New targeted therapies for breast cancer: A focus on tumor microenvironmental signals and chemoresistant breast cancers

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Abstract

Breast cancer is the most frequent female malignancy worldwide. Current strategies in breast cancer therapy, including classical chemotherapy, hormone therapy, and targeted therapies, are usually associated with chemoresistance and serious adverse effects. Advances in our understanding of changes affecting the interactome in advanced and chemoresistant breast tumors have provided novel therapeutic targets, including, cyclin dependent kinases, mammalian target of rapamycin, Notch, Wnt and Shh. Inhibitors of these molecules recently entered clinical trials in mono- and combination therapy in metastatic and chemo-resistant breast cancers. Anticancer epigenetic drugs, mainly histone deacetylase inhibitors and DNA methyltransferase inhibitors, also entered clinical trials. Because of the complexity and heterogeneity of breast cancer, the future in therapy lies in the application of individualized tailored regimens. Emerging therapeutic targets and the implications for personalized-based therapy development in breast cancer are herein discussed.

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Core tip: Emerging therapeutic targets may overcome chemoresistance in breast cancer.

INTRODUCTION

The incidence of breast cancer, the most common cancer in women and the second cause of cancer death in women worldwide[1,2], is currently growing[3,4]. Cancers are diseases characterized by aberrant microenvironment and intrinsic signaling causing a continuous proliferation of affected cells ("cancer cells"). Clinical features and

prognosis of cancers vary tremendously according to the tissue and organs they originate from and affect. Breast cancer may start in milk ducts, and can be invasive [invasive ductal carcinoma (IDC)] or not (ductal carcinoma in situ). IDC would represent up to 80% of cases[5,6]. Breast cancer may also start in the lobules, with invasive features (invasive lobular carcinoma) or not (lobular carcinoma *in situ*). In metastatic breast cancer malignant cells originating from breast primary tumors invade other tissues and organs of the body, resulting in a systemic disease. As disease early detection is associated with better prognosis, screening campaigns involving healthy female subjects are performed worldwide. Notably, mammography, which requires the use of low-dose X-rays to capture images inside the breast, is the current goal standard screening for detection of breast cancer asymptomatic cases[7,8]. However, although the technique requires X-rays, the benefits of the earlier detection of breast cancer outweigh the risk of radiation exposure, which can be associated with the development of breast cancer in previously healthy women is present[9,10]. New approaches for early detection have been proposed, and may also contribute to reducing breast cancer mortality (for review see[11,12]).

Three major therapeutic approaches are used today to treat or control breast cancer: surgical removal of primary tumors, irradiation of cancer cells to stop their growth, and anticancer drugs, which kill cancer cells or inhibit their proliferation. Notably, oncoplastic surgery, a technique combining classical lumpectomy (or partial mastectomy) and plastic surgery techniques have revolutionized breast-conserving surgery for removal of lumps and malignant masses. However, surgery or radiotherapy still requires chemotherapy to eradicate remaining malignant cells and impede relapses. Anticancer drugs are based on three therapeutic approaches: (1) the classical chemotherapy, where cancer cell proliferation is stopped by the indiscriminate targeting of rapid cell divisions in the body; (2) hormone therapy, devised to stop cancer cell growth by targeting the receptors and downstream signaling molecules of hormones pivotal for the proliferation of these cells; and (3) and the emerging and promising targeted therapy, where signaling pathways deregulated in primary breast tumors are specifically targeted. Breast cancer treatment is still challenging, as drugs in use are expensive, have serious undesired effects[13-15], and drug resistance is common, particularly in metastatic cases[16,17], underlying the need for new targeted therapies. Interestingly, recent advances in the understanding of breast cancer biology have highlighted the tumor microenvironment as a major player in breast carcinogenesis and have provided new avenues for targeted therapy.

The present review summarizes and discusses the current understanding of changes affecting breast microenvironment during breast tumorigenesis, with a particular emphasis on signaling pathways currently targeted for therapy and emerging therapeutic targets. Personalized-based targeting implementation is also discussed.

TUMOR MICROENVIRONMENT IS PIVOTAL FROM BREAST CANCER INITIATION TO METASTASIS

Numerous stromal cell types are found in the extracellular matrix of the breast stroma, including endothelial cells, fibroblasts, adipocytes, and resident immune cells[18]. In addition to these cell types, cancer-affected microenvironment contains malignant cells termed as cancer-associated fibroblasts (CAFs), which are the most numerous cell type, and infiltrating macrophages termed as tumor-associated macrophages (TAMs).

Cancer-associated fibroblasts

CAFs were reported to play key roles in malignant cell proliferation and tumor maintenance[18,19]. An *in vivo* study involving xenograft of MDA-MB-231 breast cells in SCID mice revealed that CAFs induce p53-dependent antimitogenic responses in normal stromal fibroblast[20], at least partly through Notch-dependent mechanisms[21]. In another study, CAFs expressed vascular endothelial growth factor in presence of hypoxia inducible factor 1 α/G-protein estrogen receptor (HIF-1α/GPER) signaling, suggesting a role for these cells in hypoxia-dependent tumor angiogenesis[22]. Under the same conditions, CAFs were shown to express Notch molecules[23], which promotes cancer cell survival, proliferation[24,25], as well as angiogenesis[26]. In addition, Luga *et al*[27] showed that CAFs release exosomes, which stimulate invasiveness and malignant cell metastasis *via* a Wnt11-dependent mechanism. On the same hand, CAFs induced phenotypical changes in adipocytes resulting in the generation of fibroblast-like cells [adipocyte-derived fibroblasts (ADF)], which in turn increased migratory abilities of metastatic cells by releasing high levels of collagen I and fibronectin[28]. Notably, CAF-induced ADF phenotype generation was mediated by reactivation of the oncogenic Wnt/β-catenin pathway in the latter cells in response to Wnt3a produced by the cancer cells, suggesting CAFs and ADFs as potential therapeutic targets in metastatic breast cancer. Furthermore, CAFs may promote breast cancer initiation and progression to metastasis *via* tumor-α9β1 integrin signaling[29] and fibroblast growth factor signaling[30], as well as malignancy orchestration and tumor stroma reprogramming through activation of heat shock factor 1[31], a transcriptional regulator.

Interestingly, Capparelli *et al*[32,33] have hypothesized that senescent fibroblasts may promote tumor growth through an autophagy-dependent mechanism termed as "autophagy-senescence transition". In order to test such hypothesis, these authors introduced autophagy genes such as *bnip3*, *ctsb* or *ATG16L1* in immortalized human fibroblasts that resulted in the induction of a constitutive autophagic phenotype (characterized by mitophagy, aerobic glycolysis, L-lactate and ketone body production) with senescence features associated with increased β-galactosidase activity, increased level of cyclin depen-

dent kinase inhibitor (CDKI) p21, and cellular hypertrophy. Interestingly, "autophagic-senescent" fibroblasts were able to induce tumor growth and metastasis independently of angiogenesis, with stronger effects (up to 11-fold) in autophagic fibroblasts producing large amounts of ketone bodies. These observations were confirmed *in vivo*, as the lysosomal enzyme and biomarker of senescence, β-galactosidase, was also found in human breast cancer stroma. A recent *in vivo* study revealed the ability of CAF autophagy and senescence to promote tumor growth and metastasis increasing the rate of glycolysis and enhancing the generation of mitochondrial fuels including bodies[33] in a compartment-specific fashion, thus supporting the role of CAFs to metabolically regulate tumorigenesis. In this study, the injection of the antidiabetic molecule along with peroxisome proliferator-activated receptor gamma (PPARγ), known to stimulate glycolysis and pro-autophagy, into stromal cells enhanced the growth of co-injected breast cancer cells by 60%, whereas PPARγ injection in cancer cells reduced the growth of breast cancer cells by 40%[34].

Tumor-associated macrophages

TAMs infiltration into neoplastic tissues is an important negative prognostic factor[35,36], and a hallmark of triple negative breast cancer[37], a chemoresistant subtype of breast cancer[38,39]. Overall, emerging evidence suggests that TAMs are major player in anticancer drug resistance in breast cancer. For instance, Yamashina *et al*[40] recently reported that cancer stem-like cells originating from chemoresistant tumor promote macrophage colony-stimulating factor production *via* an interferon regulatory factor 5-dependent mechanism, and transform recruited CD14(+) monocytes in tumorigenic M2-macrophages (immunoregulatory), probably through CXCR3 downregulation[41]. Interestingly, the differentiation inducer dimethyl sulfoxide exerted antitumor effects in a mouse breast cancer model (4T1) possibly by inducing M1-phenotype in TAMs[42].

Furthermore, TAMs may promote carcinogenesis and metastasis *via* Wnt signaling, which mediates the angiogenic switch and metastatic processes in breast cancer[43,44]. Notably, TAMs release high levels of the Wnt family ligand Wnt7b[45], and cancer stem-like cells may trigger the metastatic effect of TAMs through enhancement of the β-catenin pathway *via* vitamin D receptor suppression by tumor necrosis factor alpha[46]. In addition, *in vivo* and *in vitro* studies supported a pivotal role for Wnt 5a signaling in TAMs-induced metastasis[47,48], and a strong correlation was found between Wnt5a expression in malignant cells and the number of CD163(+) M2-macrophages[49]. In a relatively recent study investigating the potential of the phosphodiesterase type 5 inhibitor (vasodilator) drug dipyridamole in xenograft mice, anticancer effects were mediated at least partly by decreasing β-catenin cytosolic levels[50]. Altogether, these findings implicated TAMs as a key links between chemoresistance and tumorigenic activities of cancer stem-like cells, and thus, positioning TAMs as potential therapeutic targets

for breast cancer. Figure 1 shows the main signaling pathways currently in use for targeted breast cancer therapy, as well as some possible new targets.

NOTCH SIGNALING

Notch family of molecules

The Notch family of membrane bound receptors and ligands regulate several cell processes including cell invasion, survival and apoptosis, *via* the Notch signaling pathway. The pathway comprises four receptors (Notch1 through Notch4) and five Notch ligands (Delta-like 1, 3, and 4, and Jagged1 and 2). Notch ligands include an extracellular domain containing multiple epidermal growth factor (EGF)-like repeats and an extracellular DSL where ligand binding occurs, and an intracellular domain with a PDZ-binding motif at C-terminal domain[51,52]. Notch receptors are also made of an extracellular and an intracellular domain covalently linked. Notch receptor extracellular domain also contains EGF-like repeats (26-29 depending on the Notch receptor), whereas Notch intracellular domain (NICD) presents with LIN12/Notch-related repeats preventing ligand-independent signaling, cysteine residues, and a C-terminal transactivation domain containing a PEST sequence with proteolytic activity.

Notch ligands are expressed on the plasma membrane of one cell and interact with Notch receptors on the plasma membrane of a neighboring cell, initiating the cleavage of the receptor by proteases [ADAM (a disintegrin and metalloprotease) and γ-secretase] that culminates in the release of the NICD[53]. Released NICD translocate to the nucleus and forms a transcriptional activator complex with C-promoter binding factor 1/Suppressor of Hairless and Lag-1 (CSL) transcription factor. Together with cofactors like mastermind-like protein, NICD-CSL complex induces the transcription of cell fate key target genes such as *vegfr3* and, *notch1* that regulate angiogenesis and apoptosis, *p21* that regulates the cell cycle, as well as transcription factor genes such as the basic helix-loop-helix and hairy/enhancer of split/-related (*hes* and *hey*)[54,55] (Figure 1).

Notch signaling as a therapeutic target

As already mentioned (section 2), Notch signaling is used by CAFs to promote cancer cell survival and proliferation. Early reports revealed that upregulation of Notch signaling suffices to transform normal breast epithelial cells in malignant cells *in vitro*, and that high levels of NICD are present in breast primary tumors[56-59]. Notch carcinogenic effects are mediated *via* the silencing pro-apoptotic signaling pathways and growth-inhibitory molecules like TGF-β[58]. Notch-induced TGF-β silencing also promotes bone metastasis[60,61]. In addition, Notch signaling, which is required for physiological angiogenesis, may also be a key player in neoangiogenesis[62]. A Notch 3 addiction of the lymphovascular embolus was reported in a xenograft model of inflammatory breast carcinoma, a subtype of breast cancer whose hallmark is
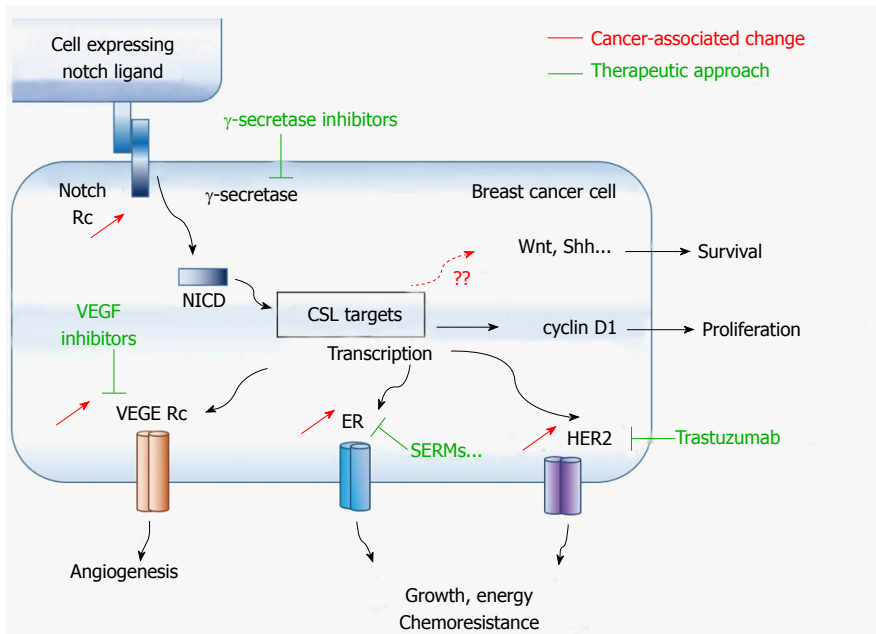
Figure 1 Notch signaling in breast cancer. In Notch-driven breast cancers, tumor cells and neighboring cells express Notch ligand and receptors. In presence of ADAM/TACE and γ-secretase enzymatic complex, Notch ligand-receptor interactions result in the release of Notch intracellular domain (NICD), which translocate to cell nucleus and activate CSL transcription factor. Target genes include signaling molecules involve in cancer cell survival, proliferation, angiogenesis, growth, energy metabolism, and chemoresistance. Inhibitors of many of these signaling molecules have been developed and are in use in various cancers, including g-secretase inhibitors, vascular endothelial growth factor inhibitors, estrogen signaling inhibitors, and HER2 inhibitors. ER: Estrogen receptor; HER2: Epidermal growth factor receptor 2; ADAM/TACE: A disintegrin and metalloprotease/tumor necrosis factor-α converting enzyme; CSL: CBF1/Suppressor of Hairless/LAG-1.

lymphovascular invasion[63].

In vitro studies in estrogen receptor (ER)-negative breast cancer cells (MDA-MB-231) performed by Lee *et al*[64] revealed that Notch signaling up-regulates the transcription of the apoptosis inhibitor survivin. In another study, these authors showed that Notch-1-survivin functional gene signature is common in basal breast cancer[65]. In addition, crosstalk between Notch and signaling pathways involved in cell growth were reported as well, including the estrogen receptor[66], human epidermal growth factor receptor 2 (HER2)[67], and the metabolic signaling pathways phosphatidylinositol 3-kinase (PI3K)/ protein kinase B (Akt)/mammalian target of rapamycin (mTOR)[68,69] and MAP kinase/ERK[70,71]. Interestingly combined targeting of Notch and EGFR signaling suppressed chemoresistance in a basal-like breast cancer *in vivo* model[72], suggesting that co-targeting of Notch and associated pathways may represent a new avenue for overcoming chemoresistance (Figure 1).

Tumor initiating cells of tumors overexpressing HER2/neu also express high levels of Notch molecules, whose signaling is known to enhance HER2 expression[73]. Chemoresistance to HER2+ breast cancers to trastuzumab, a monoclonal antibody against HER2, is associated with the overexpression of Notch-1 and its ligand Jagged-1[74,75]. Similarly, cancer stem-like cells also achieve resistance against chemotherapy and radiotherapy *via* Notch signaling[76], and targeting of this signaling pathway reduces the stem-like population[77]. The γ-secretase inhibitor MRK-003 induced long-term recurrence-free survival in a transgenic mouse model of HER2+ breast cancer[78]. Similarly, co-targeting of Notch and HER2

signaling pathways prevented breast tumor recurrence in orthotopic breast tumor xenograft using trastuzumab-resistant BT474 cells[79].

Platelet-derived growth factor-D, another marker of breast cancer poor prognosis, may increase breast tumor aggressiveness by activating Notch and NF-κB signaling pathways[80]. Furthermore, Notch-1 and Notch-4, established bio-markers of the chemoresistant breast cancer subtype[81], were reported as novel transcriptional targets in triple negative breast cancer[82,83]. Jagged1/Notch4 signaling was shown to induce epithelial-to-mesenchymal transition[84]. Notch signaling was also reported as a mechanism of resistance to PI3K inhibitors[85] and hormone therapy[86].

Clinical evaluation of Notch signaling targeting
Notch signaling inhibitors have a promising clinical efficacy as they abrogate HER2-Notch axis of chemoresistance. Notch silencing by ɤ-secretase inhibitors (GSIs) inhibited the proliferation of breast cancer cells partly by causing cell cycle arrest and apoptosis[76], and by sensitizing chemoresistant breast cancer cells to the BH3 mimetic ABT-737[87]. Notably, GSIs induce toxicity to breast cancer both *in vitro* and *in vivo* models, however mechanisms of such cytotoxicity are complex and may involve proteasome inhibition and downregulation of Bax and Bcl-2[88,89].

Following encouraging pre-clinical studies[83,90,91], the oral gamma secretase inhibitor R04929097 recently entered phase-I trial in patients with advanced solid tumors. Early reports of combination therapies with the kinase inhibitor temsirolimus[92], the antimetabolites of the
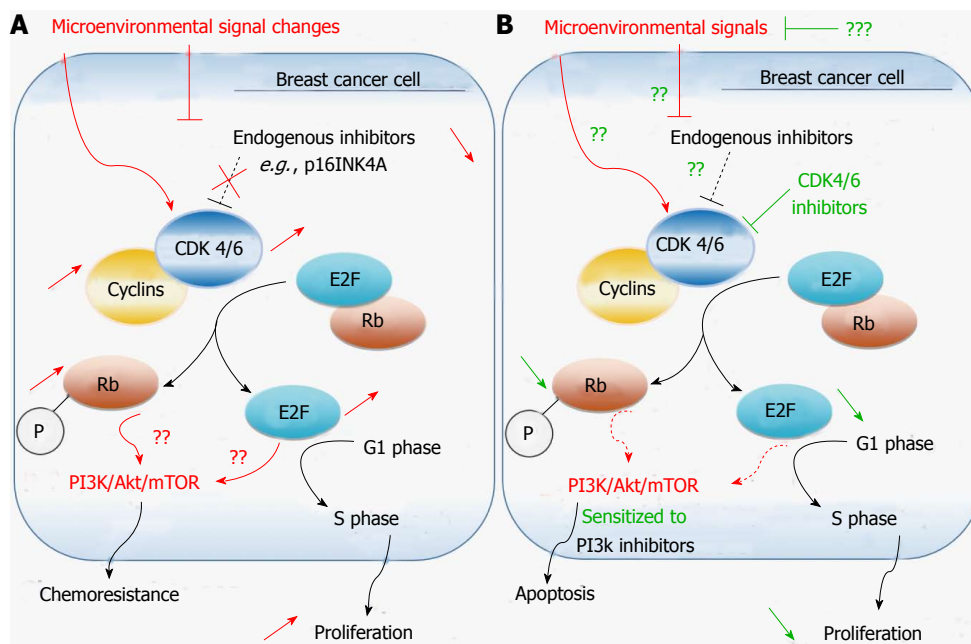
Figure 2 CDK4/6 signaling in breast cancer. A: Cyclin dependent kinases (CDK) 4/6 signaling is overexpressed in breast cancer. Such overexpression, which results from the silencing of CDK endogenous inhibitors, participate directly to cancer cell proliferation by triggering G1-S transition, and indirectly to chemoresistance via a PI3K/Akt/mTOR-dependent mechanism; B: CDK4/6 inhibitors sensitize chemoresistant cells to PI3K inhibitors and various other anticancer agents. PI3K: Phosphatidylinositol 3-kinas.

pyrimidine analog family gemcitabine (PHL-078/CTEP 8575)[93] or cediranib (PJC-004/NCI 8503) revealed that the combinations were safe and promising in breast, tracheal, and pancreas cancer patients. However, anemia, diarrhea, fatigue, hypertension, neutropenia, and nausea were observed, among other side effects. GSI reported side effects seem to be mediated primarily through proteasome inhibition[88,94]. Thus, CSL inhibition, which was reported to mediate a more effective inhibition of Notch-dependent carcinogenic processes than GSIs[95], may represent a less toxic approach for Notch signaling targeting.

Another GSI, PF-03084014, also presented promising results in breast xenograft models[96], with gastrointestinal toxicity easily abrogated by glucocorticoids[97]. Other promising pre-clinical observations included a synergistic effect with the antimitotic drug docetaxel in breast cancer[98], colorectal cancer[99], and metastatic pancreatic cancer[100] models. Antiangiogenic effects where also reported in combinations with the tyrosine kinase inhibitor sunitinib in solid tumors[101], whereas in chronic lymphocytic leukemia cells combinations with the nucleoside metabolic inhibitor fludarabine inhibited angiogenesis as well as migration and invasion of Notch 1-mutated cancer cells[102,103]. PF-03084014 therefore appears as an appealing GSI for both solid and blood cancers and may be a good targeted-therapy drug in breast cancer.

CDK

CDKs, cyclins and CDKI
Cyclins, CDK inhibitors (CDKIs, *e.g.*, p16INK4, p15INK4B, p18INK4C. p21WAF1/CIP1[104,105]) and CDKs are the three key classes of regulatory molecules that deter-

mine cell cycle progression through the G0-G1-S-G2 and M phases[106,107]. Numerous CDKs are found in eukaryotic cells, of which some are pivotal cell cycle regulators, such as CDK1/2/4/6 (Figure 2). CDKs (catalytic subunits, heterodimeric serine/threonine kinase class) associate with cyclins (regulatory subunits) to form an active catalytic complex favoring G1/S cell-cycle progression in mitosis. For instance, CDK1/A2 or CDK1/B1 complexes trigger mitosis in mammalian cells by phosphorylating downstream cell cycle regulatory proteins[108]. Other CDKs are involved in the regulation of cellular transcription, such as CDK7-11[107,109]. A recent proteomic analysis of the CDK family in human cells has identified a CDK5 complex as a key regulator of non-neural cell growth and migration factor[110].

CDK involvement in breast cancer
Early and emerging evidence suggests that cyclin D1 promotes breast tumorigenesis[111,112]. CDK1 activity was recently reported as a powerful predictor of taxane chemosensitivity, indicating a role for CDK1 in breast tumorigenesis[111]. Notably, taxanes are the drug class most used for breast cancer pre-operative chemotherapy; they induce apoptosis in malignant cells by stopping their replication[113,114]. Moreover, studies investigating genes that are synthetically lethal in Myc-dependent cancer identified numerous CDKs as Myc synthetic-lethal genes[115-117]. Interestingly, in one of such studies CDK1, but not CDK2 or CDK4/6 was selectively lethal to Myc-dependent breast cancer cells[117]. This observation indicates that targeting CDK1 may induce apoptosis in Myc-dependent cancers, where Myc drives cancer cell growth and cycle progression[118]. Increases in activities and levels of other CDK complexes were also reported in breast cancer

primary tumors and experimental models, including CDK4/6 and cyclin E/CDK2 complexes[119-121]. The occurrence of cyclin E/CDK2 proteolytic cleavage products associates with poor clinical outcome in breast cancer patients and increases tumorigenicity in experimental models at least partly by promoting stem-like properties of tumor cells[120]. Transcriptional regulator CDK8 targeting was also recently reported to inhibit both the proliferation and the migration of breast cancer cells[122]. In addition, *BRCA2* gene, whose aberrant activating mutations associate with familial breast cancer[123,124], was reported to induce genomic stability in malignant cells through a CDK-dependent mechanism[125].

A link between the cell cycle and steroid hormone metabolism involving CDK4/6 was recently uncovered in breast cancer primary tumor cells[126]. In this study, malignant cells appeared to control the activity of steroid metabolic enzymes, *i.e.*, the expression of steroid hormone receptors (including ER), by alteration of CDK4/6-levels (overexpression of CDK4 and decrease of its homolog CDK6). Such mechanism may play a pivotal role in the carcinogenesis and chemoresistance of steroid hormone-dependent cancers. In another recent study the newly synthesized compound KU004 that had a potent anticancer effect by targeting HER2 induced a decrease in CDK4 expression[127]. On the same hand, CDK 4/6 inhibitors sensitized *PIK3CA* mutant breast cancer to PI3K inhibitors in a xenograft study[128] (Figure 2), further suggesting a role for CDK4/6 imbalance in breast tumorigenesis.

CDK inhibitors

CDK4/6 inhibitors are more efficient and less toxic antineoplastic agents than molecules targeting other CDKs[129]. The selective cyclin D kinase 4/6 inhibitor palbociclib (PD-0332991) is currently entering phase III trial for ER+ breast cancer patients, following encouraging results in progression free survival in phase II trials[130]. Using the bioluminescence imaging technology, an early study in xenograft models displaying metastatic progression revealed powerful antimetastatic effects, comparable to avastin, and docetaxel effects[131]. In addition, palbociclib, preferentially inhibited the proliferation of luminal ER+ breast cancer cell lines *in vitro*[132], suppressed malignant cell proliferation in approximately 85% of cases irrespective of ER+/- or HER2+/- statuses[133]. Furthermore, palbociclib induced growth arrest in hormone-resistant MCF-7 breast cancer cells by a mechanism consistent with cellular senescence[134]. This observation is not surprising considering the functional link between tumor microenvironment carcinogenic activity, ageing, and autophagy discussed above (section 2.1), and indicate that the drug may also affect metabolic processes in CAFs and stem-like tumor cells[33,34].

Chemoresistance to CDK4/6 inhibitors has been reported[133,135]. Analyses of primary tumor cells of cases resistant to CDK4/6 inhibitors showed that these cells lack the tumor suppressor retinoblastoma protein (RB)[133],

which is necessary for CDK4/6 control of the cell cycle restriction point[135]. Interestingly, RB-deficient chemoresistant breast cancers, such as RB-deficient triple negative breast cancers, are more sensitive to the metabolic inhibitor of the folate analog family methotrexate and to the anthracycline topoisomerase inhibitor doxorubicin compared to RB+ cell lines[136], indicating that combination therapy may improve CDK4/6 inhibitor response in resistant cases. However, a report by Roberts and colleagues cautioned against the use of these agents in combination with DNA-damaging drugs (*e.g.*, doxorubicin, carboplatin), considering the potential genotoxic side effects[129]. The dangers that may result from such combination also emerged in other pre-clinical studies[137,138].

The CDKI dinaciclib (MK-7965), which selectively binds to the ATP site of CDKs and acts as a protein-protein inhibitor of bromodomains[139,140], also displayed encouraging anticancer properties in pre-clinical studies in human cancer models[141,142]. The drug recently entered phase III in leukemia[139] and phase II trial in solid cancers. The drug is well tolerated in monotherapy, but revealed an antitumor activity whose efficacy was not superior to the nucleoside metabolic inhibitor capecitabine in a phase II trial in advanced breast cancer patients[143]. Comparable observations were reported in non-small cell lung cancer where the drug was compared with the protein kinase inhibitor erlotinib[144]. Similar combination therapy studies in progress for breast cancer[143,144] may provide alternative strategies for breast cancer therapy.

OTHER EMERGING THERAPEUTIC TARGETS

Wnt signaling

A number of reports have suggested that Wnt signaling pathway, which is normally involved in embryonic induction and cell fate[145,146], is aberrantly activated in blood cancers[147-149] and solid cancers, such as head and neck, lung, gastrointestinal, and breast cancer[27,150-155]. Wnt5a and Wnt11 are major players in macrophage-induced malignant invasion in metastatic breast cancer[27,151], and several breast tumors constitutively release-inducible Wnt ligands[156]. In addition, the naturally occurring pentacyclic triterpenoid ursolic acid, which is known to exert antitumor activity in various solid cancers including breast cancer, may act through inhibition of canonical (Wnt/β-catenin) signaling[150]. Similarly, the natural plant polyphenol rottlerin was reported to inhibit Wnt/β-catenin signaling in cancer cells by promoting the degradation of Wnt co-receptor LRP6 (low density lipoprotein receptor-related protein 6)[157]. Such inhibition resulted in cell death in various cancer cell lines, including MDA-MB-231 and T-47D breast cancer cells. Salinomycin, another novel LRP6 inhibitor, induced comparable effects in breast and prostate cancer cell lines, by inhibiting both Wnt/β-catenin and PI3K/Akt/mTOR signaling[158].

The development of specific Wnt inhibitors is in

progress. Recently, a specific inhibitor of Porcupine (PORCN, an O-acyltransferase required for the secretion of Wnt ligands[159]) termed as LGK974 was developed. LGK974 displayed potent anticancer properties in *in vitro* and *in vivo* models of breast cancer and pancreatic adenocarcinoma mediated by reduction of the transcriptional expression of Wnt target genes[147,160]. However, another recent report revealed that Wnt signaling molecules are differentially expressed in breast cancer clinical subtypes and in cancer stem-like cells, indicating that the development of more specific Wnt-targeted therapies in breast cancer may be necessary[161]. Wnt signaling was also reported a major role in malignant cell acquired resistance to classical chemotherapy, including resistance to tamoxifen[162], and in chemoresistant cells from triple negative breast cancer patients[163], suggesting the potential of Wnt inhibitor combination therapies.

Shh signaling

Early studies have suggested that Sonic Hedgehog (Shh) overexpression, mediated by both NF-κB up-regulation and *shh* promoter hypomethylation in breast cancer[164], is a critical event in the development of various solid cancers[165-167]. For instance, Shh signaling was reported to promote the survival of cancer epithelial cells, but not their normal counterparts[168]. Targeting of Shh transcription activator Gli1 enhanced apoptosis and attenuated migration in inflammatory breast cancer cells[169]. In addition, Shh non-classical activation was reported as a multidrug resistance enhancer, including resistance to Smo inhibitors[170], suggesting that targeting these pathways specifically may abrogate the associated chemoresistance.

Smo inhibitor anticancer drug cyclopamine, which inhibits Shh signaling by antagonizing its downstream target Smo, is metabolically stable and is currently investigated for the treatment of various cancers[171-173]. The chemotherapy drug paclitaxel used in combination with cyclopamine was shown to antagonize chemoresistant breast cancer cells both *in vivo* and *in vitro*[174], suggesting Shh signaling as a candidate for targeted therapy in chemoresistant cancer cells. Similarly, cyclopamine also sensitized chemoresistant tumor cells to taxane drugs in ovarian cancer[175], another hormone-related cancer. Not surprisingly, Shh targeting was reported as a therapeutic option in endocrine-resistant breast cancer due to its ability to sensitize PI3K/AKT signaling-induced tamoxifen chemoresistant malignant cells[176].

Notably, ER-α physiologically regulates non-canonical Shh signaling in the mammary gland, and is essential for mammary gland morphogenesis at puberty[177,178]. However, Gli1 expression also enhances migration and invasion of malignant cells in ERα-negative and triple negative breast cancers, where it represents a predictor of poor prognosis[179]. These observations indicate that Shh signaling involvement in breast cancer cells is complex and therefore targeting Shh in chemoresistant cancer therapy can also compromise its normal physiological function.

FUTURE DIRECTIONS: PERSONALIZED-BASED THERAPY AND EPIGENETIC TARGETS

Personalized-based therapy

The major challenges in breast cancer treatment include resistance to chemotherapy, hormone therapy and even targeted therapy (Table 1), which underline the need for developing novel targeted therapies. Although the main molecular events driving cancer involve the activation of proto-oncogenes or the inactivation of tumor suppressors, deregulation of various signaling intermediates and metabolic factors have been well documented[72,77,82,83,149,161]. The events triggering cancer development affect proto-oncogenes such as Notch, Wnt, and Shh, which are the developmental genes driving embryonic induction and organogenesis during fetal life. These genes, whose expression is normally transcriptionally reduced or silenced in most adult tissues (except stem-like cells) by regulator molecules, are aberrantly overexpressed in cancer cells, conferring them stem-like properties[72,77,82,83,149,161].

Concomitantly, neoplastic tissue growth is fuelled by the upregulation and overexpression of receptors such as HER2, ER and, IGF-1R[70,71,180], the upregulation and/or activation of signaling molecules associated with cell proliferation[111,112], cell migration[181,182], oxidative stress, hypoxia and neoangiogenesis[22,26], all which are characteristic of tumor microenvironment. Thus, the complete characterization of all these tumor promoting events will pave the way for the development more efficient and less toxic anticancer drugs. Computational causal network models aimed at improving the current understanding of signaling molecule interactions in breast cancer, which will allow the determination of specific subsets of patients susceptible to a given therapeutic approach, are currently in development[156,183]. Although the complexity of such networks makes this effort challenging, nonetheless, the development of such tool would allow implementation of a highly efficient personalized-based therapy in breast cancer.

Epigenetic changes drive tumorigenesis

Epigenetics describes heritable alterations in gene expression patterns that do not alter the primary DNA sequence, but play critical roles in normal differentiation and development. Epigenetic alterations include modifications such as DNA methylation, histone modifications and nucleosome remodeling. The plasticity and reversibility of epigenetic events enable a better control of the dynamism of cellular processes. However, deregulation of the normal epigenetic patterns can lead to aberrant expression of cell growth regulatory genes that can culminate in cancer. Epigenetic factors affect gene expression both pre- and post-transcriptionally and probably account for the high inter-individual variability in clinical course and treatment outcome of both blood and solid cancers[184,185]. There is ample evidence linking

Table 1 Current therapeutics for breast cancer

Drug	Trade name	Class	Anticancer mechanism
Classical chemotherapy			
Methotrexate	Abitrexate®, Mexate®, Folex®	Antimetabolites, folate analogs	Folate receptor competitive antagonist[218]
5-fluorouracil	Adrucil®, Efudex®, Fluroplex®, prodrug capecitabine/Xeloda®	Antimetabolite, pyrimidine analogs	Inhibition of the phosphatase and tensin homolog thymidylate synthase[219]
Gemcitabine hydrochloride	Gemzar®		
Doxorubicin hydrochloride	Adriamycin®	Anthracycline	Deoxyribonuclease inhibitor[220]
Epirubicin hydrochloride	Ellence®		
Pamidronate disodium	Aredia®	Nitrogen-containing bisphosphonate	Inhibition of farnesyl pyrophosphate synthase activity[221]
Cyclophosphamide	Clafen®, Cytoxan®, Neosar®	Nitrogen mustard alkylating agent	Inhibition of DNA replication by interacting with the alkyl group of DNA guanine base[222]
Paclitaxel	Abraxane® Taxol®	Taxanes	Microtubule Inhibitors[223,224]
Docetaxel	Docecad®, Taxotere®		
Ixabepilone	Ixempra®	Epothilone B analog	
Targeted therapy			
Everolimus	Afinitor®	mTOR inhibitor	Silencing of PI3K/Akt/mTOR signaling[225]
Trastuzumab	Herceptin®	HER2 inhibitor	Anti-HER2 monoclonal antibodies[226,227]
Pertuzumab	Perjeta®		
Ado-Trastuzumab Emtansine	Kadcyla®	Antibody-drug conjugate	HER2 inhibitor and cytotoxic agent[228]
Lapatinib ditosylate	Tykerb®	Dual tyrosine kinase inhibitor	EGFR/HER2 inhibitor[229]
Hormone therapy			
Toremifene	Fareston®	Selective ER modulator	Silence ER signaling[230,231]
Fulvestrant	Faslodex®	ER antagonists	
Tamoxifen citrate	Nolvadex®		
Anastrozole	Arimidex®	Aromatase inhibitors	Inhibit estrogen synthesis[232-234]
Exemestane	Aromasin®		
Letrozole	Femara®		
Goserelin acetate	Zoladex®	GnRH agonist	
Megestrol acetate	Megace®	Progesterone derivative	Progestational and antigonadotropic effects[235]

PI3K: Phosphatidylinositol 3-kinase; Akt: Protein kinase B; HER: Epidermal growth factor receptor 2.

the etiology of breast to abnormal genetic and epigenetic events[180,186,187]. Cancer-specific DNA methylation changes and well as dysregulation of histone modification have been characterized as contributors to breast cancer development. Progress in our understanding of epigenetics mechanisms in breast cancer have led to the identification of novel therapeutic targets. Recent therapeutic strategies involving the use of epigenetic agents alone or in combination with chemotherapy and/or endocrine therapy are showing promising results in breast cancer patients including chemoresistant cases[186,188].

The technological breakthrough of "omics era" has allowed the development of high-throughput sequencing technology allowing both global and comprehensive investigations of the interactome, the epigenome, and the transcriptome (*i.e.*, active signaling pathways, cascades of pre- and post-translational changes affecting specific genes, and changes in gene expression)[189-191] at individual level. Epigenetic alterations in cancer constitute appealing therapeutic targets due to their pivotal roles in disease initiation, progression, and chemoresistance, and to their reversibility. For instance, chemoresistance to the ER antagonist fulvestrant is mediated by epigenetic modulation (more specifically hSWI/SNF-mediated chromatin remodeling) of GPER and CDK6 expression[192], suggesting that adjuvant therapy targeting SWI/SNF activity may induce apoptosis in resistant cancer cells. SWI/SNF

tumor-dependency has also been reported in other solid cancers and in leukemias[193,194].

Epigenetic targets in breast cancer: histone deacetylation and DNA hypermethylation

Studies have shown that the transcriptional expression of various signaling molecules associated with breast cancer and other cancers may result from selective epigenetic silencing of regulator genes mediated by histone deacetylation and gene promoter (DNA) hypermethylation[195-197], among other potential epigenetic mechanisms[186,198]. For instance, the reduction in ER expression observed in various chemoresistant breast tumors may be mediated by epigenetic silencing (*e.g.*, er*β1* silencing)[199]; and some histone deacetylases (HDACs) such as HDAC3/8 were reported to play pivotal regulatory roles in the proliferation of normal and MDA-MB-231 cells[200].

Data from numerous pre-clinical *in vivo* and *in vitro* studies support the potential of DNA methylation status targeting in breast cancer. Both the HDAC inhibitor (HDACI) trichostatin A and the DNA methyltransferase (DNMT) inhibitor (DNMTI) deoxycytidine (5-aza-2'-deoxycytidine) induced apoptosis in various breast cancer cell lines[201-205]. The HDACI Romidepsin (FK-288) eliminated both primary and metastatic tumors in combination with Paclitaxel in the Mary-X pre-clinical model of inflammatory breast cancer[206]. The green tea-derived

anticancer molecule epigallocatechin-3-gallate suppressed invasiveness in MDA-MB-231 and MCF-7 breast cancer cells by silencing matrix metalloproteinase 2 (MMP2) and MMP-9 and inducing TIMP-3 through increased activities of the enhancer of zeste homolog 2 and HDACs[207]. Suberoylanilide hydroxamic acid, another naturally occurring HDACI, restored radiosensitivity and suppressed breast cancer lung metastasis *in vitro* and *in vivo*[208].

The HDACI Vorinostat sensitized mesenchymal-like triple-negative breast cancer cell lines to hormone therapy by reactivating ERα[209] and PI3K/Akt/mTOR signaling sensitivity[210], corroborating the role of epigenetic alterations in chemoresistance development in breast tumors. Furthermore, the HDACI abexinostat induced cancer-like stem cells differentiation in 16 breast cancer cell lines[211]. Because of these interesting observations, the HDACIs belinostat, panobinostat, and vorinostat, previously used only in blood cancers, have entered phase I and Ⅱ clinical trials in solid tumors, such as lung, prostate, gastrointestinal, ovarian and breast cancer, where they are showing encouraging results (for review see[212]). Various DNMTI are also showing encouraging responses in metastatic and chemoresistant breast cancers in monotherapy and in combination therapies in phase I and Ⅱ trials[213-217].

CONCLUSION

Targeted therapies are associated with reduced adverse effects and better outcome. Tumor microenvironment cells such as cancer-associated fibroblasts and tumor-associated macrophages undergo aberrant genetic and epigenetic changes that trigger the overexpression of signaling molecules promoting neoplasia and neoplastic tissue survival. Many therapeutic targets have emerged. They include Notch, CDKs, mTOR, Wnt, and Shh, whose inhibitors are showing promising results in ongoing clinical trials, both in monotherapy and in combination therapy. Similarly, epigenetic drugs are also showing encouraging results in breast cancer, particularly in advanced and chemoresistant cases. New technological advances will enable the identification of precise alterations affecting the interactome, transcriptome, and the epigenome, leading to the design of more specific tailored therapies. Such therapeutic approach may also be beneficial in the treatment of chemoresistant breast cancers.

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