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Stem Cells in Relation to Invasive Lobular Carcinoma

Hetvi Solanki[1], Mohammed S. Inayat[2] and Vincent S. Gallicchio[1]*

[1]Department of Biological Sciences, College of Science, Clemson University, Clemson, South Carolina.

[2]Department of Internal Medicine, Division of Hospital Medicine, University of Cincinnati, College of Medicine, 231 Albert Sabin Way, ML 0535, Cincinnati, Ohio.

***Correspondence:**
Dr. Vincent S. Gallicchio, Department of Biological Sciences, 122 Long Hall, College of Science, Clemson University, Clemson, South Carolina, USA.

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ABSTRACT

The most frequently diagnosed cancer and primary cause of cancer mortality in women is breast cancer. Numerous risk factors contribute to the development of breast cancer including gender, age, ethnicity, family history, female hormone exposure, and genetic risk-factors. Invasive lobular carcinoma (ILC) makes up 10-15% of all breast cancers and is highly understudied. ILC is often difficult to detect clinically due to variations in presentation. As of right now, the modes of breast cancer treatment include surgery, chemotherapy, radiotherapy, and hormone therapy. Each of these treatments have numerous side effects including diarrhea, alopecia, arthralgia, and anesthesia. Stem cells possess the ability to continuously self-renew and differentiate. Tumor-tropism effects are observed in neural stem cells, neural progenitor cells, and mesenchymal stem cells. For this reason, these cells are attractive for use as targeted delivery vectors for antitumor therapies. Genetic engineered stem cell (GESTEC)-based therapy can utilize neural stem cells (NSCs) derived from human fetal telencephalon to treat numerous types of cancers and brain diseases. The regulatory mechanisms resulting in the contribution of cancer stem cells (CSC) to breast cancer requires further investigation.

Keywords

Invasive lobular carcinoma, Breast cancer, Stem cells.

Abbreviations

ILC: invasive lobular carcinoma, IDC: invasive ductal carcinoma, CSC: cancer stem cell, BRCA: breast cancer gene, P53: tumor protein 53, PTEN: phosphatase and tensin homolog deleted on chromosome 10, CHEK2: checkpoint kinase 2, ATM: ataxia-telangiectasia mutated, E2: estrogen, P2: progesterone, AI: aromatase inhibitor, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor, CBP: catenin binding protein, FOXA1: forkhead box A1 gene, RUNX1: runt-related transcription factor 1, CDH1: cadherin 1, EGFR: epidermal growth factor receptor, GATA3: GATA binding protein 3, CD133: prominin 1, GEPT: gene-directed enzyme/prodrug therapy, MRI: magnetic resonance imaging, EMT: epithelial mesenchymal transition, NSC: neural stem cell, MSC: mesenchymal stem cell, SDF-1: stromal cell-derived factor-1, SCF: stem cell factor, HGF: hepatocyte growth factor, VEGF: vascular endothelial growth factor, VEGFR: vascular endothelial growth factor receptor, MCP-1: monocyte chemoattractant protein-1, HMGB1: high-mobility group box 1, GESTEC: genetically engineered stem cells, FGFR1: fibroblast growth factor 1, TIL: tumor infiltrating lymphocytes, Ck5: cytokeratin 5, SMA: smooth muscle alpha-actin.

Introduction

Breast cancer, further classified into ductal and lobular carcinoma is the most prevalent cancer in women [1]. Gender, age, ethnicity, family history, female hormone exposure, and genetic risk-factors all contribute to its development [1]. Lobular carcinoma (ILC) is a less prevalent form of breast cancer that cancer presents with atypical imaging features, excess of fibrous connective tissue, and unique cell architecture [2]. Due to these variations in presentation, ILC is often difficult to detect clinically [3]. Surgery has been the primary treatment for breast cancer [3]. In addition, hormonal therapies are used that include administration of tamoxifen, raloxifene, and aromatase inhibitors [1]. Use of chemotherapy is limited by its serious side-effects and high-dose requirements

[1]. To address these treatment limitations stem cells, possess the ability to continuously self-renew and differentiate [1]. Associated with tumor pathogenesis are tumor-tropism effects observed in neural stem cells, neural progenitor cells, and mesenchymal stem cells [1]. For this reason, these types of stem cells are attractive for use as targeted delivery vectors for anti-tumor therapies [1] and concurrently along with their therapeutic use could address therapy resistance, tumor heterogeneity, and metastasis that is observed attributed to cancer stem cells [4].

Epidemiology

The most frequently diagnosed cancer and primary cause of cancer mortality in women is breast cancer [1]. Women are most susceptible to developing breast cancer during adolescence [5]. Until menopause the risk of developing breast cancer doubles each year because within mammary glands possess the highest number of cancer stem cells during this period [1,5]. Breast cancer, further classified into ductal and lobular carcinoma is the most prevalent cancer in women [1]. Invasive ductal carcinoma is the predominant subtype of breast cancer [3]. ILC, on the other hand, makes up 10-15% of all breast cancers and is highly understudied [3].

Pathophysiology

Numerous risk factors contribute to the development of breast cancer including gender, age, ethnicity, family history, female hormone exposure, and genetic risk-factors [1]. BRCA1, BRCA2, p53, PTEN, CHEK2, and ATM are all genes associated with a high risk of acquiring breast cancer [1]. Lobular carcinoma is a less prevalent form of breast cancer that originates in the milk-producing lobules of the breast and is primarily composed of acini filled with small, round, polygonal, or cuboidal cells [1]. This subtype of breast cancer presents with atypical imaging features, excess of fibrous connective tissue, and unique cell architecture [2].

A good prognostic phenotype is seen with ILC. It is often low grade (well-differentiated), has a low-to-moderate proliferation index (Ki67), and is ER/PR positive and HER2 negative [3]. In classic ILC, cells are uniform with spherical nuclei and indistinct nucleoli [3]. Pleomorphic ILC is triple negative for ER, PR, and HER2 and consists of larger cells with expansive eosinophilic cytoplasm [3]. Methylation or mutation of the CDH1 gene and loss of heterozygosity in the chromosome region 16q leads to E-cadherin loss [3]. Downregulation of CBP enables ILC cells to survive and proliferate in single-file [3]. In comparison with IDC, ILC is enriched for inactivating PTEN alterations, FOXA1 mutations, and RUNX1 mutations [3]. A more aggressive phenotype of ILC results from loss of the tumor suppressor PTEN, because of homozygous chromosomal loss at 10q23, which is associated with increased Akt phosphorylation that upregulates EGFR [3]. ILC has a relatively low frequency of GATA3 mutations, which is a key transcriptional regulator of ER activity along with FOXA1 [3]. Mutations in FOXA1 may alter ligand-dependent ER binding to DNA thus resulting in an altered response to ER-targeted therapies such as tamoxifen [3]. For this reason, further investigation is needed to determine the role of FOXA1 in the pathophysiology of ILC [3]. Synchronous contralateral disease occurs more frequently in ILC than in IDC [3]. Metastatic sites of ILC include the gastrointestinal tract, peritoneum, ovaries, bones, and skin [3]. Knowing the histological subtype is vital in predicting the spread of ILC post-adjuvant therapy [3]. To improve outcomes for ILC patients, further research is needed to determine the biological basis of observed differences between ILC and IDC [3].

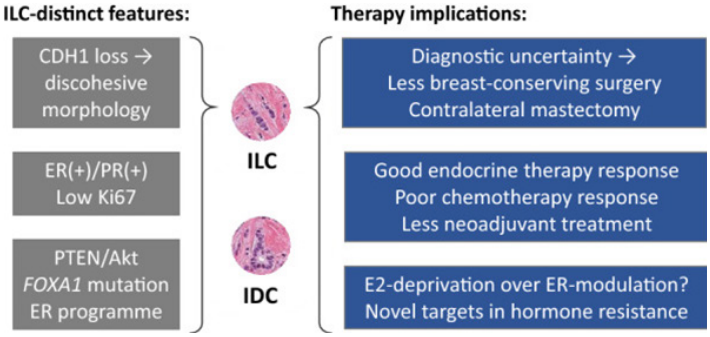

Figure 1: The distinct features of ILC and its therapeutic implications are shown in the figure above [3].

Current Standard of Care

ILC is often difficult to detect clinically due to variations in presentation [3]. Signs and symptoms of ILC may consist of a firm lump in the breast, swollen or thickened area in the breast, change in nipple shape, and dimpling of the skin [3]. Mammograms are often unable to assess the extent of a primary ILC lesion due to its infiltrative growth pattern into the stroma without desmoplastic reaction [3]. MRI is suboptimal at assessing suitability for breast-conserving surgery and may lead to inappropriate rates of mastectomy in patients with ILC due to false-positive detection of regional disease [3]. As of right now, the modes of breast cancer treatment include surgery, chemotherapy, radiotherapy, and hormone therapy [1]. Surgery is a primary treatment for breast cancer [3]. Mastectomy/lumpectomy procedures are performed to remove cancerous lesions from the breast along with some surrounding tissue [1]. 17-65% of ILC patients often must undergo a second surgical intervention [3]. Evidence shows that mastectomy and breast-conserving surgery do not show viable differences in long-term survival [3].

Hormonal therapies include administration of tamoxifen, raloxifene, and aromatase inhibitors [1]. AIs have been found to be more effective than tamoxifen, however a higher prevalence of side effects including osteoporosis, bone fractures, and musculoskeletal symptoms such as joint pain and stiffness, have been observed [2]. A major clinical obstacle associated with breast cancer is aromatase inhibitor resistance [6]. As of right now, there is no cure for AI-resistant metastatic breast cancers, for this reason, further research is needed in this area [6]. Chemotherapy is limited by its serious side effects and high-dose requirements [1]. The purpose of chemotherapy is to slow or stop the growth of cancer cells. 5-fluorouracil, cyclophosphamide, methotrexate, anthracyclines, trastuzumab, and taxanes are primarily used [1]. If the cancer is HER-2 positive, it will be treated with trastuzumab

(Herceptin) [1]. In 99% of cases, ILC persists post-neoadjuvant chemotherapy [3]. In addition, neoadjuvant chemotherapy is not likely to improve rates of breast-conserving surgery [3]. For these reasons, neoadjuvant chemotherapy is generally not considered for ILC patients to avoid exposing them to life-threatening toxicities [3]. Endocrine therapy, in combination with other targeted therapies, possess potential to reduce rates of mastectomy in ILC [3]. Each of these treatments have numerous side effects including diarrhea, alopecia, arthralgia, and anesthesia [1].

Stem Cells in Relation to ILC

Stem cells possess the ability to continuously self-renew and differentiate [1]. Tumor-tropism effects are observed in neural stem cells, neural progenitor cells, and mesenchymal stem cells [1]. Multiple cell-surface and secreted proteins, and candidate cytokines/receptors mediate these tumor tropism effects including SDF-1/CXCR4, SCF/c-kit, HGF/Met, VEGF/VEGFR, MCP-1/CCP, and HMGB1/RAGE [1]. For this reason, these cells are attractive for use as targeted delivery vectors for antitumor therapies [1]. In comparison with MSCs, NSCs migrate to cancer cells more efficiently and display a greater tropism towards tumor cells [1]. GESTEC-based therapy can utilize NSCs derived from human fetal telencephalon to treat numerous types of cancers and brain diseases [1]. A reduction of breast tumor mass in the brain was observed in an animal model treated with NSCs expressing CD or CE genes [1]. GESTECs using GEPT systems present as a potentially effective modality for treating breast cancer [1]. GEPT uses prodrugs that are primarily antimetabolites which are inactive against normal cells and require cell cycling to induce cytotoxicity [1].

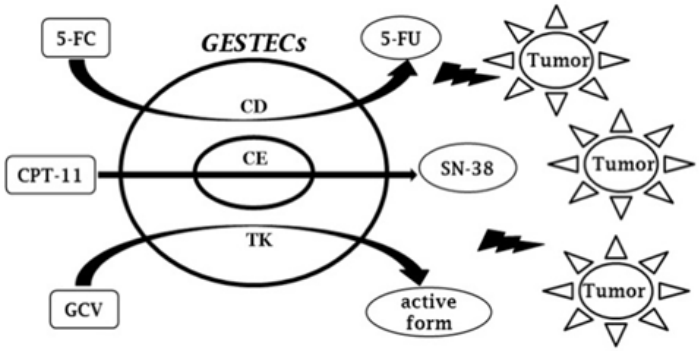

Figure 2: The pathway of genetically engineered stem cell-based therapy is shown above [1].

Therapy resistance, tumor heterogeneity, and metastasis can be partially attributed to cancer stem cells [4]. In invasive carcinomas, a small number of fluorescence-weakly-positive cells have been observed [7]. These cells appeared to be intermediate cells possessing the morphological structures of both epithelial and myoepithelial cells and show a stronger tendency for arranging in contact with the stroma at the margin of carcinoma nests [7]. Based on this observation, the possibility that breast cancer arises from common stem cells which possess the ability of differentiating into both epithelial and myoepithelial cells due to the presence of intermediate cells, presents itself [7]. The regulatory mechanisms resulting in the contribution of CSC to these conditions requires further investigation [4].

A higher risk of developing breast cancer is present in nulliparous women when compared to parous women [8]. This indicates a biological difference in Lobules type 1 between these two groups [8]. A recent study postulated that in the breast tissue of nulliparous women and parous women with breast cancer, differentiation did not occur in Lobule type 1 leading to the retention of a high concentration of epithelial cells that can be targeted by carcinogens and become susceptible to neoplastic transformation [8]. These epithelial cells are called Stem cells 1[8]. In contrast, it is hypothesized that Lobules type 1 in early parous postmenopausal women are made up of epithelial cells that are refractory to transformation [8]. These cells are categorized as Stem cells 2 [8]. Current data suggests that pregnancy shifts Stem cells 1 to Stem cells 2 via cell differentiation and this process could be responsible for the refractoriness of mammary glands to carcinogenesis [8].

Clinical Trials

In a study with 61 ER positive ILC patients, tumor size was reduced by a mean of 66% at 3 months and the rate of successful breast conservation was 81% post treatment with neoadjuvant letrozole. Compared to IDC, ILC has an inferior prognosis in high-risk cases of primary disease when treated with adjuvant chemotherapy. Taxane based chemotherapy is less effective in patients with lobular histologic subtype tumors. ILC patients exhibited a lower survival rate (66%) in comparison with IDC patients (75%) 8 years post adjuvant tamoxifen administration. On the other hand, both subtypes of patients showed an 82% survival rate 8 years after adjuvant letrozole administration. This suggests that ILC has an intrinsic resistance to tamoxifen and adjuvant aromatase inhibition should be offered preferentially to ILC patients. ILC patient survival is improved with adjuvant radiotherapy, however further research is needed in this domain. Studies suggest inhibition of FGFR1 (fibroblast growth factor 1) could reverse the intrinsic resistance of ILC cells to tamoxifen. CDK4/6 inhibitors in combination with endocrine therapy are used as first line treatments for advanced ER+, HER2- breast cancers. Numerous trials are ongoing to investigate the use of CDK4/6 inhibitors in both neoadjuvant and adjuvant conditions for ER+ breast cancer. Immunotherapy is also being investigated in ILC. An ongoing trial is investigating the efficacy of carboplatin and atezolizumab in metastatic lobular breast cancer [3].

Another study was conducted to compare the levels, prevalence, and composition of tumor-infiltrating lymphocytes (TIL) in ILC to IDC. The comparisons were performed for ER+, HER2- tumors. TIL levels were found to be significantly lower in ILC compared to IDC. High levels of TIL in ILC were affiliated with young age, lymph node involvement, and highly proliferative tumors [9]. An unidentified cell population within the epithelial compartment of the breast has been recently visualized. This population displays the phenotypic characteristics of a committed stem cells. Normal

breast tissue, noninvasive breast cancer, and invasive breast cancers underwent immunofluorescence double labeling with digital imaging and Western blotting via the use of antibodies to basal cytokeratin 5 (Ck5), glandular cytokeratins 8/18/19, and smooth muscle alpha-actin (SMA) as markers for myoepithelial cells. In the absence of Ck8/18/19 and SMA, a distinct cell population was identified that expressed CK5. Ck5 positive cells exhibit committed stem cell function that is responsible for the regeneration of the human adult breast epithelium. These neoplastic cells could derive from a late stage of the glandular epithelium differentiation pathway based on most breast cancers displaying the glandular epithelium immunophenotype. This new cell model could function as a tool to analyze the regulatory mechanisms that govern regeneration and abnormal proliferation of breast epithelium at the cellular level [10]. In addition, a recent study found that normal breast tissue cells did not express CD133. With the progression of invasive carcinoma, the expression rate of CD133 increased which suggests that CD133+ breast cancer cells are correlated to invasiveness and may lead to a poor prognosis [11].

Lastly, despite Wnt signaling being implicated in stem cell regulation, the role of this pathway in relation to cancer stem cell regulation remains unclear. A recent study found that in cancer tissues, Wnt pathway signaling increased compared to normal tissues [12]. ER expression was found to be correlated with the expression of the Wnt pathway. Recurrence within subtypes of breast cancer can be predicted by specific Wnt pathway genes. In comparison to normal breast stem-cell populations, breast cancer stem-cell enriched populations exhibited an increased amount of canonical Wnt pathway genes. Further data showed that in breast cancer mammospheres, the Wnt pathway is aberrantly activated. Wnt-targeted treatment in breast cancers possess potential based on this data.

Future Direction

Invasive lobular carcinoma is highly understudied [3]. To improve outcomes for ILC patients, further research is needed to determine the biological basis of observed differences between ILC and IDC [3]. A major clinical obstacle associated with breast cancer is aromatase inhibitor resistance [6]. As of right now, there is no cure for AI-resistant metastatic breast cancers, for this reason, further research is needed in this area [6]. In addition, due to the numerous side effects and potential life-threatening toxicities that accompany current treatments, it is necessary to investigate alternative therapies [1,3]. Lastly, therapy resistance, tumor heterogeneity, and metastasis are additional concerns [4]. Stem cells could be the answer to many of these issues due to their tumor tropism effects and innate connection with the development of ILC.

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