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REVIEW ARTICLE

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Breast tumor stroma: A driving force in the development of resistance to therapies

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Breast cancer is the most common cancer and the second leading cause of cancer-related death in women worldwide. In spite of huge advancements in early detection and ever-increasing knowledge of breast cancer biology, approximately 30% of patients with early-stage breast cancer experience disease recurrence. Most patients are chemosensitive and cancer free immediately after the treatment. About 50% to 70% of breast cancer patients, however, will relapse within 1 year. Such a relapse is usually concomitant with adenocarcinoma cells acquiring a chemoresistant phenotype. Both de novo and acquired chemoresistance are poorly understood and present a major burden in the treatment of breast cancer. Although, previously, chemoresistance was largely linked to genetic alterations within the cancer cells, recent investigations are indicating that chemoresistance can also be associated with the tumor microenvironment. Nowadays, it is widely believed that tumor microenvironment is a key player in tumor progression and response to treatment. In this study, we will review the interactions of breast tumor cells with their microenvironment, present the latest research on the resistance mediated by the stromal component in breast cancer, and discuss the potential therapeutic strategies that can be exploited to treat breast cancers by targeting tumor microenvironment.

KEYWORDS

breast cancer, chemotherapy, drug resistance, microenvironment, tumor stroma

1 | INTRODUCTION

Resistance to chemotherapy is still a problematic issue and challenging factor in the breast cancer treatment.[1] As a second common cause of cancer death in women, the importance of focusing on the underlying mechanisms of multidrug resistance (MDR) in breast cancer has been increased.[2] Therefore, in the last decade, considerable attention has been dedicated to the role played by multifactorial MDR. Advances in the MDR research show that various mechanisms are involved in the development of resistance to chemotherapeutics.[3] A number of mechanisms responsible for MDR have already been recognized, including altered membrane transport of water-soluble drugs, altered drug metabolism, altered DNA repair, and reduced apoptosis as a result of mutations, for example, in p53 protein.[4] Therefore, it appears that we still have a long way to go to overcome MDR. Generally, any functional genetic and/or epigenetic alterations influencing the expression of genes involved in the uptake, metabolism, and export of chemotherapeutics may lead to MDR.[5] However, recent studies have shed light on the fact that tumor microenvironment is another substantial factor mediating drug resistance.[6] Efficient delivery of chemotherapeutic agents to a solid tumor, and eradication of a high population of cancer cells, is dependent on drug uptake across the tumor vessels.[7,8] As a result, the heterogeneous distribution of chemotherapeutics within a given tumor may expose just a little proportion of tumor cells to an effective lethal concentration of cytotoxic agents.[8]

A heterogeneous population of stromal cells surround the tumor cells and their microenvironment.[9] Fibroblasts, immune/inflammatory cells, endothelial or mesenchymal cells, adipocytes, and bone marrow-derived stem cells reside in the tumor microenvironment, are embedded in an extracellular matrix (ECM), and are nourished by a vascular network.[10] In addition to the confirmed role in the tumor initiation, progression, and metastasis, stromal cells are emerging as new research targets in the MDR field.[11] It has been reported that the organization of stromal cells and the composition of ECM are involved in the generation of a significant drug concentration gradient, metabolic changes, and increased interstitial fluid pressure, all of which can significantly enhance the resistance of tumor cells to chemotherapeutics.[6]

Studies have revealed that autophagy is a main factor in the tumor microenvironment. The underlying mechanism of autophagy interfaced with tumor microenvironment still remains unclear and needs to be explored. But previous studies reported that the tumor microenvironment can trigger autophagy through various pathways, and autophagy can modify the tumor microenvironment by stimulating angiogenesis, providing nutrients, and controlling the inflammatory response and thus supporting the cells in the tumor microenvironment to overcome metabolic stress and to survive in poor microenvironment.[12] MDR is also associated with autophagy. Different tumor-associated animal models have confirmed that autophagy inhibition has the effects of improving chemosensitivity and promoting tumor relapse. Of the known autophagy inhibitors, only chloroquine and hydroxychloroquine have been evaluated in human clinical trials.[13,14] A combination of an autophagy inhibitor with a chemotherapeutic drug possibly is an alternative treatment for advanced or resistant tumor. However, autophagy-targeted therapy still should be cautious because autophagy has dual roles during tumor progression.

In this study, we briefly define the breast cancer microenvironment, subsequently review the resistance mediated by the stromal component in breast cancer, and finally discuss different approaches for targeting breast cancer microenvironment.

2 | BREAST MICROENVIRONMENT

Tumor microenvironment supports the tumor cells by a scaffold-like structure and provides an enriched source of cytokines and growth factors for different cell types.[15] Furthermore, it has already been confirmed that cancer cells can shape their surrounding microenvironment to fit their needs.[16] In other word, on the contrary to the previous beliefs, which suggested that mutations occur in some of the cells within tumor microenvironment, new studies show that mutations are only restricted to tumor cells, and these cells induce epigenetic modifications in other non-tumorigenic cells residing in the tumor microenvironment.[17] In addition, as a result of reciprocal interaction, tumor cells also undergo epigenetic modifications from non-tumorigenic cells.[17] As previously indicated, the cellular composition of breast cancer tumor microenvironment includes stromal cells embedded within an ECM.

2.1 | Fibroblasts

Fibroblasts represent the most abundant cell type in tumor microenvironment and act as a structural framework for the stroma.[18] While under normal condition, fibroblasts are in a quiescent and inactive state, but in a number of physiological conditions such as inflammation, when tissue remodeling is needed, fibroblasts enter a proliferative and highly active state.[19] Cancer-associated fibroblasts (CAFs) are activated fibroblasts within tumor microenvironment which produce α-smooth muscle actin (α-SMA). There are various CAFs with different origins. Some CAFs are derived from activated local fibroblasts, vascular smooth muscle cells and pericytes, and bone marrow-derived mesenchymal stem cells, while some others might originate from endothelial–mesenchymal transition/epithelial–mesenchymal transition (EMT). CAFs with different origins have distinct markers; for example, the most acceptable CAFs express high levels of α-SMA, fibroblast activator protein (FAP), fibroblast-stimulating protein-1 (FSP-1), platelet-derived growth factor α and β receptor (PDGFR-α and -β) and vimentin, and meanwhile, exhibit loss of PTEN, p21 and CAV-1 or TP53 mutation.[20] In breast cancer, FAP is an important marker; however, some researchers believe that the combination of α-SMA and PDGFR- α is a distinguishing marker.[21,22]

2.2 | Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are defined by three main features including adherence properties, ability to differentiate into different cell types, and surface markers (CD73, CD90, and CD105).[23] It is reported that at least 20% of CAFs originate from MSCs and recruitment is dependent on TGF-β and SDF-1.[24] CAFs abundantly express these chemotactic signals. In addition, cancer cells can induce differentiation of MSCs to CAFs. Indeed, the exposure of human MSCs to conditioned media from MDA231 breast cancer cells stimulated expression of myofibroblast markers such as α-SMA.[25] Weinberg et al. [26] emphasized the importance of MSCs for breast cancer metastasis. Once recruited to the TME, stromal MSCs secrete CCL5 (RANTES) and increase the metastatic capability of breast cancer cells.

2.3 | Immune/inflammatory cells

Macrophages are usually present in the tumor microenvironment of all types of malignancy.[27] Tumor-associated

macrophages (TAMs) are immunosuppressive (M2) phenotype of macrophages, because M2-polarizing cytokines (IL-4, IL-10, IL-13) are most abundant in tumor.[28] Chemo-attractants released by tumor microenvironment recruit macrophages into tumor, which subsequently enables tumor cells to produce different chemo-attractants consisting of VEGF, colony-stimulating factor-1 (CSF1), and monocyte chemotactic protein-1.[29] In breast cancer, TAMs are associated with higher tumor grade, poor prognosis, and enhanced necrosis.[30,31] In a recent study, it was reported that the expression level of chemokine (C-C motif) ligand-18 (CCL-18) is very high in TAMs and is correlating with invasion and metastasis of breast cancer cells.[32] In addition, other infiltrating leukocytes can promote breast cancer progression. In a study on a spontaneous mouse model of breast cancer, it was shown that CD4+ T lymphocytes increasingly infiltrated in tumor cells and their depletion could inhibit tumor growth. On the other hand, it was suggested that the infiltrating population of CD8+ T lymphocytes positively correlate with overall survival.[33]

2.4 | Endothelial cells

Endothelial cells such as human umbilical endothelial cells are important players in breast cancer growth and invasion.[34] Additionally, endothelial cells are involved in angiogenic switch which might lead to the vascularization of the growing tumor. VEGF and FGF-2 are among the angiogenic factors secreted by cancer cells and contribute to the regulation of angiogenesis.[35]

2.5 | Adipocytes

Adipocytes are another class of predominant stromal cell type in the microenvironment of mammary tissue, as well as bone marrow, the latter being a target for metastasis during breast cancer progression.[36] Cancer-associated adipocytes (CAAs) are peritumoral adipocytes exhibiting a tumor-modified phenotype, are able to cause a modification in the phenotype of cancer cells, and, as such, favor metastasis behavior.[37] The most important feature of CAAs is the high expression levels of IL-6. CAA contribution in breast cancer progression may elucidate why obesity is a negative prognosis factor for breast cancer.[38]

2.6 | Extracellular matrix

The extracellular matrix (ECM) consists of a large complex of biochemically distinct components including proteins, glycoproteins, polysaccharides, and proteoglycans with different biochemical and physical features.[39,40] ECM is produced by mesenchymal cell types including fibroblasts, chondrocytes, and osteoblasts.[41] From the structure point of view, these components make up both interstitial matrix, which is primarily produced by stromal cells, and basement membrane, which is made jointly by endothelial, epithelial, and stromal cells to separate epithelium or endothelium from stroma. As a specialized ECM, basement membrane is more compact and less porous than interstitial matrix. It has a specialized composition which contains type IV collagen, laminins, fibronectin, and linker proteins such as entactin and nidogen that connect collagens with other protein components. In spite of basement membrane, interstitial matrix is rich in fibrillary collagens, proteoglycans, and different glycoproteins such as fibronectin and tenascin C and is thus highly hydrated, charged, and involved greatly in the tensile strength of tissues.[42] ECM has the capacity to both initiate and channel signaling cascades within the tumor microenvironment, and via bidirectional interplay with malignant cells, it has effects on tumor progression and metastasis.[43] Moreover, its biomechanical features determine to an extent the dynamics of ECM turnover, thus affecting the ability of malignant cells to invade.[42] On the other hand, ECM may provide a "cancer stem cell" niche and is involved in inflammation and angiogenesis pathways which contribute to a pro-metastatic tumor microenvironment.[44] A growing part in ECM biology is how its biomechanical properties, including the elasticity of the ECM, involve in the development of cancer.[45] Indeed, the focal adhesion complex, which is composed of integrins and a multicomplex of adaptors and signaling proteins, can be viewed as a mechanosensor linking the actomyosin cytoskeleton with the ECM. Many of the focal adhesion components, including p130Cas and talin, undergo conformational changes that impart functional consequences in response to applied force.[46,47] Together with the cytoskeleton and nuclear matrices, chromatin, and nuclear envelope, they constitute a very complex mechanosensing machinery that determines how cells react to forces from the ECM.[48]

3 | RESISTANCE TO THERAPIES MEDIATED BY BREAST TUMOR STROMA

3.1 | Fibroblast-mediated resistance

As mentioned before, cancer cells interact co-ordinately with their surrounding microenvironment. As a major cell type in tumor stroma, CAFs have an undeniable importance in progression, metastasis, and MDR of various cancer types including breast cancer.[49] In particular, CAFs usually express several growth factors, for example, hepatocytes growth factor (HGF) and WNT16B, as well as chemokine (C-C) ligand 2 (CCL2) and chemokine (C-X-C) ligand 12 (CXCL12), plus a number of other ECM-related proteins.[50–52] CAF-expressed proteins are main links of CAFs with MDR (Figure 1). Accumulating studies have

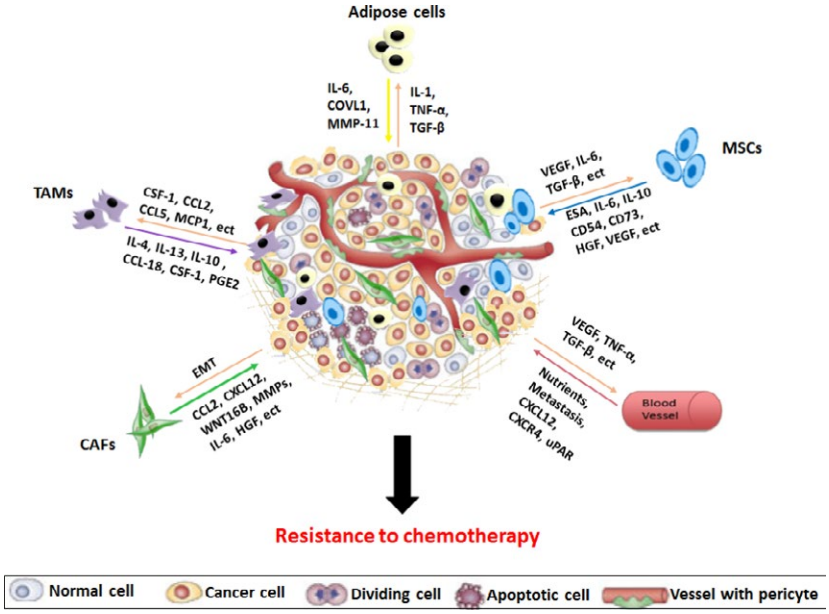

FIGURE 1 Role of tumor microenvironment in the development of chemoresistance in breast cancer [Colour figure can be viewed at wileyonlinelibrary.com]

shown that HGF signaling is involved in the progression of MDR by activating both MAPK and PI3K-AKT signaling pathways and consequently inhibiting the drug-induced apoptosis.[53,54] Therefore, HGF signaling confers MDR via upregulation of AKT and MAPK signaling pathways. In addition, fibroblast-derived HGF is involved in the proliferation of cancer stem cell population and eventually enhanced tumor progression.[55] As cancer stem cells are drug resistant in nature, the relationship between HGF modulation of cancer stem cells and tumor recurrence has been under investigation.[55,56] WNT16B, a member of WNT family, is secreted from CAFs and modulates the MDR in cancer cells. The underlying mechanism is the activation of NF-κB signaling pathway due to DNA damage response caused by chemotherapeutics.[57]

As a member of chemokine superfamily, CCL2 is expressed in fibroblasts and regulates the macrophage recruitment in cancer.[58] CAF-derived CCL2 can affect cancer cells via CCR2 receptors and modulate survival, metastasis, migration of cancer cells, and, in particular, MDR.[59] In some cancer cell lines, CCL2 inhibits cell death induced by chemotherapeutics.[59] In breast cancer, CCL2 is a major regulator of cancer progression via recruitment of macrophages.[60] Additionally, it also increases aldehyde dehydrogenase activity, which is an important cancer stem cell marker.[61] Therefore, it has been suggested that CAF-derived CCL2 is a substantial mediator of cancer stem cell renewal in most breast cancer cell lines.[62]

CXCL12, a member of C-X-C superfamily of chemokines, modulates the trafficking of hematopoietic stem cells and lymphocytes during inflammation.[63] It has been reported that CXCL12 also promotes MDR in different solid tumors.[64] In MCF7 breast cancer cells, CAF-derived CXCL12 promotes EMT and inhibits doxorubicin-induced apoptosis.[65]

Moreover, there is accumulating evidence showing that communication between stromal and cancer cells via exosomes contributes to the generation of MDR in cancer cells, and particularly in breast cancer.[66] The exosome-mediated exchange of RNA and protein between stromal and cancer cells can potentially influence the chemotherapy outcome and radiation resistance through antiviral and Notch3 signaling pathways.[67] Exosomes derived from CAFs enhance interferon-related DNA damage resistance signature and increase the expression levels of Notch target genes, and therefore promote MDR in breast cancer cells.[68] Exosomes derived from drug-resistant breast cancer cells transmit MDR via delivery of P-glycoprotein and miRNAs.[69,70]

3.2 | Mesenchymal stem cell-mediated resistance

The bidirectional paracrine signaling between MSCs and breast cancer cells is reported to stimulate tumor growth, enhance angiogenesis, and promote metastasis formation through the release of a large spectrum of cytokines and growth factors.[71–73] MSCs also stimulate tumor cell migration, an epithelial-to-mesenchymal transition (EMT), and enhance chemoresistance in breast cancer cells.[26,74,75] Growth patterns of cancer cells in coculture change from a clustered to a single cell distribution, and these morphological alterations have been related to a significant downregulation of cell adhesion molecules E-cadherin and epithelial-specific antigen (ESA).[76] MSCs are also believed to modulate the response to drugs including trastuzumab either by direct cell–cell interactions with tumor cells or by the local release of soluble factors such as IL-6, promoting survival and tumor growth.[77–79] Daverey et al. [80] reported that breast cancer cells in coculture with MSCs conferred trastuzumab

resistance in vitro as observed in the lack of inhibition of proliferative and migrative properties of the cancer cells. They also found that MSCs presence causes overexpression of HER-2 and loss of PTEN. This indicates that MSCs regulate the functional cross-talk between the HER-2 receptor and the PTEN tumor suppressor in breast cancer cells via Src. Src plays important oncogenic functions (e.g., inactivates PTEN) when bound to and activated by overexpressed HER-2, which contributes to the trastuzumab resistance. They showed that MSCs are potent mediators of resistance to trastuzumab and might reveal targets to enhance trastuzumab efficacy in patients.

3.3 | Immune-mediated resistance

Immune/inflammatory cells such as lymphocytes, mast cells, neutrophils, eosinophils, and macrophages are attracted to tumor microenvironment by wide range of environmental and physiological factors.[81] These cells produce a huge array of compounds that can affect tumor progression (Figure 1).[82] Due to their multifunctional nature, macrophages are of utmost importance in cancer pathogenesis. Upon activation, TAMs influence diverse processes such as antigen presentation, angiogenesis, neoplastic cell mutagenesis, matrix degradation, and drug resistance.[83] On the other hand, several studies have indicated a positive correlation between increased number of infiltrated macrophages in breast tumors and known poor prognostic signs, including high tumor mitotic activity and tumor grade, as well as low estrogen and progesterone receptor status.[84]

As such, several studies have investigated the involvement of TAMs in the MDR of breast cancer. For example, Yang et al. [85] reported that TAMs increase MDR in breast cancer through IL10/STAT3/bcl2 signaling pathway. In this study, THP-1 cell line was stimulated with PMA and IL4/IL13 to form TAMs. They showed that TAMs significantly protect breast cancer cells from paclitaxel-induced apoptosis. In addition, the high levels of IL10 secreted by TAMs were responsible for MDR in breast cancer cells. The authors further demonstrated that bcl2 gene expression levels and overexpression of STAT3 signaling in tumor cells are possibly responsible for chemoresistance.

An alternative mechanism was introduced by Shree and et al.[86] In this study, it was shown that cathepsins expressed by macrophages are responsible for paclitaxel resistance trait in breast tumor cells, which was manifested by the prevention of paclitaxel-induced cancer cell death. Similarly, macrophages also protected cells from death induced by additional chemotherapeutic agents, particularly etoposide and doxorubicin. As a result, therapeutic interventions can deeply change tumor microenvironment, and these alternations can affect the final efficacy of treatment. In other words, high-dose paclitaxel treatment elevates TAMs, which then protect tumor cells from cell death induced by a wide range of chemotherapeutics.

Induction of an immune response against breast cancer can cause T-cell-dependent outgrowth of a tumor and EMT. Santisteban et al.[87] showed that CD8+ T cells could cause EMT in tumor cells and generate cells with features of breast cancer stem cells, including capability to reestablish epithelial tumors, potent tumorigenicity, and enhanced resistance to chemo- and radiation therapy. The observed chemoresistance was linked to elevated expression of breast cancer-resistant protein (BCRP) and P-glycoprotein (P-gp) in breast cancer stem cells.[34] In addition, in these cells, the expression levels of key DNA repair enzymes, particularly O6-methylguanine DNA methyltransferase, were evaluated.

3.4 | Vascular endothelial-mediated resistance

Endothelial cells play an important role in the initiation of breast cancer. Resting and activated endothelial cells are responsible for synthesis and secretion of a diverse set of compounds including chemokines.[88] The impact of endothelial cells on the aggressive behavior and invasiveness of breast carcinoma cells was studied by Serrati et al.[62] It was reported that incubation of breast cancer cells with either normal endothelial or epithelial mammary cells caused an increase in the invasion of tumor cells. These effects resulted from the interaction of CXCL12 (SDF1) with its receptor (CXCR4), consequently leading to overexpression of the receptor for urokinase-type plasminogen activator (uPAR) on the surface of tumor cells (Figure 1).[89]

3.5 | Adipocytes-mediated resistance

Extensive studies have elucidated the impact of tumor-associated adipocytes (TAAs) on breast cancer development and progression.[38] As adipocytes are located in close proximity to invasive cancer cells, their deleterious effects are dependent on their cross-talk with invasive breast cancer cells.[90] The results of such an interaction are significant phenotypic or functional modification of both cell types. Moreover, particularly in the breast cancer development and metastasis, adipocytes have been shown to contribute to radiotherapy and chemotherapy resistance.[91] For instance, Bochet et al. [92] showed that breast tumor cells cocultivated with adipocytes developed radioresistance, and the levels of effector kinase Chk1 were increased in the tumor cells. This phenotype was associated with a significant decrease in cell death. Furthermore, significant increase in IL-6 expression levels in breast cancer cells may well account for tumor cell protection from radiotherapy.

Involvement of TAAs in the MDR of breast cancer cells was investigated by Duong et al..[93] In this study, the impact

of TAAs on the antibody-dependent cellular cytotoxicity was evaluated. Resistance to Trastuzumab, which is used in the treatment of human epidermal growth factor receptor 2 (HER2)-expressing breast cancers, was explained by different mechanisms, and recently tumor microenvironment. They showed that adipocytes and peri-adipocytes inhibited Trastuzumab-mediated antibody-dependent cellular cytotoxicity in HER2-expressing breast cancer cells, via the secretion of soluble factors. In fact, adipocytes caused a decline in the secretion of interferon-γ by natural kill cells, but did not change natural killer cells' cytotoxicity. Additionally, preincubation of breast cancer cells with conditioned medium derived from adipocytes decreased the sensitivity of cancer cells to antibody-dependent cell death. Similar results were also reported when breast tumors were grafted with lipoma and resistance to trastuzumab developed.

4 | TARGETING THE BREAST TUMOR MICROENVIRONMENT IN THE CLINIC

With increase in our knowledge of the impact of stroma in tumor cell response to anticancer therapies, therapeutics targeting the elements of tumor microenvironment or signaling pathways induced by tumor stromal interactions are turning out to be novel and useful strategies against tumor progression.[94] In other words, therapeutic approaches, targeting multiple pathways in tumor, and stromal cells in the tumor microenvironment may offer a therapeutic benefit with high efficacy.[95] Unlike tumor cells which are genetically unstable and thus more susceptible to acquiring drug resistance, non-tumor cells in tumor microenvironment are genetically stable and increase the interest in the therapeutic targeting of microenvironment.[96] However, targeting the stromal cells in cancer therapy poses several obstacles; that is, as the fibroblasts, endothelial cells, and immune cells are not malignant in themselves, potential therapies must be directed to phenotypic changes unique to the cells. In addition, defective vascular structure, pH alternations, and hypoxic microenvironments might hinder the successful delivery of therapeutics to the stromal cells.[97] These challenges not only dampen our enthusiasm for using stroma as a target in cancer therapy, but also increase our knowledge for designing more effective therapeutics.[97]

4.1 | Targeting stromal fibroblasts

Cancer-associated fibroblasts act as a niche-promoting tumor progression by conferring metastatic, invasive, and cancer stem cell phenotypes upon cancer cells.[98] Moreover, it has been reported that there are a number of tumor-promoting signaling pathways which mediate interactions between different tumor and non-tumor cells and CAFs.[98] Therefore, targeting CAFs and signaling pathways promoting tumor growth is considered to be a new and effective therapeutic strategy.[99] Presence of CAFs with genetically stable nature in the tumor stromal compartment makes them potential targets for breast cancer therapy. To specifically kill CAFs, Loeffler et al.[100] constructed an oral DNA vaccine which target fibroblast activation protein (FAP). FAP, a type II transmembrane protein that acts as a serine protease, is overexpressed in CAFs.[101] Upregulation of FAP has been shown to result in the promotion of tumor growth and enhancement of metastatic potential.[102] Therefore, treatment with anti-FAP antibodies inhibits tumor progression, and FAP can serve as a novel target for active vaccination against cancer. In the study by Loeffler et al., it was reported that the orally administrated DNA vaccine encoding murine FAP could suppress primary tumor growth of multidrug-resistant breast cancer cell lines. In addition, vaccine against FAP decreases growth of established metastasis. In other words, mice treated with vaccine showed a significant decrease in metastasis on the lung surface. The vaccine also increased the intratumoral uptake of doxorubicin and the concentration of this anticancer agent increased in tumor. Finally, it was demonstrated that the DNA-based vaccine against FAP, in combination with doxorubicin, was able to suppress tumor growth and complete tumor rejection in 50% of mice.

In another study by Mercier et al.,[103] caveolin-1 (CAV-1) in CAFs was targeted in breast cancer. The downregulation of CAV-1 in CAFs is a well-known marker during the oncogenic transformation of fibroblasts.[104,105] The author showed that downregulation of CAV-1 in CAFs is responsible for the hyperproliferative phenotype in breast tumor. The replacement of CAV-1 function with a cell-permeable CAV-1 mimetic peptide abolishes this hyperproliferative behavior. Additionally, the effect of CAV-1 in CAFs is mediated through the inhibition of RB phosphorylation and reduction in downstream RB targets such as PCNA and MCM7.

4.2 | Targeting immune cells

Tumor-associated macrophages as key components of immune/inflammatory system in tumor microenvironment are the main orchestrator of the link between cancer progression and inflammation.[106] Because of the pro-tumorigenicity of TAMs, they can be assumed as novel attractive candidates for cancer therapy.[107] At present, major therapeutic strategies are effective only against actively proliferating cells.[108] Therefore, other quiescent neoplastic cells and tumor-associated cells such as macrophages remain unaffected. Such unaffected cells could increase the risk of cancer recurrence.[109] Three key aspects of TAMs can be exploited for therapeutic intervention: (i) the effects of TAM inhibition on tissue remodeling and angiogenesis; (ii) reversal of

immune-suppression effects and restoration of anticancer cytotoxicity; and (iii) inhibition of TAM recruitment and survival in tumor microenvironment.[106] TAMs are found in high-grade hormone receptor-negative breast cancer.[110] So far, many macrophage-targeting agents have been developed, some of which have been listed in Table 1.

CCL2 and its receptor CCR2 play an important function in monocyte recruitment in tumor.[111] CCL2 is a major chemoattractant for monocytes and is produced by tumor and stromal cells.[112] In a study by Lu et al.,[113] it was reported that overexpression of CCL2 promotes both lung and bone metastases in breast cancer. They also showed that CCR2 expression in stromal cells is essential for tumor-derived CCL2 to recruit macrophages. In addition, targeting tumor-derived CCL2 by a neutralizing antibody significantly decreased metastasis to both lung and bone.

Another alternative mechanism is inhibition of VEGF receptor 2 pathway to reduce infiltration of macrophages and angiogenesis in breast cancer models, which is reported in a study by Roland et al..[29] Macrophage activation can be suppressed by targeting colony-stimulating factor 1/colony-stimulating factor 1 receptor (CSF1/CSF1R signaling). Genetic loss of CSF1 causes a significant decrease in the metastasis and tumor progression of breast cancer.[114] In another study, CSF1 receptor, c-Fms, was targeted in breast cancer. The authors employed the tyrosine kinase inhibitor imatinib mesylate to block c-Fms signaling pathway and showed that suppression of c-Fms signaling decreases bone metastasis in breast cancer.[115]

Decreasing survival or triggering apoptosis of TAMs is another attractive strategy for targeting TAMs. Zoledronic acid is a bisphosphonate compound, investigated for its role in macrophage depletion.[116] In breast cancer, zoledronic acid was reported to selectively deplete MMP-9-expressing TAMs and induce the differentiation of myeloid cells into TAMs.[117] As a result, the tumoricidal activity of macrophages was improved and survival rate of cancer patients increased.[118] In addition, the positive effect of zoledronic acid in reducing breast cancer cell migration was in the focus of another study.[119] Legumain is a novel member of C13 family of cysteine proteases and is overexpressed in many human tumor tissues.[120] In fact, legumain is a stress protein overexpressed by TAMs.[121] A legumain-based DNA vaccine was developed, which induced a CD8+ T cell response against TAMs and resulted in a decrease in TAMs density in tumor microenvironment and consequently a decline in the proangiogenic factors released by TAMs, including TGFβ, MMP-9, TNFα, and VEGF. This effect, in turn, led to inhibition of tumor angiogenesis, growth, and metastasis of breast cancer.[122]

TABLE 1 Macrophage stimulant agents that modulate TAMs' effects

Macrophage-targeting agent	Effects
Trabectedin	Exhibits cytotoxic activity against TAMs
Linomide	Blocks the angiogenic effects of TAMs
Zoledronic acid	Inhibits MMPs and reduces angiogenesis
Imatinib mesylate	Blocks c-Fms signaling
Ki20227 and JNJ-28312141	Targets c-Fms signaling

4.3 | Targeting vascular endothelial cells

It is currently entrenched that all together for a tumor to develop past a specific size, it needs to recruit its own blood supply to convey nutrients and oxygen. This size constraint is administered by as far as possible for oxygen from the closest vein, which is 100–200 μm. The tumor vasculature is resulting by angiogenesis, new recruits vessel development from previous vessels, and vasculogenesis, the enlistment of flowing endothelial progenitor cells. In addition, abnormal tumor vasculature affects both directly and indirectly the tumor responsiveness to chemotherapy.[123] The vasculature influences the sensitivity of the tumor to drugs because anticancer chemotherapeutic agents gain access to tumors via the blood and as the limited supply of nutrients in tumors leads to metabolic changes and to gradients of cell proliferation that influence drug sensitivity.[124] Blood vessels in tumors are often convoluted and dilated and, in comparison with normal tissues, have branching patterns that feature excessive loops and arteriolar–venous shunts.[125] The vessels in some tumors are not organized into arterioles, capillaries, and venules but instead share features of all of these structures.[124]

The idea of angiogenesis as an objective for cancer treatment, at first proposed by Hanahan, was met with suspicion for a considerable length of time; however, it is presently generally accepted and being connected to the armament of tumor therapeutics.[126] A plenty of antiangiogenic mediators obstructing either angiogenic growth factors or their receptors have been produced and tested in preclinical tests. Lately, tumor vascular focusing on has been extended to include pericytes, which provide both structural backing and survival signals to endothelial cells, contributing to a mature, functional vasculature. The process of vascular maturation involves interactions between endothelial cells and pericytes, employing several growth factor signaling pathways; and VEGF-A/VEGFR2, PDGF-B/PDGFRβ, TGF-β1, and the angiopoietin/Tie-2 system.[94]

4.4 | Targeting adipocytes

Adipocytes are the primary constituents of the heterogeneous breast cancer microenvironment. The importance of adipocyte function in progression and metastasis of breast cancer is confirmed in various studies; hence, it is rational to assume that inhibition of adipocyte–cancer cell interaction has

a potential to suppress cancer stem cell activity and prevent tumor initiation and progression.[127] Mantles et al. [128] reported that postweaning exposure to soy protein isolate and its bioactive isoflavonate genistein decreases both mammary adiposity and expression levels of mammary tumor suppressor PTEN and E-cadherin. Genistein inhibition of adipose differentiation is concomitant with the upregulation of estrogen receptor b (Erb (Esr2)). Also, decrease in the Erb expression increased PPARγ transcript levels and reduced the differentiation of stromal fibroblast into mature adipocytes. Conditioned medium from genistein-treated adipocytes declined anchorage-independent mammosphere formation of human MCF-7 breast cancer cells.[129,130]

In addition, Li et al.[131] used sulforaphane to suppress mammary adipogenesis by targeting adipose mesenchymal stem cells. Sulforaphane is a bioactive compound found in broccoli and has been shown to mediate lipolysis in adipocytes. It was demonstrated that sulforaphane could suppress adipocyte differentiation. Furthermore, it inhibited the interaction between adipocytes and breast cancer cells, consequently suppressing the formation of breast cancer. Therefore, genistein and sulforaphane are representative examples of cancer-preventive compounds that significantly suppress tumor development via targeting TAAs and cutting off the interactions of cancer cells with the tumor microenvironment.

4.5 | Therapeutic combinations

The fundamental problem encountered in the targeting tumor microenvironment as a therapeutic strategy is the possibility of converting cancer into a chronic disease.[15] Therefore, the majority of efforts have been focused on approaches that simultaneously target microenvironment and tumor cells.[132] Several studies have already shown the therapeutic benefits of such combination therapies. The use of compounds blocking pathways responsible for the activation and recruitment of stromal cells in the tumor microenvironment is one of the well-studied strategies.[133] Dougall et al.[134] illustrated the efficacy of targeting receptor activator of NF-kB ligand (RANKL) in bone metastasis with denosumab. Denosumab is a fully human mAb against RANKL, for which three phase III clinical trials were recently completed in patients with bone metastasis from advanced malignancies including breast cancer. RANKL is also a key mediator of the mitogenic function of progesterone in mouse mammary epithelium. As a result, the pharmacologic suppression of RANKL in progesterone-dependent mouse mammary tumors inhibits tumorigenesis.[15] In a study by Liao et al.,[135] a DNA vaccine targeting CAFs improved the antimetastatic effects of doxorubicin, suppressed the expression of IL-6 and IL-4 in the protein level, and enhanced the recruitment of dendritic and CD8+ T cells. The combination therapy also led to the downregulation of tumor-associated VEGF, PDGFc, and GM-CSF. They showed that DNA vaccine-mediated modulation of immunity in the tumor microenvironment can effectively inhibit lymphangiogenesis and tumor angiogenesis by reducing stroma-related expression of pro-angiogenic cytokines and growth factors. Similar results were also shown by Loeffler et al. who developed an oral DNA vaccine targeting FAP in breast cancer. Mice treated with a combination of FAP and doxorubicin had a threefold prolongation in life span and showed significant inhibition of tumor growth.[100] Fifty percent of the animals completely rejected a tumor after combination therapy.

5 | CONCLUSIONS AND FUTURE DIRECTIONS

The focus of this review was to explain the mutual crosstalk between breast cancer and tumor microenvironment, and how such interactions influence breast cancer progression and metastasis. We described the formation of the resistance to chemotherapies mediated by tumor stroma. Targeting breast cancer through its microenvironment is an emerging field of research. For some of the processes involved in the tumor stroma interaction and chemoresistance, clinical evidence for positive intervention already exists, supporting the notion of targeting these processes. Further optimization of this approach is necessary, with regard to combinations of agents, timing, improved knowledge of breast cancer subtype-specific aspects, and predictive markers, to improve this approach for comprehensive implementation in breast cancer care and overcoming chemoresistance in the clinic.

CONFLICT OF INTEREST

None.

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