

Breast cancer stem cells – from origins to targeted therapy

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Abstract: Breast cancer is marked as one of the leading causes of malignancy-related morbidities worldwide. In spite of aggressive interventions, the inevitability of relapse and metastasis severely impede survival rates. Mounting evidence highlight the insidious role of cancer stem cells (CSCs), a small but significant subpopulation of undifferentiated cells that drive tumour progression, spread and resistance to conventional therapy. The nature and significance of breast CSCs remains poorly understood, and even disputed by many researchers. This review discusses the origins, biomarkers, signalling pathways, regulatory mechanisms, and targeted therapy of breast CSCs.

Keywords: Breast cancer stem cells (BCSCs); origins; biomarkers; signalling pathways; microRNAs; regulatory mechanisms; targeted therapy

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Introduction

Breast cancer is one of the most common causes of cancer-related deaths in women worldwide (1). Gratifyingly, improvement in recent advances of breast cancer screening methods and treatment strategies such as chemotherapy and radiotherapy contribute to a significant eradication of primary tumour bulk, thereby increasing chances of survival for breast cancer patients (1). However, despite available interventions, patients under remission may still develop breast cancer relapse and metastasis (2,3). Accumulating evidence suggests that the underlying presence of a small subpopulation of undifferentiated cells, termed breast cancer stem cells (BCSCs), are most likely give rise to tumour progression, spreading and resistance to conventional therapy (2,4).

However, the real nature of BCSCs remains unclear. Much research is still ongoing to foster a deeper understanding of BCSCs on the formation of breast cancer which is essential for pursuing new therapeutic strategies and to improve diagnosis and prognosis for breast cancer

patients. Hence, this article aims to discuss the current literature on the origin of BCSCs, stem cell biomarkers for identification and development of new targeted therapy strategies that are available for breast cancer treatment.

Origin of BCSCs

The origin of BCSCs has stirred much controversy among researchers. Current experimental evidence proposed different theories about the origin of BCSCs, in which stem cells, progenitor cells or differentiated cells can be a potential model for BCSC formation (*Figure 1*).

The concept of BCSCs arising from either mammary stem cells or progenitor cells seems more plausible among various hypotheses (5,6). 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 (6). Besides, the population

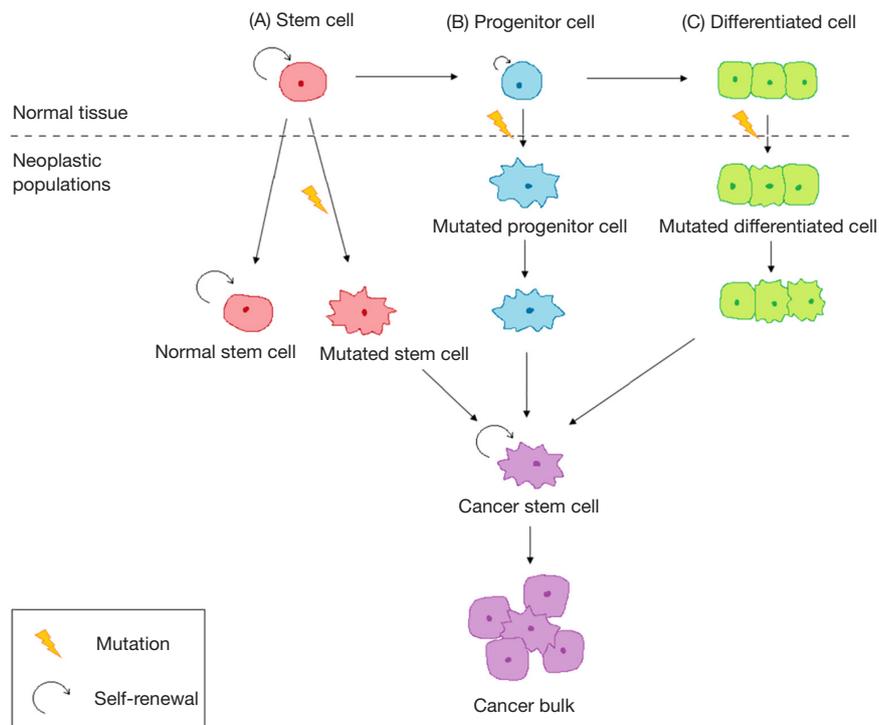


Figure 1 Models of BCSC formation. (A) Model 1: BCSCs originate from mammary stem cells. Several effective mutations that occurred during the quiescent state of stem cells initiate oncogenic transformation; (B) Model 2: BCSCs originate from mammary progenitor cells. Accumulation of multiple mutations at the level of transient amplifying progenitor cell leads to transformation and initiate malignancy; (C) Model 3: BCSCs originate from differentiated mammary cells. Differentiated cells are de-differentiated to re-acquire stem-cell properties. BCSC, breast cancer stem cell.

of BCSCs also shared specific properties highly similar to normal mammary stem cells or partially differentiated mammary progenitor cells (7). They are characterised with the 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. Apart from 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 differentiated cells, which constantly undergo cellular turnover. Therefore, stem cells are more likely to acquire multiple genetic alterations which are crucial for oncogenic transformation.

Contrary to previous concepts, another school of thought suggests that the BCSC model can be derived from non-stem cells—differentiated mammary cells. Exposure to damaging environmental factors including chemotherapy and radiotherapy lead to genetics and heterotypic alterations of non-malignant somatic cells and hence causing *de novo*

generation of CSC in which those cells undergo de-differentiation to regain its stem-like properties, which then leads to enrichment of BCSCs (8,9). Emerging evidence also suggests that microenvironment stimuli can trigger malignant transformation of differentiated cells into BCSCs (10). Regardless of all those different theories proposed, to date, there has been no concrete evidence to confirm the origin of BCSCs.

Biomarkers for isolating BCSCs

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 (11). Other, less

Table 1 Breast cancer stem cell biomarkers

Biomarkers	Characteristics	References
CD44	Cellular adhesion Intracellular signalling process Cellular proliferation Tumour angiogenesis Migration and differentiation Invasive properties in breast cancer	(8,9)
CD24	Cellular adhesion Tumour metastasis and proliferation Poor prognosis marker when applied independently	(12)
ALDH1	Cellular proliferation and differentiation Poor prognosis marker when applied independently	(13)
CD133	Cellular differentiation	(14)
CD49f	Cellular distribution of basal and endothelial cells Tumour initiation Tumour metastasis	(15,16)
CD61	Tumour initiation	(15,16)
CD44 ⁺ /CD24 ⁻ Lin ⁻	First marker isolated from BCSCs population Tumourigenic potential Retain heterogeneity	(17)
CD44 ⁺ /CD49f ⁺ /CD133/2 ⁺	Tumourigenic potential Self-renewal Retain heterogeneity in breast cancer	(18)

BCSC, breast cancer stem cell.

renowned biomarkers are also discussed (*Table 1*).

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 (8,9). CD44 shows strong expression in BCSCs as well as numerous human cancers. CD44 acts to retain tumourigenicity and multipotency of the population (19). Another study showed that CD44 interacts with hyaluronic acid to promote cell invasiveness and metastasis, however the mechanism remains unknown (20). Pham *et al.* [2011] demonstrated

that BCSCs were able to differentiate into normal cells when the expression of CD44 decreases (21). Also, inhibition of CD44 expression decreases anti-tumour drug resistance (19).

CD24

CD24 is also a cell surface glycoprotein which enhances adhesion properties and promotes tumour metastasis and proliferation (22). Conversely, a study proved that upregulation of CD24 was capable to inhibit stemness in breast cancer cells (22). CD24 was found to express in a wide variety of cancers. Ahmed and colleagues [2012] showed that expression of CD24 was not associated with aggressive breast cancer subpopulation (23). Hence,

this marker was considered a poor prognostic tool for identifying breast cancer when evaluated independently (12).

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. Moreb *et al.* [2012] revealed that 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 (13). Overexpression of ALDH1 leads to chemoresistance (13).

Other biomarkers

The other biomarkers involved in identification of BCSCs population includes CD133 which is found in triple-negative breast cancer and BRCA-1 tumours (14,24). The specific function of CD133 expression in cancer cells has not been defined, but it is known to be associated with cholesterol binding, and thus suspected to be involved in Hedgehog (Hh) signalling responsible for cell differentiation and epithelial-mesenchymal transition (24). In addition, Desgrosellier *et al.* [2014] demonstrated that CD49f and CD61 were found to be associated with tumour initiation properties through an *in vivo* study of breast cancer in mice (15,16).

Combinatorial expression

Evaluation of combinatorial expression of surface markers has been proven to yield a better prognostic value for identifying BCSCs. In a study done by Al-Hajj and his coworkers [2003], a subpopulation of human BCSCs exhibiting the CD44⁺/CD24⁻Lin⁻ phenotype had been identified (17). Cells expressing this phenotype show strong tendency to transform into CSCs. However, not all are associated with aggressive metastatic growth (2). More recently, CD44⁺/CD49f⁺/CD133/2⁺ was found to demonstrate increased tumourigenic potential, self-renewal and heterogeneity in breast cancer (18).

Signaling pathways regulating BCSCs

Notch, Hh and Wnt pathways are essential signalling pathways that are responsible for the normal process of

tissue maintenance. Any deregulation of these pathways in mammary glands may lead to transformation of normal stem cells into CSCs.

The Notch signalling pathway is responsible for the regulatory process of self-renewal and cellular differentiation during the developmental stage of cells (25). Since the Notch pathway mainly targets genes with high proliferation and apoptosis inhibition properties, therefore activation of this pathway in breast cancer results in uncontrolled development and maintenance of BCSCs. D'Angelo *et al.* [2015] showed malignant transformation of cells when Notch-4 activity was increased in several *in vitro* studies (26). A recent study demonstrated the application of antibodies specifically towards Notch receptors enable inhibition of tumour growth (27). Furthermore, Simmons *et al.* [2012] also showed that inhibiting Notch-1 is capable of inducing tumour regression in a mouse mammary tumour model (28).

The Hh pathway is associated with tissue patterning, development and progression. Increased activation of the Hh pathway has been identified in several CSCs models including breast cancer (29,30). Deregulation of the Hh pathway initiates increased expression of Sonic hedgehog (Shh), one of the ligands in the Hh pathway or Gli1, a downstream transcription factor in human breast cancer that supports the development and progression of breast cancer by promoting angiogenesis (29,31). In the same study, silencing CYR61 from Shh-expressing Hh cells inhibited the malignant behaviour of tumour cells, leading to limited vasculature and metastasis (31).

The Wnt signalling pathway plays a crucial role in regulating stem cell division and self-renewal. Activation of Wnt/ β -catenin signalling pathway initiates stem cell and progenitor cell proliferation, hence resulting in an increase of mammary tumour bulk. The Wnt pathway was also found to aid in chemoresistance and radioresistance of BCSCs (32). Tumour progression can be curbed by suppressing the activation of Wnt/ β -catenin pathway. Jang *et al.* [2015] revealed potential therapeutic advantages of shRNA-mediated Wnt1 silencing (33). Suppression of Wnt protein leads to a significant decrease in stem cell marker expression, and in turn indicating the reduction of BCSC population. Such inhibition can restrain self-proliferation and migration of CSCs, suggesting that targeting the Wnt/ β -catenin pathway could be a key therapeutic approach in removing BCSCs.

These three pathways play essential roles in regulating BCSC self-renewal, and are similarly involved in normal

Table 2 Expression of miRNAs associated with breast cancer development

Expression	MicroRNAs	Characteristics	References
Downregulated	MiR-200c	Invasion and metastasis	(34)
	MiR-205	Drug resistance	(35)
	MiR-141	Cellular proliferation, invasion and metastasis	(36)
	MiR-1	Cellular proliferation, invasion, metastasis and drug resistance	(37)
	MiR-34a	Cellular proliferation, invasion, metastasis and drug resistance	(34)
Upregulated	Let-7	Cellular proliferation	(31)
	MiR-221	Cellular proliferation and drug resistance	(38)
	MiR-21	Cellular proliferation, invasion, metastasis and drug resistance	(39,40)

stem cell development. From a clinical prospective, further studies are required to elucidate the mechanisms regulating BCSCs, in order to achieve the desired elimination of BCSCs without ablating normal cell function.

MicroRNAs regulating BCSCs

MicroRNAs (miRNAs) are short, non-coding regulatory ribonucleic acids (RNAs) that aid in regulating crucial biological processes and usually deregulated in cancer. Recently, numerous miRNAs are revealed to be upregulated or downregulated in breast cancer. Deregulation of miRNAs expression associated with carcinogenesis and drug resistance in BCSC populations (Table 2).

Loss of miR200c is associated with tumorigenicity of BCSCs and normal mammary stem cells. Jurmeister *et al.* [2012] revealed that downregulation of miR-200c helps in triggering breast cancer cells to invade and migrate (34). Hence, a future treatment for metastatic progression of breast cancer can be developed by re-expressing miR-200c.

Besides that, suppression of miR-205 in BCSC populations showed drug resistance properties (35). MiR-141 is also downregulated in BCSCs, which contributes to dedifferentiation of breast cancer cells which in turn enhances the population (36). Decreased expression of miR-34a in human mammary cancer results in suppression of stem cell properties. Study from Kang *et al.* [2015] revealed that miR-34a targeted the involvement of the Notch-1 pathway in maintaining stem cell properties of BCSC populations, hence suggesting that the miR-34a/Notch-1 pathway may be a potential therapeutic target for treating breast

cancer (41).

Apart from that, elevated expression of let-7 miRNA is involved in carcinogenesis and tumour development of BCSCs. Sun *et al.* [2016] discovered that isoform let-7c interrelated with Wnt signalling pathway *in vivo* to regulate BCSC renewal (42). Furthermore, miR-1 also associated with Wnt signalling pathway which is crucial for aggressiveness of breast cancer (37). Most of these findings provide a reference for the future development of miRNA-based therapy. However, further studies are still needed required to target the mechanism regulating breast cancer stemness.

Targeted therapy of BCSCs

Most conventional therapies currently available are capable of eliminating primary tumour bulk, but may not be able to provide durable clinical results in treated patients. This is because conventional therapy has limited application toward eliminating BCSC population, thus providing an opportunity for breast cancer to relapse. Therefore, a new targeted therapeutic strategy that aim for specific biomarkers, signalling pathways and microRNAs has been developed to provide a safer and more effective treatment selectively for breast cancer.

Nanoparticles that encapsulate low dose decitabine was developed by Li and colleagues [2015] to sensitize chemotherapeutic response of CSC populations with high ALDH activity (43). In the same study, combined treatment of nanoparticles loaded with low dose decitabine and doxorubicin showed significant decreased of CSC population with high ALDH expression *in vitro* and showed increased sensitivity of BCSCs towards administered drugs (43). In

addition, application of novel multifunctionalized iron oxide magnetic nanoparticles (MNPs) with anti-CD44 antibody and gemcitabine derivatives showed significant effects on CD44 positive cancer cells (44). Since BCSCs overexpressed CD44 biomarkers as previously mentioned, MNP is a potential approach for eliminating BCSCs.

Besides targeting biomarkers, nanoparticles also affect signalling pathways regulating CSCs. Nanoparticle-specific therapy has been designed to target specific signalling pathways regulating the stemness of BCSCs populations such as Wnt/ β -catenin, Notch (45), and Hh pathway. Application of nanoparticle drug delivery system promises higher efficiency, lesser side effects and more CSC specificity towards treatment, however extensive research is still required to ensure safety for *in vivo* applications.

Conclusions and future directions

Over the decades, accumulating studies have strengthened the concept of breast cancer as a disease of BCSCs. In fact, plasticity of BCSCs plays a vital role in determining the evolution of disease. Targeting BCSCs possesses a great implication on new therapeutic strategies development which offers long-lasting disease remission and long-term survival of breast cancer patients.

However, the theory of BCSC origin has not been proven to explain cancer initiation. Also, there is no universal biomarker that is specific for identification of breast cancer. Unique tumorigenic mechanisms operating within BCSCs to make it distinct from the tumour bulk is yet to be investigated. Nevertheless, extensive study has to be done towards a new therapeutic approach in the form of nanoparticles, to ensure the safety of application *in vivo*. CSC research no doubt enables better understanding towards the nature of BCSC which can greatly aid in development of new therapeutic targets and enhance current therapeutic strategies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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