



Inflammation, immunosuppressive microenvironment and breast cancer: opportunities for cancer prevention and therapy

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Abstract: Breast cancer is the most commonly diagnosed malignancy and a leading cause of cancer-related death in women worldwide. It also exhibits pronounced racial disparities in terms of incidence and clinical outcomes. There has been a growing interest in research community to better understand the role of the microenvironment in cancer. Several lines of evidence have highlighted the significance of chronic inflammation at the local and/or systemic level in breast tumor pathobiology. Inflammation can influence breast cancer progression, metastasis and therapeutic outcome by establishing a tumor supportive immune microenvironment. These processes are mediated through a variety of cytokines and hormones that exert their biological actions either locally or distantly via systemic circulation. Targeting of immune and inflammatory pathways has met tremendous success in some cancers underscoring the importance of research to further our understanding of these systems in breast cancer. This knowledge can be helpful not only in the development of novel prevention and therapeutic strategies, but also help in better prediction of therapeutic responses in patients. This review summarizes some of the significant findings on the role of inflammation in breast cancer to gain collective molecular and mechanistic insights. We also discuss ongoing efforts and future outlook to exploit the existing knowledge for improved breast cancer management.

Keywords: Breast cancer (BC); inflammation; immune suppression; tumor microenvironment (TME)

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Introduction

Breast cancer (BC) remains the foremost cause of cancer-related death and most frequently diagnosed non-cutaneous malignancy in women in the United States and worldwide (1). According to an estimate by American Cancer Society, this year ~268,600 women are expected to be diagnosed with BC and about 41,760 will die because of it in the United States (2). Moreover, an increase in BC incidence has been reported in recent decades among women who are older than 50 years of age, while a reduced rate of survival is reported for women below 50 years (3-5). Furthermore,

significant race-associated disparities in BC incidence and clinical outcomes has also been reported (6,7). Women of African origin are affected most disproportionately exhibiting an early onset of disease, more likely diagnosis of aggressive BC subtypes and significantly greater mortality (8,9). In the past, overall incidence rate of BC used to be lower in African American women than that in Caucasian women, but it is catching up fast, while mortality gap continues to widen between these racial groups (10-12).

Many risk factors have been recognized for BC development including advancing age, family history,

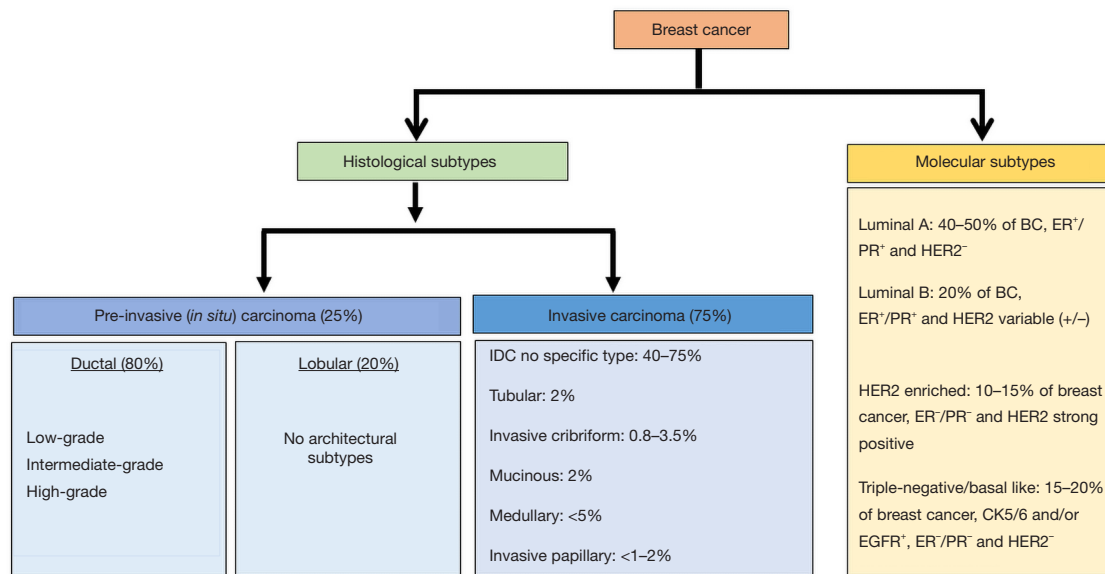


Figure 1 Histological and molecular classification of breast cancer. Classification is based on architectural features, growth pattern and the genetic landscape of breast tumors. IDC, invasive ductal carcinoma.

certain genetic mutations (such as BC gene, *BRCA1* and *BRCA2*), obesity and drinking habits to name a few (13–15). Chronic inflammation at the local and systemic level has also been suggested to be an important driver of BC (16,17). Indeed, tumor development is a complex and evolutionary process that involves changes not only in the tumor initiating cells, but also in the surrounding environment comprising of other cells and secreted biomolecules (18,19). An inflammatory tumor microenvironment (TME) can influence BC progression in various ways and numerous studies have been conducted to better understand the role of inflammatory pathways in BC pathobiology. In this review, we will discuss findings pertinent to the role of inflammation in BC to gain collective molecular and mechanistic insights and envision how this knowledge could be translated into strategies for disease prevention and therapy.

BC: histological and molecular subtypes

BC is a heterogeneous group of neoplasms. The disease can differ greatly at the histological and molecular levels among cancer-bearing individuals and also within a single tumor (20,21). Considering this high degree of diversity, breast tumors are classified into various histological and molecular subtypes for their effective clinical management (Figure 1).

Histological subtypes

Based on their histological features, breast tumors are largely divided into two subtypes, pre-invasive or *in situ* breast carcinoma and invasive breast carcinoma.

Pre-invasive (*in situ*) breast carcinoma

The *in situ* breast carcinoma is referred to the localized cancer that has not spread beyond the primary site. It is further sub-classified as either ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS). DCIS is diagnosed more commonly in the United States than LCIS accounting (22–24). It is characterized by BC cells that are restricted to the lining of the milk ducts and have not invaded into the surrounding breast tissue or any other parts of the body. However, if left untreated, it can spread to nearby tissue over time, and develop into an invasive BC. On the basis of histological appearance, DCIS is further subdivided into several subtypes including micropapillary, papillary, solid, cribriform and comedo (25,26). LCIS, on the other hand, develops in the lobules and usually does not ever spread to the surrounding breast tissue (24), although patients with LCIS remain at higher risk of developing BC. About 20–25% of women with LCIS are estimated to develop some form of invasive BC (either lobular or infiltrating ductal carcinoma) within her lifetime (24,27).

Invasive breast carcinoma

As the nomenclature suggests, this cancer histological type has invaded into the surrounding breast tissues at the time of diagnosis. Also, similar to *in situ* carcinomas, invasive carcinomas are a group of tumors that are further categorized into several histological subtypes, such as infiltrating ductal, invasive lobular, ductal/lobular, mucinous (colloid), tubular, medullary and papillary carcinomas. Of these, invasive ductal carcinoma (IDC), which develops in the milk ducts and spreads to the fatty tissue of the breast outside the duct, is the most common and accounts for about 70–80% of all invasive lesions (28,29). IDC is further sub-classified based on mitotic index, nuclear pleomorphism, and glandular/tubule formation into well-differentiated (grade 1), moderately differentiated (grade 2) or poorly differentiated (grade 3) carcinomas (28). Unlike DCIS, where the use of molecular markers including estrogen receptor (ER), progesterone receptor (PR), and HER2/neu is still a subject of debate, IDC sub-classification based on the molecular markers is well accepted (30).

Molecular subtypes

Classification of BC based on molecular components is more useful than that based on histology for the treatment planning and development of newer targeted therapies. It is achieved by obtaining the molecular and genetic information from the cancerous breast tissue. Broadly, five major molecular subtypes of BC have been defined that include luminal A, luminal B, triple-negative or basal-like, HER2-enriched and normal-like. Two additional molecular subtypes that are less common and poorly described are claudin-low and molecular apocrine BC. The claudin-low BC has low-to-absent expression of luminal markers and elevated expression of epithelial-mesenchymal transition (EMT) markers, whereas molecular apocrine tumors are characterized by an ER negative/androgen receptor (AR) positive phenotype (31,32).

Luminal A

This subtype is hormone-receptor positive (ER⁺ and/or PR⁺) and HER2 negative. It also expresses low levels of Ki-67 protein. Tumors of this subtype are low-grade, grow slowly and have the best outcomes among all other molecular sub-types (32,33).

Luminal B

This subtype is hormone-receptor positive, but can be

either HER2 positive or HER2 negative with high Ki-67 levels. Tumors of this subtype grow slightly faster, have poorer tumor grade and poorer prognosis as compared to subtype luminal A (32,33).

Triple-negative BC (TNBC)/basal-like

This subtype is estrogen-receptor, progesterone-receptor and HER2 negative. It is considered the most aggressive. Also, for not yet established reasons, this subtype is more common among younger African American women (26,32,33).

HER2-enriched

This subtype is hormone-receptor negative, but HER2 positive. Tumors of this molecular subtype grow faster than luminal A and B subtypes; however, can be effectively treated with anti-HER2 drugs such as trastuzumab (herceptin) (26,32,33).

Normal-like

This subtype is hormone-receptor positive, HER2 negative, and has low levels of KI-67. Their prognosis is generally good, but slightly worse than luminal A subtype (26,32,34).

Inflammation and inflammatory mediators

Inflammation is a process by which our immune system protects us from foreign invaders, such as viruses and bacteria, and helps in the healing and repair of the damaged tissue. However, if not regulated correctly and remained prolonged (chronic inflammation), it can actually contribute to the development of diseases including BC (16,17). Chronic inflammation can be induced by abnormal immune reactions, infections that perpetuate, or conditions such as obesity. In obese condition, excessive accumulation of macronutrients in the adipose tissues stimulates the release of inflammatory mediators to maintain the tissue homeostasis, thus creating a pro-inflammatory tumor supportive environment. Similarly, poor lifestyle (smoking habit, unhealthy diet, alcohol overuse, etc.) and inadequate relief of chronic stress can also lead to long-term inflammation and contribute to the development, progression, and recurrence of BC (35–37). Indeed, inflammatory BC, a rare type of cancer often negative for triple receptors, develops rapidly and is considered one of the most aggressive BC subtype (38–40).

Chronic inflammation is mediated through a variety of cytokines and hormones, which also contribute to BC

progression, metastasis and therapy-resistance in various ways. These inflammatory mediators are the cell and/or plasma-derived soluble and diffusible molecules that exert their biological actions either locally or distantly via systemic circulation. Some of the important categories of inflammatory mediators are described below:

Complement system and kinins

The complement system is a collection of soluble proteins and membrane receptors in the bloodstream that works together to destroy the pathogens, provoke inflammatory reactions, and remove debris from cells and tissues. The complement systems proteins are numerically labeled with the prefix C (e.g., C1–C9) and are primarily synthesized in the liver. These proteins are largely enzyme precursors which catalyze a series of enzymatic reactions leading to the formation of products that have multiple immune effects. The mediators of inflammation in complement system include complement and complement-derived peptides (mainly C3 and C5) and kinins (bradykinin) that are released via the classical or alternative pathways. Complement component increase vascular permeability, activate leukocytes and induce mast-cell degranulation (41-43). Also, they work as a potent chemotactic factor for neutrophils and mononuclear phagocytes.

Vasoactive amines

Vasoactive amines are amino groups such as histamine or serotonin, derived from decarboxylation of amino acid histidine that alter the permeability of blood vessels or cause vasodilation. Histamine is produced by mast cells, basophils and circulating platelets in response to heat, cold, irradiation, trauma injury or immune reactions (44-46). Histamine increases the vascular permeability by increasing the blood flow and disrupting the endothelial barriers. Also, histamine promotes vasodilatation by inducing the nitric oxide release. It helps in maintaining the acute-phase response during inflammation (45,47). Histamine is shown to induce the proliferation of several cancer cells including BC (48-50). Histamine receptors that aid in cellular proliferation, expressed in vast variety of cancer cells (50,51). Mice lacking histamine H4 receptor (H4R-KO) show reduced breast tumor size and weight, decreased number of lung metastases reduced percentage of CD4⁺ tumor-infiltrating T cells, indicating that histamine receptor is associated with BC progression and regulates

antitumor immunity (52). Another vasoactive amine, serotonin is produced by decarboxylation of tryptophan within enterochromaffin cells of the intestine and released into the bloodstream. It is stored in the platelets and mast cells. Platelets stores serotonin is secreted upon activation at the site of thrombus formation or inflammation (53,54). The actions of serotonin and similar to histamine but they are less potent. Serotonin also exhibit cancer cell growth stimulatory effects and suggested to be involved in tumor cell migration, metastasis and tumor angiogenesis (55,56). One of the mechanisms through serotonin exerts its effects on tumor progression by increasing the blood supply to tumors (55).

Cytokines

Cytokines are a large group of proteins that are produced by a broad range of cells, including immune cells, endothelial cells, stromal cells, and cancer cells that mediate important biological processes such as growth, proliferation and mobilization of cells. Cytokines modulate the biological activities of multiple cell types, however, they are of particularly important due to their role in regulation of the immune system to coordinate and control the inflammatory response to pathogens (57-60). They are the core components of the inflammatory milieu and play an important role in mediating innate and adaptive immune responses. They help in the recruitment and activation of leukocytes, increase cytotoxicity of natural killer (NK) cells and enhance proliferation of B and T cells (58,60,61). Interleukin-1 (IL-1), IL-6, IL-12 and IL-33, resistin, tumor necrosis factor alpha (TNF- α), granulocyte-macrophage colony stimulating factor (GM-CSF) and interferon gamma (IFN- γ) are important inflammatory cytokines among several others.

Hormones

Hormones are chemical messengers produced by different cell types that regulate the homeostasis of the body and the cross-talk between the cardiovascular, endocrine, and immune systems. In the early 1990s, Garcia-Leme *et al.* demonstrated that hormone receptors are expressed at reactive structures in inflamed areas where hormone molecules bind and generate signals affecting cell functions important for the development of inflammatory responses, thus suggesting that inflammation is not only a local response but also a hormone-controlled process (62).

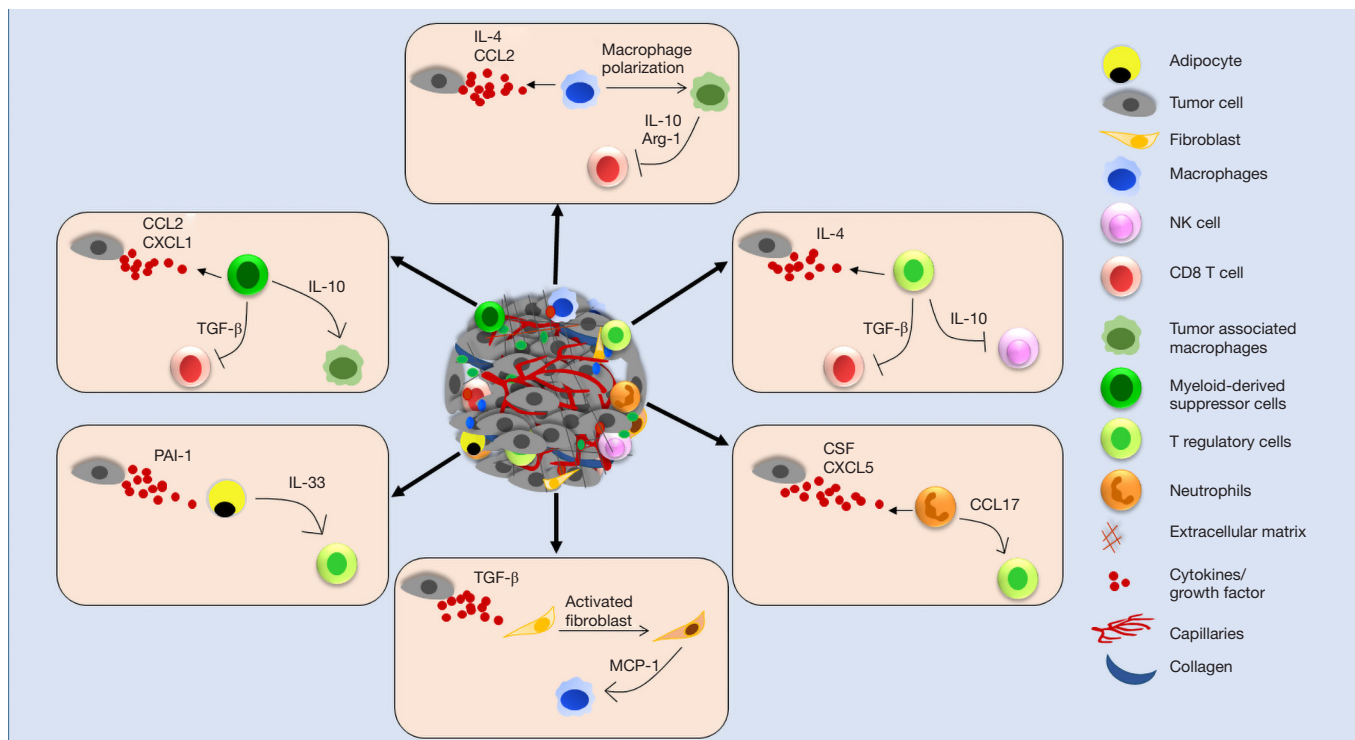


Figure 2 Schematic representation of the components of the inflammatory tumor microenvironment. Tumor-derived soluble factors induce mobilization and reprogramming of immune cells and activation of stromal cells in the tumor-adjacent extracellular matrix. Cytokines and/or growth factors secreted by these immune or stromal cells further regulate the activity of recruited immune cells leading to the sustenance of tumor favoring inflammatory tumor microenvironment. IL, interleukin; TGF- β , transforming growth factor β ; MCP-1, monocyte chemoattractant protein-1; CSF, colony stimulating factor; NK, natural killer; PAI-1, plasminogen activator inhibitor-1; Arg-1, arginase 1.

Leptin, a hormone predominantly made by adipose cells was shown to reverse the immunosuppressive effects of acute starvation in mice model (63). In hyperleptinemia, chronic low-grade inflammation was observed via elevation of the production of IL-1, IL-6, IL-12, and TNF- α (64). Elevated expression of leptin in serum and its receptor in human BC cells were associated with BC risk (65,66). Leptin treatment significantly induces the proliferation of T47-D BC cell line (67). Moreover, leptin-induced cell signaling axis is suggested to be involved in the increased risk for cancer development (68). Cortisol is another hormone which has been extensively studied for its role in immune function and the body's anti-inflammatory processes. Alteration in cortisol has been suggested to cause acute proinflammatory stress response resulting in extensive inflammation (69). Significant advances have been made in understanding the molecular mechanisms by which cortisol regulates inflammation and inflammatory diseases (70). It has been demonstrated that corticosteroids regulate the

expression of various inflammatory genes such as annexin-1 (lipocortin-1), SLPI, and the inhibitor of NF- κ B (I κ B- α) (70-72). Importantly, activation of glucocorticoid receptor is suggested to be increase BC metastasis (73).

Role of inflammation in tumor immune microenvironment

Immune cells [macrophages, dendritic cells, T cells, myeloid-derived suppressor cells (MDSCs), etc.] are an important component of the TME that greatly impact tumor development and therapeutic outcomes (74-76). Tumor cells and residing non-tumor cells in the TME build up tumor supportive immune microenvironment by releasing soluble factors such as cytokines, growth factors and hormones (76-78). Interaction of these factors with receptors present on the immune cells determines the mobilization of immune cells into the TME and their fate (Figure 2). For instance, CCL2 secreted by breast tumor cells promotes the trafficking of CCR2⁺ macrophages into

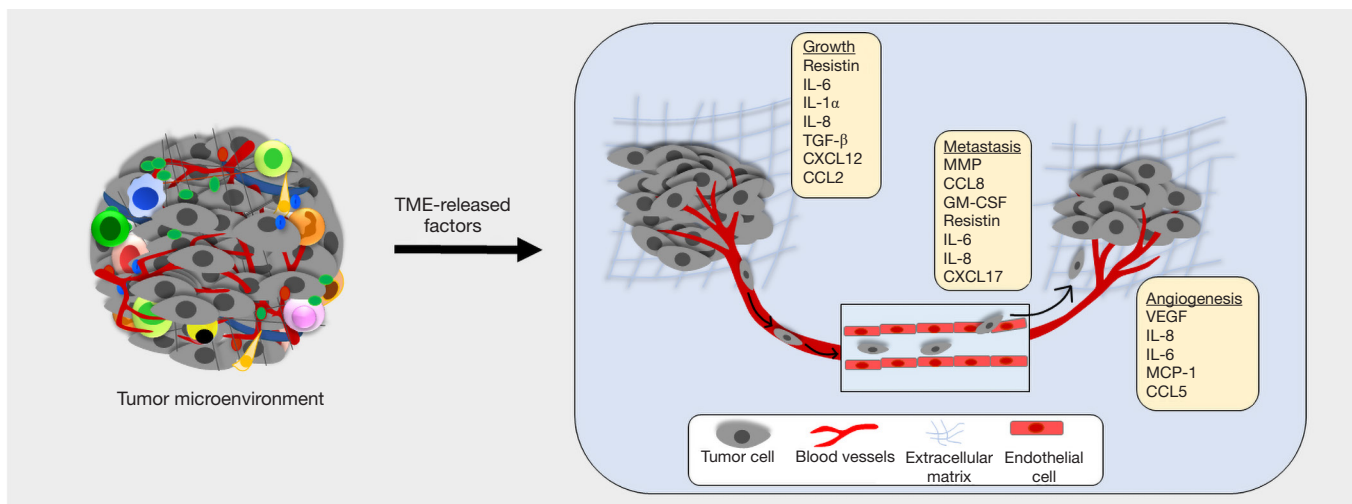


Figure 3 Contribution of inflammatory tumor microenvironment in breast cancer progression. Interaction between the cells in the tumor microenvironment leads to enhanced production of cytokines, growth factors, angiogenic factors and proteolytic enzymes that help in sustaining tumor growth, promoting angiogenesis, and tumor cell invasion and metastasis. IL, interleukin; TGF- β , transforming growth factor β ; MMP, matrix metalloproteinase; GM-CSF, granulocyte-macrophage colony stimulating factor; MCP-1, monocyte chemoattractant protein-1; VEGF, vascular endothelial growth factor.

the TME (79). Furthermore, it is thought that the diverse chemokine ligand-receptor interactions determine, at least in part, the heterogeneity of immune cell infiltration into the TME. Indeed, some chemokines can bind to multiple receptors (for example CCL5 binds to CCR1, CCR3, CCR5) or conversely a single chemokine receptor can also bind to multiple ligands (for example CCR5 binds to both CCL3 and CCL5). These interactions also help create an immunosuppressed milieu within the TME by maintaining a tumor supportive balance of pro- and anti-tumor immune responses through a complex cellular communication network. Recruitment of MDSCs and macrophages among others in the TME impairs T cell infiltration and/or favor the accrual and activation of regulatory T (Treg) cells. Tumour-associated macrophages (TAMs) or M2 macrophages are the most extensively studied and their high density in primary BC is associated with worse patient prognosis (80-82). M2 polarized macrophages secrete factors (arginase, IL-10, TGF- β , etc.) to promote an immunosuppressive TME. For example, arginase derived from TAMs can deplete a critical amino acid, arginine, which is crucial for T cell survival and antitumor activities (16,83,84). IL-10 derived from TAMs is also shown to inhibit T cell proliferation (85). MDSCs present in the TME are shown to promote their immune suppressive activities by upregulation of programmed cell death protein

1 (PD-1), PD-1 ligand 1 (PD-L1), cytotoxic T lymphocyte antigen 4 (CTLA4) on CD4⁺ or CD8⁺ T cells (86). Thus, heterocellular interactions facilitated through inflammatory mediators help build immune-suppressive TME to support tumor growth.

Effect of inflammation on breast tumor growth, angiogenesis and metastasis

Inflammatory TME positively influences tumor growth and metastasis either via direct impact of the factors secreted by the immune cells on the tumor cells or indirectly through their effect on other resident cells within the TME including fibroblasts and endothelial cells (Figure 3). Infiltrated and adipose tissue-resident macrophages are crucial in nurturing the inflammatory TME by releasing several inflammatory cytokines including resistin. Our recent findings demonstrated that the levels of resistin are elevated in BC patients and support breast tumor cell growth, aggressiveness, and stemness (87,88). In another report, the elevated levels of resistin were shown to positively correlate with breast tumor size and stage, and negatively associated with disease-free and overall survival in BC patients (89). IL-6 release from TAMs is also shown to increase BC cell proliferation by inducing phosphoinositide 3-kinase (PI3K)-Akt signaling pathway as

well as apoptosis inhibition through enhancing BCL-2 and decreased BAX expression (90). Also, a positive correlation between increased macrophage index and high vascular grade, and reduced relapse-free survival in BC patients (91). It is shown, TAMs produce pro-angiogenic factor, YKL-39, which promotes angiogenesis in BC (92). Also, elevated levels of YKL-39 in tumor mass after neoadjuvant chemotherapy are shown to positively correlate with the increased risk of metastasis and poor clinical responses in patients with BC (92). A positive feedback loop between BC secreted GM-CSF and TAMs produces CCL18, which is suggested to be essential for BC metastasis (93). GM-CSF secreted by BC cells polarizes the macrophages to TAM phenotype and in return, TAMs secrete CCL18 to induce EMT and metastasis of BC cells. Furthermore, inhibition of either GM-CSF or CCL18 led to significant reduction of BC metastasis (93). In another report, TAMs were shown to produce matrix metalloproteinases (MMPs), cysteine cathepsins and serine proteases, which degrade and loosen the extracellular matrix (ECM) to support cancer cell invasion (94). TAMs also release proteins such as SPARC and epidermal growth factor (EGF) that promote malignant behavior and metastasis of the breast tumor cells (95,96). In a preclinical mouse model, deletion of intercellular cell adhesion molecule-1 (ICAM-1), which is inversely associated with macrophage infiltration and M2 polarization, inhibited metastatic tumor progression (97). Other crucial cells of breast TME, MDSCs, are also associated with tumor grade, stage and poor prognosis in patients with BC (98). A recent study showed that CXCL17 secreted by lung metastasized BC cells recruits MDSCs and induces the expression of platelet-derived growth factor (PDGF)-BB in them, which in turn, contributes to MDSC-mediated angiogenesis and further supports the colonization of BC cells (99). Along with suppressing the adaptive immune responses, MDSCs also regulate innate immune responses by altering the cytokine secretion of macrophages, which facilitate tumor growth, angiogenesis, and metastasis (100,101).

Effect of inflammation on BC therapy resistance

Intrinsic or acquired therapy resistance is a significant clinical problem that could occur through a variety of mechanisms (102-104). Inflammatory TME-induced alterations in the gene expression and tumor cell secretome have been recognized as an important mechanism in chemotherapy resistance (75,105,106). We recently

demonstrated that inflammatory cytokine, resistin, protected BC cells from doxorubicin-induced cell death through activation of STAT3 (88). Also, IL-6 has been demonstrated to induce stem cell phenotype in BC, and initiate an inflammatory feedback loop of IL-6/STAT3/Akt/NF- κ B, leading to trastuzumab resistance (107). IL-6 confers doxorubicin resistance in BC by activating the CCAAT enhancer-binding protein, leading to the expression of the downstream genes, such as multidrug resistance-1 (MDR1) (108). Further, several chemotherapeutic drugs are shown to induce the expression of IL-8 and its receptor CXCR1/2 in BC as a counter defense mechanism (109,110). IL-8 confers docetaxel resistance to BC cells through activation of PI3K/Akt and NF- κ B pathways (111). TGF- β 1 that is often elevated in the plasma of BC patients, is also shown to be associated with increased tumorigenicity and therapy resistance (112). Another report suggested the role of TGF- β pathway in epirubicin resistance in BC where it promoted cancer stemness (113). In some studies, mobilization of immune cells to the TME in response to chemotherapy-induced cytokine release is suggested to determine the therapeutic efficacy of treatment. Chemotherapeutic drugs such paclitaxel considerably increases the recruitment of cathepsin-secreting TAM in BC (114). These macrophages-released cathepsin proteases, partially cathepsins B and S, prevent paclitaxel-induced breast tumor cell death. Importantly, combining paclitaxel with cathepsin inhibition significantly increased the therapeutic efficacy in primary and metastatic breast tumors (114).

Targeting of inflammatory pathways for the management of BC

Strategies to intervene inflammation have been and are being sincerely investigated for cancer management. Multiple preclinical studies have reported the inhibitory effect of nonsteroidal anti-inflammatory drugs (NSAIDs) against mammary carcinogenesis (115-118). In an observational study of the prospective Women's Health Initiative data, Harris and coworkers (2003) examined the effects of the usage of ibuprofen, aspirin, and acetaminophen on BC risk. Their investigation revealed that the regular use of NSAID for 5-9 years resulted in the reduction of BC incidence by 21% and its usage for 10 or more years decreased the incidence by 28% (119). Further, the deep analysis indicated that the risk reduction in the group using ibuprofen in long-term was greater than that for aspirin, while no relation between acetaminophen use

and BC incidence was observed. In a rat model, where rats were fed Ibuprofen prior to mammary tumor development, only 74% rats developed tumors as compared to 86% tumor incidence in control rats (116). Apart from NSAIDs, anti-oxidants have also been suggested as chemopreventive agents. A population-based case-control study, where correlation between antioxidants and BC risk was examined, suggested that the long-term supplementation (10 years or more) of multiple vitamins, vitamin C, vitamin E, beta-carotene, and zinc in postmenopausal women was effective in prevention of BC development (120).

In multiple studies, application of neutralizing antibodies for tumor-promoting cytokines and/or chemokines, small-molecule inhibitors of chemokines/receptor signaling, and selective depletion of tumor supportive immune suppressive cells is suggested to be a potential strategy for BC treatment. CXCR1/2 antagonists, AZD5069 and reparixin, are being evaluated in the early phase of the clinical trial to impede granulocyte recruitment to tumors (121). CXCR1/2 receptor-expressing inflammatory immune cells are recruited to breast TME by their tumor cell-derived ligand, CXCL8, which in turn help in tumor promotion via reciprocal signaling (122,123). In HER2-negative BC, reparixin (CXCR1/2 inhibitor) in combination with paclitaxel produced favorable responses in a phase I clinical trial (124). A phase II trial is currently ongoing to explore the safety, pharmacokinetics, and biological effects of the reparixin with paclitaxel in a combination therapy (125). High indoleamine 2,3-dioxygenase (IDO) expression in TME is associated with breast tumor growth, metastasis and poor prognosis (126,127). A clinical trial is exploring the efficacy of chemotherapy (docetaxel or paclitaxel) with or without the addition of indoximod (IDO inhibitor) in metastatic BC (128). CD47 expressed on cancer cells interacts with signal regulatory protein- α (SIRP- α) present on the surface of macrophages, which helps in their evasion of phagocytosis (129-131). Overexpression of CD47 in breast tumors is associated with tumor progression, metastasis and poor prognosis (132-134). Preclinical studies have evaluated the efficacy of anti-CD47 therapy and found that the blockade of CD47 inhibited BC growth and enhanced macrophage-mediated clearance of BC cells (135). Another phase II clinical trial study is evaluating the efficacy of PLX3397, a CSF1R antagonist, in combination with eribulin chemotherapy in patients with metastatic BC (136). CSF-1/CSF-1R signaling pathway has been associated with poor prognosis in many cancers including BC (137,138). Inhibition of CSF-1/CSF-1R signaling using

a monoclonal antibody is also shown to regulate both the infiltration and function of tumor-infiltrating MDSCs and critically influence the response to CTLA-4 checkpoint immunotherapy (139).

Conclusion and future perspective

Significant epidemiological, experimental and clinical data now exist to not only support, but convincingly prove, an association of inflammation with BC pathogenesis and therapeutic outcomes. Indeed, emerging data continue to strengthen this association further and provide evidence that local or systemic inflammation may be an important risk factor for breast and other malignancies as well as be an important underlying cause of prevalent cancer disparities. These findings have strongly supported the relevance of inflammation as a clinically significant drug target for cancer prevention and therapy. There are; however, still some gaps that need to be filled before we can take a significant leap forward in clinically exploiting the association of inflammation and cancer. We need to better understand the complex nature of inflammatory and immune cell drivers of cancer-associated local and systemic inflammation. We also need to precisely define the impact of this inflammation and associated immune suppression on therapy-resistance including the drug pharmacokinetics in well-defined diverse sets of cancer populations. It is also required that we define how these changes affect drug availability to the tumor cells, drug activity and utilization, and/or responses resulting from changes in drug target excess and accessibility. On a positive note, we now have well-annotated clinical datasets available to us in addition to the state-of-the-art technology (high throughput approaches and automated systems, etc.) that can help us address these important questions. Cancer is a significant clinical problem and many investigational drugs fail in clinical trials. Having established a role of inflammation in therapeutic outcome will help us develop newer and more effective combination therapeutic approaches. In addition to identification of actionable drug targets, future research could also help develop clinical tests for risk prediction, early diagnosis and therapeutic planning. Clearly, we have significantly advanced our understanding of pathobiological association of inflammation with cancer through years of research. We can very well anticipate that novel clinical management approaches will emerge from this knowledge to improve the life-expectancy of cancer patients and impact the quality of life for patients.

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Footnote

Conflicts of Interest: AP Singh and S Singh are co-founders, and serve on the executive management team of Tatva Biosciences. SK Srivastava serves as the Director of Cell Biology and Genetics at Tatva Biosciences. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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