize some of the key developments in breast CICs which will include discussion of some of the key genes implicated: estrogen receptor (*ER*), *HER2*, *BRCA1*, *TP53*, *PIK3CA*, *RB*, *P16INK1* and various miRs as well some drugs which are showing promise in targeting CICs. In addition, the concept of combined therapies will be discussed. Basic and clinical research is resulting in novel approaches to improve breast cancer therapy by targeting the breast CICs.

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Overview of breast cancer

Breast cancer affects nearly 1 in 7 women. It is the second leading cause of cancer death in women in the USA (Siegel et al., 2013). Breast cancer is a diverse disease with mutations and changes in gene expression occurring in diverse genes and pathways. Thus there is not one specific treatment which can be used to treat all patients. Breast cancer can be classified into many classes, the more common types are: luminal breast cancers which are usually estrogen receptor+ (ER+) and have a relatively good prognosis and response rate to hormonal based therapies, HER2+ cancers which have a poor prognosis if untreated but are initially responsive to herceptin, and basal-like breast cancers which have a poor prognosis and lack expression of HER2, estrogen and progesterone receptors (PR) and are referred to as "triple-negative". There are two types of luminal breast cancer, luminal A which is ER+/PR+/HER−, low Ki67 (a marker of proliferation associated with ribosomal RNA transcription and production) and luminal B which is ER+PR+/HER2+, high Ki67. In addition, there are other types and subtypes of breast cancer including: "normal-like", luminal ER−/AR+ (which express androgen receptor and may be responsive to antihormonal treatment with bicalutamide and other AR targeting drugs), claudin-low (often ER−, PR− and HER2−), metaplastic breast carcinoma (similar to basal-like cancer, HER2-, ER-, epidermal growth factor receptor+ [EGFR1+]), medullary breast cancer (a subtype of invasive ductal carcinoma, where the tumor is soft and resembles the medullar in the brain), inflammatory breast cancer (the breast cells block lymph vessels and the breast looks swollen and red and it hence called inflammatory), ductal carcinoma *in situ* (DCIS; also known as intraductal carcinoma which is non- or pre-invasive breast cancer in which the cells in the ducts have begun to look cancer-like) and invasive ductal carcinomas. Breast cancer patients often develop resistance to certain treatments such as hormonal, chemo-, radiotherapy perhaps due to resistance of CICs. Furthermore, various therapeutic approaches may result in the selection of even more resistant CICs. Many genes have been implicated in breast cancer and sensitivity to therapy (e.g., *BRCA1*, *BRAC2, HER2*, *ER*, *PIK3CA*, *AKT1*, *EGFR*, *PTEN*, *TP53, RB* and others) (Faber et al., 2010; Guirouilh-Barbat et al., 2010; Rudloff and Samuels, 2010; Steelman et al., 2008, 2011). In addition, other genetic and epigenetic events can occur which result in deregulated expression of many other types of genes including tumor suppressors (Jiang et al., 2011; Musgrove and Sutherland, 2010) and cell cycle regulatory molecules (Caldon et al., 2010) which in some cases can lead to resistance.

Physiological and genetic events may be altered or provoked in breast cancer and contribute to tumor progression and metastasis including: loss of hormone receptor expression, epithelial to mesenchymal transition (EMT), survival and expansion of CICs (Jordan et al., 2011) genomic instability (Guirouilh-Barbat et al., 2010), epigenetic modifications (Kutanzi et al., 2010) microRNA (miR) expression (Radojicic et al., 2011; Chang and Sharan, 2012) changes in the tumor microenvironment and stroma (Martinez-Outschoorn et al., 2010), senescence and other biochemical processes. Thus there are many different genetic, biochemical and physiological processes which are involved in breast cancer progression. Scientists and clinicians have attempted to target various events and processes.

Concept of CICs

Over the past 20 years the concept of CICs or cancer stem cells (CSCs) has emerged (Lapidot et al., 1994). The cancer cells with certain stem-like properties may be responsible for cancer initiation and reemergence after various therapeutic approaches. CICs are the key cells in the tumor which have the important capacity for self-renewal. Importantly they can lead to the generation of heterogeneous lineages of cancer cells that comprise the tumor. The origins of CICs are not clear; it has been hypothesized that CICs can arise from stem, progenitor or differentiated cells (Chaterjee and van Golen, 2011). CICs are often thought to be resistant to classical cancer treatments such as chemotherapy, radiation and surgery and persist after "standard" treatments or may evolve, or be selected for, after targeted therapeutic approaches. Unfortunately CICs may repopulate the patient with a more aggressive, metastatic or drug resistant cancer. Thus it is necessary to develop novel approaches to target CICs. The development of appropriate targeting techniques is a very active area of research.

CICs were originally observed and characterized in acute myeloid leukemia (AML) cells, but have since been documented in numerous other cancer types including: breast, cervical, colorectal,