

乳腺疾病病理学及基础研究专题 • 综述 •

Breast cancer stem-like cells and breast cancer therapy

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Until the early 1990s, human cancers were considered a morphologically heterogeneous population of cells. In 1997, Bonnet *et al*^[1] demonstrated that a small population of leukemia cells was able to differentiate in vivo into leukemic blasts, indicating that the leukemic clone was organized as a hierarchy; this was subsequently denoted as cancer stem-like cells (CSCs). CSCs are cancer cells that possess characteristics associated with normal stem cells and have the specific ability to give rise to all cell types found in a particular cancer. One reason for the failure of traditional anti-tumor therapies might be their inability to eradicate CSCs. Therefore, therapies must identify and destroy CSCs in both primary and metastatic tumors.

In breast cancer, the discovery of tumor cells that behave like stem-like cells [breast cancer stem-like cells (BCSCs)] offers a possible explanation for difficulty in eradication of breast cancer and suggests a new BCSCs-targeted therapy. This review will first discuss the possible sources of BCSCs and dysregulated pathways, following which we will insights into the mechanisms by which BCSCs are resistant to anti-tumor therapies.

1 Breast stem cells and BSCSs

The incidence of primary and early breast cancer has increased dramatically, suggesting the need for more information on the biology of breast cancer and new diagnostic and therapeutic ways to detect and treat it. Previously, it was thought that any cancer cell would have the same probability of exhibiting proliferation potential in an assay of clonogenicity or tumorigenicity and would also be able to form new tumors on transplantation. However, an alternative view is that cancer

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may be a “stem cell disease” and that there is a distinct subpopulation of cancer cells that is enriched for the ability to form new tumors, whereas most cancer cells do not possess this ability^[2]. Increasing evidence suggests that the latter may be a more accurate model of cancer. Stem cells are capable of self-renewal and differentiate into a diverse range of specialized cell types. It is generally agreed that breast stem cells exist in the terminal end bud of the mammary glands and give rise to mammary epithelial cells. Three main functions of breast stem cells are observed: (1) to develop into adult mammary glands; (2) to expand and remodel the mammary gland during pregnancy, lactation, and involution; and (3) to repair the mammary gland when it is damaged^[3]. The breast stem cell does not express ER or PR but can give rise to ER-expressing and PR-expressing cells.

There is a close relationship between stem cells and CSCs: (1) Stem cells and CSCs share a relatively undifferentiated state, the ability to self-renew and the activation of cytoprotective mechanisms; (2) Both give rise to phenotypically heterogeneous cells that exhibit various degrees of differentiation; (3) Both are regulated by similar signaling pathways; and (4) Telomerase activation has been observed in both stem cells and CSCs^[2]. Due to long exposure to genotoxic stress, signaling pathways in stem cells are deregulated, which leads to disinhibition of cell growth that ultimately drives tumorigenesis. On the other hand, CSCs also have their own characteristics: (1) CSCs show a disorderly proliferation; (2) CSCs lack the ability to mature; and (3) CSCs decline as replication errors accumulate. For breast cancer, Al-Hajj et al^[4] first demonstrated that when as few as 100 cells were transplanted, CD44⁺ CD24⁻ Lin⁻ cells were able to establish tumors in recipient animals.

2 BCSCs and intrinsic subtypes of breast cancer

Breast cancer has been classified into five molecular subtypes: the luminal subtype including luminal A[ER α (+), PR(+), and HER2(-)] and luminal B[ER α (+), PR(-), and HER2(+/-)], the HER2(+) subtype[ER α (-), PR(-), and HER2(+)], the basal subtype[ER α (-), PR(-), and HER2(-)] and the claudin-low subtype[ER α (-), PR(-),

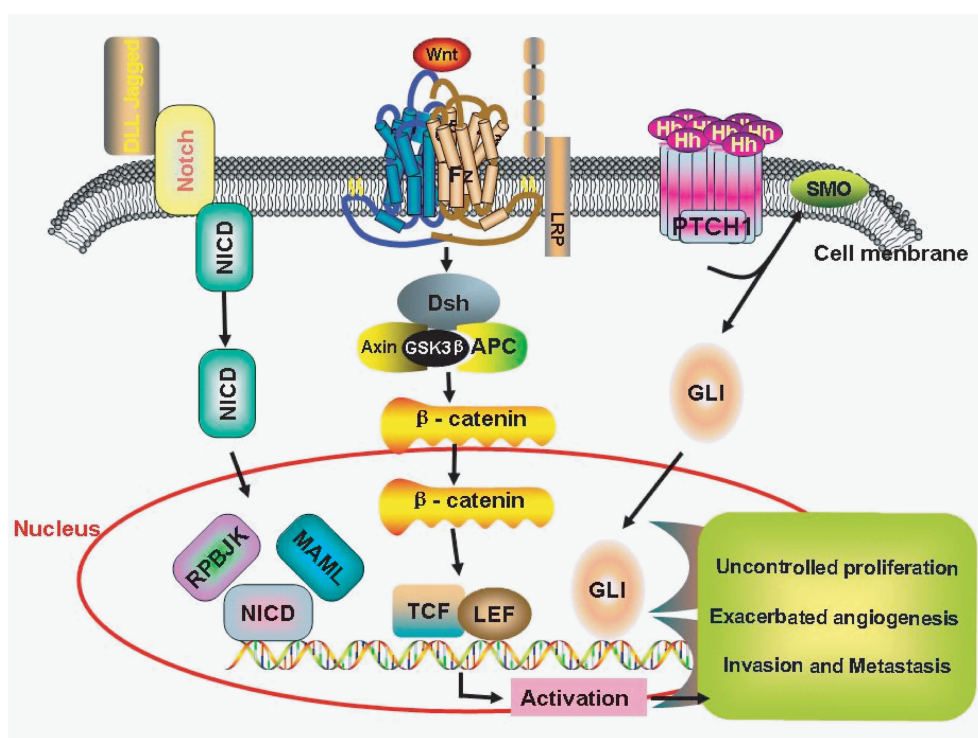
and HER2(−)]^[5]. In normal breast, stem cells are known to possess a basal phenotype and be mainly ER(−). In breast cancer, high expression of multiple epithelial-mesenchymal-transition (EMT) markers have been observed in the basal subtype and this has also been found to have a close relationship with BCSCs. Several gene products in the basal cluster are expressed in stem cells of various tissue types, including c-KIT, α6 integrin, CK5, and prion protein. Furthermore, Sheridan *et al*^[6] demonstrated that CD44⁺CD24[−] BCSCs were mainly in the basal/mesenchymal or myoepithelial cell lines. Aldehyde dehydrogenase 1 (ALDH1) is a well-accepted marker for BCSCs. It also has a direct correlation with basal-like CK 5/6 and CK14^[7]. Horwitz *et al* showed that a small basal-like phenotype[ER(−)PR(−)CK5(+)] was present within the luminal type cell line T47D, which had the capacity to generate the majority of ER(+)PR(+)CK18(+)CK5(−) cells^[8]. There is no evidence, however, that BCSCs are yielded by ER(+) cancer cells.

3 Molecular signaling of BCSCs

3.1 Wnt signaling pathway

The Wnt signaling pathway is a conserved pathway involved in development and tissue homeostasis in multicellular organisms (Fig1). Binding of Wnt ligands regulates β-catenin activity, an adherence-associated protein, which travels to the nucleus bound to Tcf/Lef transcription factors and activates Wnt target genes. Additionally, the Wnt signaling receptors Lrp5/6, which are uniquely required for canonical Wnt activity, are expressed by mouse breast stem cells and are required for maintaining the basal lineage. The expression profile of Wnt signaling molecules was measured in a variety of tumors including those in cases of breast cancer. Li *et al* suggested that expression of the Wnt-1 proto-oncogene in the mammary glands of transgenic mice expanded the population of epithelial cells expressing progenitor cell markers CK-6 and Sca-1; moreover, subsequent tumors still expressed these markers and contained luminal epithelial and myoepithelial tumor cells that shared a secondary mutation and loss of phosphatase and tensin homolog (PTEN), implying that they

arose from a common progenitor^[9].



BCSCs; breast cancer stem cells; NICD; Notch Intracellular domain; RBPJK; recombination signal-binding protein 1 for J-kappa; MAML; mastermind-like; Dsh; dishevelled; GSK3 β ; glycogen synthase kinase3 β ; APC; adenomatous polyposis coli; TCF; T cell factor; LEF; lymphoid enhancer factor. Hh; Hedgehog; PTCH1; Patched 1; SMO; smoothened; GLI; glioma-associated oncogene

Figure 1 Three classic regulatory pathways, Wnt, Notch and Hedgehog, which are required for proliferation, differentiation and self-renewal of BCSCs. Activation of target genes in BCSCs leads to uncontrolled proliferation, exacerbated angiogenesis, invasion and metastasis.

3.2 Notch signaling pathway

Notch signaling is vital for numerous cell fate specification events in multicellular organisms, and dysregulated Notch signaling causes several diseases with underlying developmental defects (Fig1). In vertebrates, notch proteins are transmembrane receptors that are activated by five transmembrane ligands that are named DLL-1, -3, and -4 and Jagged-1 and -2. Binding of the ligand to the Notch receptor induces cleavage of the intracellular component NICD, which translocates to the nucleus and participates in transactivation of target genes. Active Notch signaling may play a role in mammary carcinogenesis by deregulating the self-renewal of

breast stem cells. Bouras *et al* showed that knockdown of the Notch effector Cbf-1 (Cp-binding factor 1) in the breast stem cell caused increased stem cell activity with aberrant end bud formation, implying a role for Notch signaling in the link between breast stem cells and BCSCs^[10].

3.3 Hedgehog signaling pathway

The Hedgehog signaling network regulates pattern formation, proliferation, cell fate and stem/progenitor cell maintenance, and self-renewal through three glycoprotein ligands in mammalian cells: Shh, Dhh, and Ihh (Fig1). These ligands bind to PTCH1, a transmembrane receptor, and release another transmembrane receptor, Smo. Smo activation leads to a cascade of activation of transcription factors, the zinc finger transcription factors GLI-1, GLI-2, and GLI-3. GLI then translocates to the nucleus and activates transcription of a subset of genes such as cyclins, c-Myc, EGF, and VEGF among others. Hedgehog signaling is involved in several types of breast cancer to which it confers growth promoting and/or survival capabilities by different mechanisms. PTCH1, GLI-1, and GLI-2 are highly expressed and down regulated when breast stem cells are induced to differentiate. Activation of Hedgehog signaling increases the mammosphere-initiating cell number and mammosphere size, whereas inhibition of the pathway results in reduction of these effects^[11].

4 Mechanism of resistance of BCSCs to anti-tumor therapy

4.1 BCSCs and chemotherapy resistance

The CSCs hypothesis has led us to believe that CSCs may display resistance to chemotherapy. In the tumor, CSCs are likely to share many properties of normal stem cells such as resistance to drugs and toxins through the expression of ABC transporter proteins, particularly BCRP. Thus, CSCs can survive chemotherapy and repopulate the tumor. Chemotherapy targets rapidly dividing cells. However, CSCs survive due to high BCRP (breast cancer resistance protein) expression that increases their resistance toward chemotherapeutic agents and repopulate the tumor. Subsequently, CSCs could differentiate into new mature tumor cells with a

chemoresistant phenotype. Katayama *et al* indicated that BCRP mRNA in all the SP cells of the tested breast cancer cell lines was higher than that of the non-SP cells^[12]. Fillmore *et al.* reported similar results^[13]. Shafee *et al*^[14] demonstrated that BCSCs increased in platinum-refractory secondary tumor transplants and had greater colony-forming ability in the presence of cisplatin. In addition, thymosin β 4 (TB4) is also involved in BCSC chemotherapy resistance. siRNA-mediated knockdown of endogenous TB4 decreased chemotherapy resistance in MCF7 Cells^[15]. Moreover, Gupta *et al.* suggested that breast cancer cell populations induced through an EMT displayed an increase in the proportion of BCSCs, indicating the possibility of EMT mechanism^[16]. In addition, BCSCs could be enriched under the pressure of chemotherapy^[17]. In addition to the basic correlations, decades of clinical science have attempted to correlate BCSCs with chemotherapy resistance. BCSCs increased significantly following chemotherapy in a study of 108 breast cancer patients who had breast biopsies prior to neoadjuvant chemotherapy with paclitaxel and paclitaxel followed by mastectomy^[18]. Similar findings were also reported by Li *et al* for 52 patients with primary breast cancer. Importantly, lapatinib treatment could reduce the percentage of BCSCs^[19]. Recently, Chang *et al* showed that BCSCs increased significantly after conventional chemotherapy due to the Notch-1 and Wnt signaling pathway^[20]. Tables 1 and 2 summarize the clinical and basic evidence and the postulated mechanism of chemotherapy resistance of BCSCs.

4.2 BCSCs and radiation resistance

Radiation is an integral component of breast cancer therapy for majority of breast cancer patients with all stages of disease, and is often used to destroy any remaining breast cancer cells after surgery. Yet, radiation accelerates repopulation and increases cancer growth rate observed during breast cancer radiation and is thought to be responsible for tumor recurrence. More and more evidence shows that BCSCs are involved in resistance to radiation. Phillips *et al* found that BCSCs were more radioresistant

Table 1 Basic evidence and possible mechanisms of chemoresistance of BCSCs

Reference	Cell origin	BCSCs represented	Postulated mechanism	Drugs	Evidence
Katayama ^[12]	HBC-4 HB0C-5 BSY-1	SP	Higher expression of BCRP	Dofequidar CPT mitoxantrone topotecan	BCRP mRNA in all the tested SP cells was higher.
Fillmore ^[13]	SUM159 (basal) SUM1315 (basal) MDA-MB231 (mesenchymal)	CD44 ⁺ CD24 ⁻ ESA ⁺	Higher expression of BCRP	5-FU paclitaxel	BCSCs were enriched 5- to 30-fold in chemotherapy treated cultures.
Shafee ^[14]	Brcal ^{fp/fp} p53 ^{fp/fp} Cre mutant mice	CD29 ^{hi} CD 24 ^{med}	Higher expression of BCRP and Top2A	Cisplatin carboplatin doxorubicin	BCSCs increased in platinum-refractory secondary tumor transplants and had greater colony-forming ability in the presence of cisplatin.
Steiniger ^[15]	MCF7 (luminal) MDA-MB231 (mesenchymal)	SP	Higher expression of TB4	Doxorubicin methotrexatel	BCSCs showed a significantly greater survival rate during chemotherapy.
Gupta ^[16]	HMLER cells	CD24 ^{low} CD44 ⁺	EMT	Paclitaxel doxorubicin	BCSCs were more resistant (10- to 20- fold) to chemotherapeutic drugs
Wright ^[17]	Brcal mouse mammary tumors	CD44 ⁺ CD24 ⁻ CD133 ⁺	Higher expression of BCRP	Cisplatin	No significant signs of toxicity in BCSCs.

BCSCs; breast cancer stem cells; SP; side population; BCRP; breast cancer resistance protein; CPT; camptothecine ; 5-FU; fluorouracil; ESA; epithelial-specific antigen; TB4; thymosin β 4; SIP; Siah-interacting protein; Brcal; breast cancer gene; HMLER cells; human mammary epithelial cells overexpressing human telomerase reverse transcriptase, SV40 T/t and H-RasV12; EMT; epithelial mesenchymal transition.

Table 2 Clinical evidence for and possible mechanisms of chemoresistance of BCSCs

Reference	Case number	BCSCs represented	Possible mechanism	Follow-up period	Drugs	Hormone receptor status	Evidence
Tanei ^[24]	108	ALDH1 ⁺	N/A	N/A	Paclitaxel cyclophosphamide	ER+70/ ER-38 PR+49/ PR-59 HER2+26/HER2-82	BCSCs increased significantly after neoadjuvant chemotherapy.
Li ^[25]	52	CD24 ^{low} /CD44 ⁺	N/A	12 Weeks	Docetaxel doxorubicin cyclophosphamide lapatinib trastuzumab	ER+22/ER-36 PR+17/PR-41 HER2; N/A	BCSCs increased significantly after neoadjuvant chemotherapy.
Chang ^[26]	35	CD24 ^{low} /CD44 ⁺	Notch-1 Wnt	N/A	Docetaxel adriamycin cytotoxin	N/A	BCSCs increased significantly after conventional chemotherapy.

BCSCs; breast cancer stem cells; ALDH1; aldehyde dehydrogenase 1; ER; estrogen receptor; PR; progesterone receptors; HER2; human epidermal growth factor receptor2; N/A; not available

than non-BCSCs, both under the condition of a single dose of radiation and under fractionated radiation. Meanwhile, the levels of reactive oxygen species (ROS), which are indicative of the intracellular levels of radical scavengers, showed negative dose-dependent formation following radiation. Thus, it appears that BCSCs exhibit increased radiation resistance resulting from decreased ROS induction followed by decreased double-strand breaks.

Additionally, activated Notch-1 increased after radiation after 5 fractions of 3 Gy, which was not observed in non-BCSCs. The researchers concluded that fractionated irradiation appeared to activate the Notch-1 pathway, which may have caused the BCSCs population to increase^[21]. Al-Assar *et al* indicated that BCSCs from MDA-MB-231 were more radioresistant than unsorted cells and the expression of BCSCs surface markers in the MDA-MB-231 xenograft model was increased after exposure to fractionated radiation^[22]. Another result indicated that BCSCs developed less DNA damage and were preferentially spared after radiation^[23]. Table 3 summarizes the evidence and the postulated mechanism of radiotherapy resistance of BCSCs.

Table 3 Evidence and possible mechanisms of radiation resistance of BCSCs

Reference	Cell origin	BCSCs represented	Postulated mechanism	Evidence
Phillips ^[29]	MCF7(luminal) MDA-MB-231 (mesenchymal)	CD24 ⁻ /low/CD44 ⁺	Notch-1	BCSCs increased after short courses of fractionated irradiation.
Al-Assar ^[30]	MDA-MB231 (mesenchymal)	CD24 [±] /CD44 ⁺ CD133 ⁻ /ESA [±]	Notch-1	BCSCs had fewer residual γ-H2AX foci than unsorted cells, pointing to radioresistance of BCSCs.
Diehn ^[31]	Breast cancer patients	Thy1 ⁺ /CD24 ⁺ /Lin ⁻	N/A	BCSCs appeared to be overrepresented in ER(−) breast cancer, which was more resistant to radiation.

BCSCs: breast cancer stem cells; ER: estrogen receptor; ESA: epithelial-specific antigen; γ-H2AX: phosphorylated histone H2AX; N/A: not available

4.3 BCSCs and endocrine therapy resistance

Endocrine therapy is one of the most effective treatments for reducing the recurrence risk in initially treated surgically resected patients with hormone receptor positive breast cancer. Estrogen exposure is considered a significant risk factor for breast cancer development. ER α is expressed at low levels in normal epithelia, and its expression is dramatically up-regulated as transformation progresses during mammary hyperplasia and adenocarcinoma development. However, not all patients who have ER or PR expressing tumors respond to endocrine manipulation (de novo resistance) and most tumors eventually relapse with acquired resistance. Endocrine resistance in breast cancer can be explained by the existence of BCSCs. It is known that breast stem cells possess a basal phenotype and are

mainly ER(—). If the hierarchy in breast cancer reflects this, BCSCs may contribute to endocrine resistance because it shows reduced ER α and can be selected by endocrine therapy. BCSCs also express mesenchymal proteins, which are suppressed by ER α expression, further confirming the conclusion that BCSCs play a key role in cancer relapse and metastases after endocrine therapy. A growing body of evidence from a number of studies indicating that BCSCs are ER- suggests this view. Asselin-Labat *et al* demonstrated that mouse breast stem cells consisted of less than 0.01% ER(+) cells^[24]. In contrast, the ER(+) luminal compartment contains little in vivo breast stem cell activity. Shipitsin *et al* showed that CD44(+)/PROCR(+) ER(—) cells in breast cancers were enriched for stem cell markers and gene expression related to cell motility and angiogenesis^[25]. In primary human breast cancer samples, Holland, *et al* verified that DCIS lesions appear to be estrogen independent^[26]. Farnie *et al.* showed that more than 50% of DCIS lesions had a greater number of BCSCs; in addition, inhibition of epidermal growth factor receptor (EGFR)/Notch signaling disrupted mammosphere formation^[27]. Recently, an interesting hypothesis proposed by Horwitz *et al* based on their research results was that ER(+)PR(+) breast cancer endocrine therapy would be ineffective if it only targeted ER because the ER(+)PR(+) luminal breast cancer subtype contains a subpopulation of basal-like ER(—)PR(—)^[8]. On the other hand, several studies have shown a close relationship between BCSCs and EMT. BCSCs also express mesenchymal proteins, such as N-cadherin, vimentin, and fibronectin proteins, that are suppressed by ER α expression^[28]. One report showed HER2 overexpression enriched for BCSCs in an ER-breast cancer cell line and increased in vitro clonogenicity and tumorigenicity in SCID mice^[29]. The Notch pathway also seems to play a role in endocrine therapy resistance. As mentioned above, the Notch pathway is important for BCSC self-renewal and proliferation. In the MDA-MB 231 breast cancer cell line, Notch-induced transcriptional activity was highest in the ER(—) group, which may provide clues to BCSC regulation and endocrine resistance^[30]. Additionally, TGF- β and EGFR signaling may also be involved in endocrine therapy resistance. Suppression of TGF- β signaling is essential for the

development of breast cancer resistance to tamoxifen, which was specifically active in CD44(+) ER(−) breast cancer cells, where its inhibition induced a more epithelial phenotype. ER(−) DCIS could be promoted by the EGFR pathway, indicating the role of the EGFR pathway in endocrine therapy resistance. Table 4 summarizes the evidence and postulated mechanism of BCSCs resistance to endocrine therapy.

Table 4 Evidence and possible mechanisms of endocrine therapy resistance of BCSCs

Reference	Cell Origin	BCSCs represented	Postulated mechanism	Evidence
Horwitz ^[10]	T47D (luminal)	CD44(+) ER(−)PR(−)	N/A	ER(−) PR(−) population, which would escape from endocrine therapy, had the capacity to generate the majority of ER(+)PR(+) cells.
Farnie ^[37]	Breast cancer patients	Mammosphere	EGFR and Notch dysregulation	More than 50% of DCIS lesions were ER(−) and hormone independent DCIS had a greater number of BCSCs. Inhibition of EGFR/Notch signaling disrupted mammosphere formation.
Korkaya ^[40]	SUM159-HER2 (basal)	ALDH1(+)	HER2 overexpression	Overexpression of HER2 in ER(−) breast carcinoma cells increased the BCSCs population which displayed increased expression of stem cell regulatory genes, increased invasion, and tumorigenesis.

BCSCs; breast cancer stem cells; EGFR; epidermal growth factor receptor; DCIS; ductal carcinoma in situ; ER; estrogen receptor; HER2; human epidermal growth factor receptor2; PR; progesterone receptors; PROCR; endothelial protein C receptor; N/A: not available

4.4 BSCSs and anti-HER2 therapy resistance

Even in patients with breast cancer characterized by HER2 overexpression, some do not achieve clinical benefits with trastuzumab, which is a humanized anti-HER2 monoclonal antibody. Clinical studies involving patients with progressive disease following trastuzumab demonstrate that further manipulation of the HER2 signaling axis, through either continued trastuzumab treatment and rotation to an alternative chemotherapy or the introduction of a novel HER2 targeted agent, is a better therapeutic strategy than stopping anti-HER2 therapy^[31]. The mechanisms of trastuzumab that induce regression of HER2 overexpressing tumors are observed in in vitro and in vivo models, such as internalization and degradation of HER2 receptor protein, disruption of the PI3K/Akt signaling pathway, etc^[32]. Recent observations suggested that resistance to HER2 targeted therapies may be driven by BCSCs. There is a close relationship between HER2 and BCSCs. HER2 promotes carcinogenesis, invasion, and metastasis at least partly by maintaining and increasing

BCSCs^[33]. Hwang-Verslues *et al* showed that BCSCs presented by CD44⁺ CD24^{-/low} breast cancer cells showed reduced HER2 expression^[34]. However, different results reported by Korkaya *et al* showed that HER2 overexpression increased expression of stem cell regulatory genes, increased invasion *in vitro*, and increased tumorigenesis of BCSCs presented by ALDH(+) ^[29]. In addition, trastuzumab blocked the effects of HER2 overexpression in sensitive cell lines via PI3-kinase/Akt pathway. Magnifico *et al* demonstrated that HER2(+) cells are enriched in BCSCs and proposed that Notch signaling regulates HER2 expression^[35]. These results suggest that the effects of HER2 amplification on carcinogenesis, tumorigenesis, and invasion may be due to its effects on BCSCs. There is also growing literature documenting a variety of possible mechanisms of escape from trastuzumab, i. e., mutation in HER2, masking of extracellular trastuzumab, bypass the effect of HER2 blockade and loss of PTEN, etc, involving many of the same markers that have been implicated in the biology of BCSCs^[36]. Palyi-Krek, *et al* showed that trastuzumab blocked CD44 shedding from JIMT-1 xenograft tumors *in vivo*; Trastuzumab inhibits the heregulin- and hyaluronan oligosaccharide-induced shedding and internalization of CD44^[37]. Moreover, CD44 is one of the accepted BCSC-markers. CD44-hyaluronan interaction is thought to play a permissive role in HER2 signaling^[38]. On the other hand, CXCR4, highly expressed in BCSCs, is a regulator of HER2 and is consistently expressed in human breast cancer cells, malignant breast tumors, and metastatic tumors. Tripathy *et al* suggested a link between CXCR4 overexpression and HER2 resistance; their results showed that 4 h of trastuzumab exposure led to differential gene expression of CXCR4. HER2-epitope amplification was preserved in the trastuzumab-resistant cell line confirmed by Western-blot testing and siRNA knockdown. Addition of a CXCR4 inhibitor reversed resistance to HER2 *in vitro*^[39]. These studies provide indirect evidence that BCSCs may underlie resistance to trastuzumab via CXCR4. Moreover, the PI3 kinase/AKT pathway can be activated in response to HER2. PIK3CA phosphorylates PIP2 to PIP3. This reaction is inhibited by the tumor suppressor PTEN phosphorylation. In the absence of PTEN or the presence

of mutant PIK3CA, catalysis is driven from PIP2 to PIP3. This causes activation of AKT1 and other molecules, leading to cellular processes that favor neoplastic growth and transformation and trastuzumab resistance. The function of the PI3 kinase/AKT pathway has been proven by many studies. Additionally, in the MCF7 cell line, Nagata, et al. suggested that the PI3K/AKT pathway was important for BCSCs as represented by SP cell survival and proliferation by pathway specific inhibitors, selected gene knockdown, and in vivo tumorigenicity assays^[40]. Other possible mechanisms such as P27 may also be involved in the role of BCSCs in trastuzumab resistance.

5 Prospective

The BCSCs hold the key to understanding the origin and maintenance of breast cancer. In addition, there is a rationale for the close relationship between BCSCs and anti-tumor therapy resistance. Therefore, there is a clear need for agents that target BCSCs to enable selective killing. New targeted therapies may improve the efficacy of current treatments against aggressive cancers and thereby prevent cancer recurrence and increase the survival rate.

(Fig 1 is shown on the disk.)

【Key words】 Breast cancer stem cells; Signaling pathway; Resistance

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