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Cellular Plasticity and Treatment Resistance in Breast Cancer: A Literature Review

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ABSTRACT

Breast cancer is the most prevalent cancer with a high mortality rate especially in aggressive subtype and metastatic disease. Although there are various treatment options based on tumor characteristics such as chemotherapy, radiotherapy, endocrine therapy, and targeted therapy, treatment-resistance cases are still reported. Treatment resistance is a factor in poor outcomes and relapse in breast cancer patients. Increased plasticity of cancer cells contributes to therapeutic resistance through various pathways such as MAPK, STAT3, PI3K, Wnt, Hedgehog, and Notch. Breast cancer cell plasticity is driven by epithelial-mesenchymal transition (EMT) and cancer stem cells, enabling cells to acquire diverse phenotypes and maintain self-renewal capabilities. Gaining insight into the role of cellular plasticity in treatment resistance is essential for the development of more effective therapeutic strategies in breast cancer management. This review explores the key signaling pathways involved in regulating cellular plasticity and their contribution to therapeutic resistance in breast cancer.

Keywords: breast cancer; cellular plasticity; molecular pathway; resistance; therapy.

INTRODUCTION

Breast cancer is the most common malignancy with high mortality in women worldwide [1]. Currently, the option of breast cancer therapy is adequate with the selection of regimens based on pathological type. However, poor therapeutic response is still reported and has an impact on cancer recurrence in the future. Treatment resistance has a significant role in this poor response, either due to intrinsic factors or secondary formation after exposure to anti-cancer agents in initially sensitive cells [2]. Cellular plasticity may contribute to this process.

Cellular plasticity refers to the ability of a certain genotype to produce multiple phenotypes in response to varying external conditions [3]. Cellular plasticity is widely studied in important processes such as embryo differentiation, wound healing, and cancer progressivity and metastasis [4],[5]. Cellular plasticity can emerge from alteration in characteristics of breast cancer stem cells (BCSCs) and/or through the induction of epithelial-to-mesenchymal transition (EMT), both are key contributors to therapeutic resistance [6].

Cancer cell plasticity is a dynamic process played by various specific signaling pathways. It poses challenges in developing modalities to overcome therapy resistance, especially in breast cancer [4]. In this review, we discuss an overview of current insights into cellular plasticity in breast cancer, with a focus on epithelial-mesenchymal plasticity, BCSCs, and the signaling pathways involved in treatment resistance.

CELLULAR PLASTICITY

Cancer exhibits substantial heterogeneity, both between tumors (inter-tumor heterogeneity) and among cells within a single tumor (intratumor heterogeneity). Tumor cells can alter the normal tissue differentiation programs in their microenvironment, contributing to the development of tumor diversity [7]. This heterogeneity is influenced by the plasticity of cancer cells. Cellular plasticity allows cells to undergo dynamic phenotypic transitions during tissue development and maintain homeostasis under both physiological and pathological conditions [8].

In breast cancer, cellular plasticity is described as the ability of malignant epithelial cells to acquire mesenchymal and stem cell properties [6]. This development is important to facilitate the invasion, metastasis, and therapeutic resistance of breast cancer cells [5]. The plasticity may be induced by the expression of transcription factors (intrinsic plasticity) or by microenvironmental changes (extrinsic plasticity) [9], [10].

Cellular plasticity changes the traditional concept of differentiation as a unidirectional and irreversible process, demonstrating that terminally differentiated cells can reacquire the ability to alter their fate. This regained differentiation includes de-differentiation (cells lose their lineage-specific identity and reacquire stem-like properties) and trans-differentiation (direct transition from one differentiated cell type to another type) [9], [11], [12]. Cancer cell plasticity is mainly played by transitions or changes between epithelial-mesenchymal cell types or when cells acquire traits resembling stem cells known as breast cancer stem cells (BCSC).

Epithelial-mesenchymal Transition (EMT)

Cellular plasticity is a common property during embryonic development when cells routinely form various tissue types. Cells have the ability to transition repeatedly between epithelial and mesenchymal states during their development. Epithelial-mesenchymal transition (EMT) is a distinct type of trans-differentiation in which cancer cells undergo a reversible shift from epithelial to mesenchymal phenotype. This dynamic process is regulated by both genetic alterations and epigenetic modifications [13]. EMT is characterized by disruption of the intracellular junction, the loss of apical-basal polarity, and remodeling of the cytoskeleton. The reverse process is known as mesenchymal-epithelial transition (MET) [14].

Dynamic cell transitions, mainly involving a change from a static epithelial cell condition to a motile mesenchymal shape are advantageous for cancer cells to support migration and invasion processes, facilitating cancer cells to migrate from primary tumors and metastasize [15]. However, sustained maintenance of the mesenchymal phenotype is often unnecessary and is typically restricted to the initial formation of micrometastasis at the metastatic site. Changes back to the MET phenotype are preferred in conditions where metastasis has been achieved [14]. A range of transcription factors, including Snail, Slug, Zeb1/Zeb2, Twist, and various specific microRNAs, are involved in the regulation of both EMT and MET. These factors initiate the transitions by modulating key signaling pathways, notably Wingless/Integrated (Wnt) and Notch pathways [16].

Cancer Stem Cells (CSC)

Cancer cells may acquire stem cell-like traits, including the ability to self-renewal, differentiation, and the capacity to generate diverse cell types involved in tissue development [14]. Breast cancer stem cells (BCSCs) are key contributors in maintaining intratumor heterogeneity which is crucial for tumor development, metastasis, drug resistance, and cancer recurrence. The population of cancer stem cells (CSCs) only ranges from 0.1-1% of all tumor cells, but it plays a major role in determining the fate of tumors [17]. BCSCs could differentiate into non-BCSCs tumor cells by several markers such as MUC1, ESR1, CD44, CD24, CD34, CK6/18, LET7, miR-34a, and ALDH1 [17], [18]. Some of the intrinsic signaling pathways that play an important role in maintaining the properties of CSC, include Notch, Wnt, Hedgehog, NF-kB, and Hippo [18]. The intrinsic signaling pathways could be activated by genetic mutations, epigenetic modification, or alteration within the tumor microenvironment. As a result, it can produce BCSCs that are resistant to therapy [6], [19].

MOLECULAR PATHWAY OF CANCER CELL PLASTICITY

Several major molecular signaling pathways like mitogen-activated protein kinase pathway (MAPK), PI3K/AKT/mammalian target of rapamycin (mTOR), Hedgehog (Hh), signal transducer and activator of transcription 3 (STAT3), and wingless related integration site (Wnt) pathways may induce breast cancer cells plasticity. They are also widely reported to play a role in the initiation and progression of breast cancer [3].

The MAPK pathway is considered a major signaling pathway in regulating cell differentiation, proliferation, migration, apoptosis, and stress response. Impaired activation in MAPK may initiate the onset and progression of breast tumors related to its role in maintaining the CSC population in tumors [20]. In the triple-negative breast cancer (TNBC) subtype, loss of negative regulators of the MAPK pathway such as dual specificity phosphatase-4 (DUSP4) causes a CSC-like phenotype [21]. Another study revealed the expansion of the CD44+/CD24- cell population caused by the activation of epidermal growth factor receptor (EGFR) in TNBC. This mechanism is according to the MAPK/ extracellular signal-regulated kinase (MEK/ERK) pathway [22]. In luminal B, the development of the homeoprotein SIX1 induces the CSC phenotype through the induction of MAPK/ERK signaling [23]. In inflammatory breast cancer, MAPK signaling has an impact on NFκB signaling activation resulting in increased stem cell-resembling behavior [24].

PI3K/AKT/mTOR is the second pathway of breast cancer cell plasticity's mechanism. A previous study in the MDA-MB-231 breast cancer cell line reported that knockdown of AKT1 decreased the CSC phenotype and EMT characteristics in breast cancer cells. This indicated the involvement of the PI3K/Akt pathway in cell plasticity [25]. Activation of PI3K signaling has a role in oncostatin-M, an inflammatory cytokine, mediated BCSC and EMTs. Isolation of BCSC from ERα-positive breast cancer showed overexpression of the PIK3CA pathway gene and other PI3K pathways [26]. The most common cause of alteration in PI3K signaling is mutation which contributes to almost 47% of hormone receptor-positive breast cancer cases [27].

Another molecular signaling pathway in cellular plasticity is the signal transducer and activator of the transcription 3 (STAT3) pathway. STAT3 is always activated in all subtypes of breast cancer and induces the characteristics of EMT and CSC. STAT3 is more associated with TNBC than with other subtypes [28], although some studies report that STAT3 is downstream of HER2 [29], [30]. The VEGF/VEGFR2/STAT3 axis promotes the occurrence of BCSC self-renewal through the upregulation of Myc and Sox2 [31]. The IL-6/JAK2/STAT3 signaling pathway is essential for the proliferation of cancer cells and is constitutively activated in cancer cells enriched for CD44+CD24-stem-like phenotypes [32]. The STAT3 pathway also regulates EMTs. Previous research has shown that STAT3 phosphorylation increases EMT-related proteins, such as TWIST and MMP in breast cancer cell lines [33], [34].

Wingless-related integration site (Wnt)/β-catenin pathway also has an important role in regulating plasticity especially polarity, proliferation, migration, survival, and maintaining somatic stem cells [35], [36]. Previous studies in mouse models of breast cancer reported that Wnt/β-catenin activity in BCSC is significantly higher than in 'normal' cancer cells. Inhibition of Wnt/β-catenin signaling can also suppress the CSC phenotype [36]. The formation of BCSC could be driven by the feedback loop Wnt/β-catenin and SOX9. As a target of Wnt, SOX9 is an important pluripotent factor that enhances Wnt/β-catenin signaling and T-cell factor 4 (TCF4) transcription [37]. Wnt signaling also induces EMT-like programs through the Wnt-Axin2-GSK3β cascade and increases Snail1 in breast cancer cells [38].

The Hedgehog (Hh) pathway has a significant role in the differentiation of breast tissue prior to lactation [39]. In breast cancer cell plasticity, the Hh signaling pathway has a role in promoting and maintaining the CSC phenotype. In ER+ breast cancer, estrogen promotes the EMT and CSC phenotypes through activation of the Hh pathway downstream effector especially Gli1 [40], which targets Twist1 and Snail transcription [41], as well as the upregulation of MMP-11 [42]. In another study, activation of the Hh signaling also mediated BCSC behavior and clonogenic re-growth in post-chemotherapy breast cancer cells [41].

Notch signaling pathways are highly related to stemness, and self-renewal during mammary gland development [43]. Notch signaling pathway is involved in EMTs induction through the regulation of Slug and Snail, two main transcription factors associated with EMT [44]. Other studies have also reported that Notch2 enhances other various EMT-related markers such as Twist Vimentin, and Zeb1 in TNBC cells [45].

TREATMENT RESISTANCE

The presence of intratumor heterogenicity, which differs both genetically and phenotypically, from primary tumors or at the site of metastasis, poses challenges in diagnosis and therapy. This heterogeneity can also lead to resistance to breast cancer therapy. A subpopulation of cells that experience therapeutic resistance in the absence of mutations is known as drug-tolerant persistent (DPT). It has dormant properties, slow cycles, and stem cell capabilities [6].

Resistance-tumor may present cells with BCSC and/or EMT characteristics, which are difficult to detect and/or target by modalities. BCSC is related to the combination of resistance therapy and relapse. Compared to highly proliferated breast cancer cells, BCSCs remain in the G0 phase of the cell cycle for long periods of time. It facilitates resistance to cellular damage induced by chemotherapy and/or radiation damage [6].

Chemotherapy

Conventional chemotherapy targets cancer cells that undergo very rapid proliferation and division through exposure to cytotoxic agents [3]. Chemotherapy is the main choice for cancer, but intrinsic or extrinsic factors can encourage cancer cells to develop the ability to evade the effects of therapy. Numerous signaling pathways have been investigated related to chemotherapy resistance in breast cancer cells, particularly through the involvement of BCSC [3], [19]. Earlier studies reported the association of CD24 translocation with phenotypic alteration, driven by induction of p38 MAPK signaling cascade. Prior findings have highlighted the association between several BCSC markers and the emergence of cellular plasticity in breast cancer. CD44-/low CD24+ cell subsets are predominantly identified in the luminal type, whereas CD44+/CD24- populations are more prevalent in basal-like and mesenchymal breast cancer subtypes [46]. In particular, the CD44+/CD24- has been linked to enhanced metastatic and plasticity potential [47].

The Wnt signaling pathway has a critical role in the maintenance of CSC. Previous studies have reported an increase in Wnt/β-catenin pathway activation that correlates with stem cell marker expression in a carboplatin-resistant TNBC cell-line model taken from patients. Furthermore, inhibition of the Wnt signaling pathway in this model can cause re-sensitization to carboplatin [48]. TNBC patients who experienced chemotherapy resistance also showed increased expression of mRNA and ST8SIA1 proteins. Targeted ST8SIA1 inhibition enhances the effectivity of chemotherapy by suppressing the Wnt/β-catenin signaling pathway [49].

Chemotherapy and targeted therapy resistance are strongly played by BCSC. Previous studies have proven that chemotherapy increases the percentage of BCSCs [50]. BCSC is closely related to Notch1 and Notch4 in promoting drug resistance. A study using the MMTV-PyMT mouse model of breast cancer demonstrated an upregulation of the Notch ligand Dll1 as tumors advanced from early to late stages. These $Dll1^{+}$ cells were found to promote the expression of genes associated with chemotherapy resistance and to inhibit ligand activity that would otherwise sensitize tumor cells to treatment [51].

Additionally, in this model, silencing Notch1 via small interfering RNA (siRNA) in ALDH$^+$ cells led to suppressed tumor growth and increased levels of apoptosis [52]. Positive ALDH1 is a significant marker of BCSC and more predictive than CD44+/CD24$^-$ [50]. ALDH is related to chemotherapy resistance by increasing levels of various therapy-resistant proteins, such as p-glycoprotein, GSTpi, and/or CHK1 [53].

Radiotherapy

Radiotherapy is a common cancer therapy approach at the local stage by utilizing radiation to stop the growth and proliferation of cancer cells. Ionizing radiation can damage the DNA of cancer cells, causing cell death. Cancer cell plasticity, particularly mediated by CSCs, has contributed to radiotherapy resistance when compared to non-stem cell populations within tumors [54]. This resistance is primarily attributed to the enhanced CSCs ability to activate DNA damage checkpoints, efficiently repair radiation-induced DNA damage, and reduce overall cell death. For instance, mammospheres enriched with breast cancer stem cells and their progenitors exhibit significantly greater DNA repair capacity following radiation exposure. Furthermore, several studies have indicated that breast cancer stem cells (BCSCs) demonstrate superior efficiency in reducing intracellular reactive oxygen species (ROS) levels generated by ionizing radiation [55]. Since ROS plays a critical role in mediating radiation-induced cell death, its reduction contributes to the radioresistant phenotype observed in these cancer cells [6].

The efficacy of radiotherapy may be compromised by the adaptive mechanisms of cancer cells that lead to radioresistance. An additional contributor to this resistance is the upregulation of Epithelial Cell Adhesion Molecule (EpCAM) expression. In ZR-75-1 cell lines, EpCAM mediated increased expression of Akt, thereby increasing cell stemness and inducing cellular plasticity through the EMPT phenotype in cancer cells [57]. Radiation ion alone may induce a micro-inflammatory environment, which increases the phosphorylation of STAT3. It promotes stem cell plasticity and resistance, especially in TNBC subtypes. This inflammatory response is mediated by the interleukin-6 (IL6) [58].

Endocrine Therapy

Endocrine therapy remains a key treatment strategy for estrogen receptor (ER)-positive breast cancer, functioning by inhibiting the ER signaling pathway. It comprises three main classes: selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), and CDK4/6 inhibitors. Tamoxifen, a well-established SERM, acts as an estrogen antagonist by binding to gene targets within the ER pathway. Studies have indicated that tamoxifen-resistant MCF-7 cells possess a greater proportion of breast cancer stem cells (BCSCs) compared to their non-resistant counterparts [34]. Alterations in genes associated with stemness-related pathways—such as Wnt/β-catenin, Notch, and Sonic Hedgehog—have been implicated in the development of tamoxifen resistance. Activation of Wnt and Notch signaling pathways has been shown to promote both tamoxifen resistance and BCSC enrichment in MCF-7 cells [59], [60]. Furthermore, factors within the tumor microenvironment—including stromal cell interactions, the extracellular matrix, hypoxia, and acidity—have also been reported to influence BCSC phenotypes and contribute to resistance against endocrine therapy [19].

Targeted Therapy

Targeted therapy is one of the therapeutic options in HER-2-positive breast cancer cases which account for about 15-25% of invasive breast cancer cases. Resistance was found in two widely used anti-HER2 drugs, trastuzumab and lapatinib [19]. Trastuzumab resistance is associated with CSC through activation of the PI3K/AKT, JAK/STAT3, and NF-kB pathways [61]. Another study on TNBC /HER2+ cell lines showed that EMT-related transcription factors (Snail2 and Slug) increase resistance to trastuzumab through induction of the BCSC phenotype (CD44+CD24-/low) [62]. A decrease in PTEN can increase the BCSC population through the activation of Akt from the Wnt signaling pathway. Activation of the IL-6 inflammatory cycle that mediates BCSC expansion is also an established mechanism underlying trastuzumab resistance. IL-6 has also been reported to suppress PTEN expression while activating the NF-kB, Akt, and STAT3 signaling pathways [63]. STAT3 regulates drug resistance in breast cancer by promoting EMT through the IL-6-STAT3 feedback loop and stemness properties of CSC confer resistance to PI3K inhibitors [64].

Lapatinib is a drug targeting EGFR and HER2. Lapatinib resistance is predominantly through activation of the Src/STAT3/ERK1/2 signaling cascade, driven by interleukin-8 (IL-8) secreted from tumor macrophages [65]. Phosphorylation of Tyr705 residues from signal transducers activates the STAT3 pathway, highlighting STAT3 as a potential therapeutic target in breast cancer. Lapatinib resistance has been associated with upregulation of miR-205 through activation of the PI3K/AKT signaling pathway. Another mechanism involved in lapatinib resistance is related to CD44+/CD24-, a surface marker of CSC. CD24 inactivation can inhibit Akt phosphorylation and enhance the sensitivity of HER2-positive breast cancer cells to lapatinib [66], suggesting that CD24 is a potential therapeutic target to overcome lapatinib resistance [19].

CONCLUSION

Scientific evidence highlights the critical role of cellular plasticity in driving therapy resistance in breast cancer continues to develop. The emergence of BCSC and EMT phenotypes is central to many resistance mechanisms across various treatment modalities. Reprogramming these phenotypic to non-resistant forms presents a compelling therapeutic avenue. This can potentially be achieved by targeting the specific signaling pathways—such as Wnt, Notch, STAT3, and PI3K/Akt—that regulate BCSC maintenance and EMT induction.

As research advances, strategies aimed at disrupting these pathways may offer significant improvements in overcoming resistance and enhancing the efficacy of current breast cancer therapies.

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