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Review:

Harnessing the immune system for the treatment of breast cancer

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Abstract: Standard treatment options for breast cancer include surgery, chemotherapy, radiation, and targeted therapies, such as adjuvant hormonal therapy and monoclonal antibodies. Recently, the recognition that chronic inflammation in the tumor microenvironment promotes tumor growth and survival during different stages of breast cancer development has led to the development of novel immunotherapies. Several immunotherapeutic strategies have been studied both preclinically and clinically and already have been shown to enhance the efficacy of conventional treatment modalities. Therefore, therapies targeting the immune system may represent a promising next-generation approach for the treatment of breast cancers. This review will discuss recent findings that elucidate the roles of suppressive immune cells and proinflammatory cytokines and chemokines in the tumor-promoting microenvironment, and the most current immunotherapeutic strategies in breast cancer.

Key words: Breast cancer, Chronic inflammation, Protumorigenic immune cells, Therapeutic vaccines, Immunotherapy
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1 Introduction

Breast cancer continues to be the most common cancer in women and represents a major issue of public health (Basu *et al.*, 2013) with 1.38 million new cases and 458000 deaths yearly worldwide (Bray *et al.*, 2012). Although the incidence and mortality rates of breast cancer in western countries have decreased or at least been stable over the last few decades, both rates are increasing in many developing countries (Jemal *et al.*, 2010). In China, breast cancers are often found at more advanced stages, likely because of the incomplete nationwide screening program. These cancers require more effective treatment combinations (Li *et al.*, 2011; Wang *et al.*, 2013). The majority of estrogen receptor-positive (ER+) breast cancer patients develop resistance to adjuvant hormonal therapy (Osborne and Schiff, 2011), and triple negative breast cancers (TNBCs) (i.e., ER−, progesterone receptor negative (PR−), and HER2/neu negative) also lack effective targeted treatments (Stagg and Allard, 2013). Therefore, novel therapeutic targets are urgently needed to improve the efficacy of conventional treatments.

It has long been recognized that the immune system plays a role in the development of tumors. Immune cells can suppress tumor development by killing tumor cells or inhibiting their growth. Conversely, they can also promote tumor progression by selecting tumor cells that are fit to grow in an immune competent host or by establishing an immunosuppressive microenvironment. The interplay between the tumor and the immune system during tumor progression is called immunoediting and comprises three phases: elimination, equilibrium, and escape (Schreiber *et al.*, 2011; Vesely *et al.*, 2011). In the elimination and equilibrium phases, tumors can be completely eliminated or kept in a dormant state by tumor-inhibiting inflammation, characterized by the production of tumor-inhibiting cytokines and the infiltration of cells of both the innate immune system, such as dendritic cells (DCs) and natural killer (NK) cells, and the adaptive immune system, such as Th1 $CD4^+$ and $CD8^+$ T cells (Schreiber *et al.*, 2011;

Vesely *et al.*, 2011; Jiang and Shapiro, 2014). On the other hand, in the escape phase, breast tumors often develop multiple mechanisms to evade immunosurveillance. These include the creation of cell autonomous modifications which allow cancer cells to evade antitumor cell-mediated destruction (Shin *et al.*, 2001; Jiang *et al.*, 2006; 2007; 2008; Ryan *et al.*, 2006), and the induction of an immunosuppressive microenvironment by tumor and/or stromal cells, which diminishes the function of effector cells and directly promotes cancer cell proliferation and migration (Jiang and Shapiro, 2014). Chronic inflammation in the tumor microenvironment and the resulting tumor evasion of the immune system have recently been recognized as another hallmark of cancer (Hanahan and Weinberg, 2011). Although pre-existing inflammation and infection are not considered a risk factor for breast cancer development, it is generally accepted that infiltration of immunosuppressive leukocytes and accompanying chronic inflammation during tumor progression promote breast cancer growth (DeNardo and Coussens, 2007; Coussens and Pollard, 2011; Coussens *et al.*, 2013). This review will focus on the protumorigenic immune cell subsets and proinflammatory mediators that form suppressive tumor microenvironments and the most recent findings in human breast cancer immunotherapeutics.

2 Protumorigenic immune cells

2.1 Macrophages

Macrophages are the most plastic cells of the hematopoietic system and have diverse gene-expression profiles and functions (Murray and Wynn, 2011; Gautier *et al.*, 2012; Wynn *et al.*, 2013). Although macrophages were originally thought to be anti-tumorigenic, compelling preclinical and clinical studies suggest that in most cases macrophages promote tumor initiation, progression, and metastasis (Qian and Pollard, 2010). Increasing macrophage infiltration in the tumor is associated with a worse prognosis for both relapse-free and overall survival of breast cancer patients (Leek *et al.*, 1996; Tsutsui *et al.*, 2005; Mahmoud *et al.*, 2012). Profiling of stromal gene expression in human breast cancers showed that the expression of macrophage-associated genes predicted poorer outcomes (Finak *et al.*, 2008). Tumor-associated macrophages (TAMs) also inversely correlate with the expression of hormone receptors (i.e., ER, PR, HER2/neu), which are considered favorable prognostic factors (Campbell *et al.*, 2011). As the key element of cancer-related inflammation, macrophages are often classified into either Th1-activated M1 or Th2-activated M2 subtypes. Macrophages within tumor sites are usually of the M2 subtype (Mantovani *et al.*, 2008; Biswas and Mantovani, 2010; Ruffell *et al.*, 2012). Suppressing the signal transducer and activator of transcription 3 (STAT3) signaling pathway by hydrazinocurcumin converts the TAM phenotype from M2 to M1 and inhibits breast cancer progression and metastasis (Zhang X. *et al.*, 2013). Inhibition of cyclooxygenase (COX)-2 or enhanced expression of microRNA miR-19a-3p also suppresses breast cancer metastasis by preventing M2 phenotype polarization (Na *et al.*, 2013; Yang *et al.*, 2013a). Anti-angiogenic treatment has also been shown to reprogram TAMs from the M2 to the M1 phenotype and enhance immunotherapy (Huang *et al.*, 2012). This suggests that the M2 subtype promotes tumor progression and metastasis, and that reprogramming macrophages from the M2 to the M1 subtype can be utilized as a therapeutic strategy. Blockade of macrophage colony-stimulating factor 1 (CSF1) or its receptor (CSF1R) rapidly decreases macrophage infiltration, promotes Th1 responses in late-stage breast cancer, and prolongs survival (DeNardo *et al.*, 2011). This suggests that macrophage depletion can be another effective therapeutic strategy.

A huge body of research has demonstrated that, through various mechanisms, TAMs promote tumor angiogenesis, tumor cell proliferation, migration and metastasis, and contribute to the creation of a proinflammatory and immunosuppressive tumor microenvironment (Laoui *et al.*, 2011; Obeid *et al.*, 2013; Tang, 2013). TAMs produced vascular endothelial growth factor (VEGF) and other proangiogenic factors, such as interleukin (IL)-1, IL-8, and fibroblast growth factor (FGF)-2, which have all been shown to promote breast cancer angiogenesis (Leek *et al.*, 2000; Lewis *et al.*, 2000; Dirkx *et al.*, 2006). TAMs are also known to directly stimulate breast cancer cell proliferation by producing a wide range of growth factors, such as epidermal growth factor (EGF), FGF-2, transforming growth factor (TGF)-β, and platelet-derived growth factor (PDGF) (O'Sullivan *et al.*, 1993; Ribatti *et al.*,

2007). TAMs also promote breast cancer cell survival through α4-integrin-dependent binding of macrophage to vascular cell adhesion molecule-1 (VCAM-1)-expressing tumor cells, which favors breast cancer cell metastatic colonization (Chen *et al.*, 2011). Wolford *et al.* (2013) showed that induction of the expression of ATF3 and its downstream gene matrix metalloproteinase-9 (MMP-9) in macrophages leads to enhanced breast cancer invasiveness and metastasis. Ishihara *et al.* (2013) revealed that Wiskott-Aldrich syndrome protein (WASp)-mediated EGF shedding by TAMs was required to enhance breast cancer motility, intravasation, and metastasis. These studies suggest that TAMs promote breast tumor metastasis through enhancing breast cancer cell proliferation and migration.

Breast cancer stem cells (CSCs) represent a population of cells associated with treatment resistance and relapse following therapy (Kakarala and Wicha, 2008; Korkaya *et al.*, 2011). Yang *et al.* (2013b) showed that TAMs induce a CSC phenotype in breast tumor cells through EGF-activated EGFR/STAT3/SOX2 signaling, suggesting a novel pathway through which TAMs promote breast cancer growth, metastasis, and resistance to chemotherapy. TAMs may also promote the development of a CSC phenotype through fusion with breast cancer cells (Ding *et al.*, 2012). Macrophage-produced IL-6 has also been shown to promote breast CSC self-renewal (Iliopoulos *et al.*, 2009) (Fig. 1). Together, these studies suggest that TAMs play a profound role in many different stages of breast cancer development and may represent a promising therapeutic target (de Palma and Lewis, 2013).

2.2 T regulatory (Treg) cells

Forkhead box P3 (FOXP3)-expressing Treg cells are a potent mediator of peripheral immune tolerance and suppress a wide range of immune cells, including $CD4^+$ and $CD8^+$ T cells, NK cells, NKT cells, B cells, and antigen presenting cells, through suppression of target cell activation, proliferation, and effector functions (Shevach, 2009; Sakaguchi *et al.*, 2010; Jiang and Shapiro, 2014). Infiltration of Treg cells into breast cancers has been observed in numerous studies, and the number of Treg cells in the tumor site has been shown to be associated with a worse prognosis (Bates *et al.*, 2006; Bohling and Allison, 2008; Ohara *et al.*, 2009). Circulating Treg cells can be recruited to a breast cancer site through multiple signaling axes, including PGE2/EP2 (EP4), CCL22/CCR4, SDF1/CXCR4, and CCL5/CCR1 (Gobert *et al.*, 2009; Tan *et al.*, 2011; Yan *et al.*, 2011; Karavitis *et al.*, 2012). Interestingly, the tumor environment may play an active role in promoting Treg cell differentiation and expansion. Tumor cell activated regulatory B cells can directly convert $CD4^+$ T cells into Treg cells in a TGF-β-dependent manner (Olkhanud *et al.*, 2011). Also, impaired production of interferon-α (IFN-α) by plasmacytoid DCs favors expansion of Treg cells infiltrating breast tumor sites (Sisirak *et al.*, 2012). Enhanced TGF-β signaling stimulates tumor infiltrating DCs to produce CCL22, thus promoting Treg cell recruitment and activation (Hanks *et al.*, 2013). $CD8^+$ T cell-derived CCL22 also appears to recruit

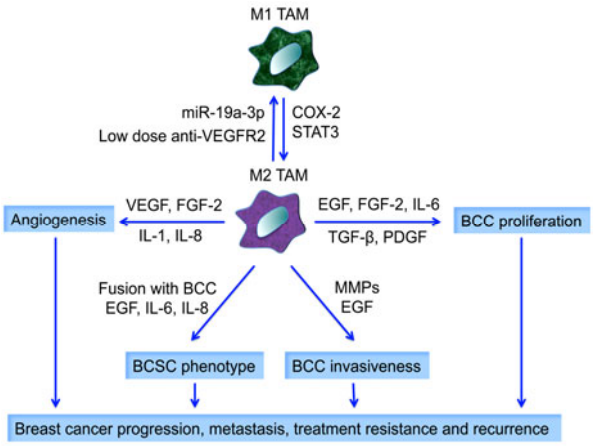

Fig. 1 M2-polarized TAM promotes breast cancer progression, metastasis, treatment resistance and recurrence
COX-2 or STAT3 activation polarizes TAM to the M2 phenotype. Expression of microRNA miR-19a-3p in TAM or low dose anti-VEGFR2 treatment polarizes TAM to the M1 phenotype. TAM promotes angiogenesis by producing VEGF, FGF-2, IL-1, and IL-8. TAM also promotes breast cancer cell proliferation by producing EGF, FGF-2, IL-6, TGF-β, and PDGF. In addition, TAM promotes the breast cancer stem cell phenotype by producing EGF, IL-6, and IL-8 or by fusing with breast cancer cells. Lastly, TAM promotes breast cancer cell invasiveness by producing MMPs and EGF. Abbreviations: TAM, tumor-associated macrophage; COX-2, cyclooxygenase 2; STAT3, signal transducer and activator of transcription 3; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; FGF, fibroblast growth factor; IL, interleukin; TGF, transforming growth factor; PDGF, platelet-derived growth factor; EGF, epidermal growth factor; MMP, matrix metalloproteinase; BCC, breast cancer cell; BCSC, breast cancer stem cell

$CCR4^+$ Treg cells which contribute to forming an immune intrinsic negative feedback loop in the tumor microenvironment (Spranger *et al.*, 2013). This suggests that the tumor-inhibiting immune response may initiate Treg cell recruitment and proliferation in the tumor microenvironment. It was recently shown that Treg cells produce large amounts of receptor activator of nuclear factor-κB (RANK) ligand (RANKL), which in turn acts on RANK-expressing breast cancer cells and promotes lung metastasis (Tan *et al.*, 2011). This suggests that Tregs can also promote tumor metastasis by directly acting on breast cancer cells in a paracrine fashion. Tamoxifen was shown in an *ex vivo* study to induce FOXP3 expression in tumor-infiltrating lymphocytes, which may represent a mechanism for hormonal therapy resistance through Treg-mediated immunosuppression (Joffroy *et al.*, 2010). Inhibition of galectin-1 expressed in breast cancer cells is associated with decreased Treg cell accumulation within the tumor and significantly decreases tumor growth and lung metastasis (Dalotto-Moreno *et al.*, 2013). This suggests direct crosstalk between the tumor cells and Treg cells. Consistent with the large body of studies showing that Treg cells are strong promoters of breast cancer progression and metastasis, anti-CD25 antibody-mediated Treg blockade or depletion leads to a stronger antitumor immune response and better clinical outcomes (Rech *et al.*, 2012; Weiss *et al.*, 2012). Together, these studies suggest that the Treg cell is a potent negative regulator of anti-tumor immune responses and represents an attractive therapeutic target in breast cancer.

2.3 Myeloid-derived suppressor cells (MDSCs)

MDSCs comprise a heterogeneous population of cells of myeloid origin that expand during pathological conditions such as cancer, inflammation, and infection (Gabrilovich and Nagaraj, 2009; Gabrilovich *et al.*, 2012). Two main populations of MDSCs have been characterized: monocytic MDSC (M-MDSC) and polymorphonuclear MDSC (PMN-MDSC), the latter of which is the prevalent population in tumor-bearing mice (Gabrilovich *et al.*, 2012). The MDSC is another major immunosuppressive cell type found in breast tumors (Markowitz *et al.*, 2013). Circulating levels of MDSCs were shown to correlate with clinical stages of breast cancer, with the highest levels found in patients with extensive metastatic tumor burden (Diaz-Montero *et al.*, 2009). Circulating levels of MDSCs, both before and after chemotherapy, also predict a patient's response to treatment (Montero *et al.*, 2012).

Factors that induce MDSC expansion include granulocyte-macrophage (GM)-CSF, PGE2, IL-6, stem cell factor (SCF), VEGF, and CCL5, while IFN-γ, ligands of toll-like receptors, IL-13, and IL-4 are associated with MDSC activation (Gabrilovich and Nagaraj, 2009; Zhang Y. *et al.*, 2013a). TGF-β-induced miR-494 was recently shown to facilitate MDSC accumulation and promote their suppressive function in breast cancers (Liu *et al.*, 2012). MDSCs suppress $CD8^+$ T cells by producing reactive oxygen species (ROS) as well as inducible nitric oxide synthase (iNOS) and arginase 1 (ARG1) enzymes (Gabrilovich *et al.*, 2012). Through nitration of tyrosines in the T cell receptor (TCR)-CD8 complexes, MDSCs also directly disrupt the binding of specific peptide-MHC dimers to $CD8^+$ T cells. This prevents cytotoxic T lymphocytes (CTLs) from binding to the peptide-MHC complex and therefore inhibits anti-tumor activity (Nagaraj *et al.*, 2007). MDSCs can also induce nitration of MHC class I molecules expressed on breast cancer cells, making them unable to effectively present specific peptides and thus rendering tumor cells resistant to antigen-specific CTLs (Lu *et al.*, 2011). More recently, MDSCs were shown to suppress T cell function through STAT3-mediated indoleamine-pyrrole 2,3-dioxygenase (IDO) production (Yu J. *et al.*, 2013). In addition to acting as potent T cell suppressors, MDSCs also promote immunosuppression by inducing Treg cell proliferation and inhibiting NK cell activity (Huang *et al.*, 2006; Mauti *et al.*, 2011). Other studies have shown that reduction of the immunosuppressive function of MDSCs is required for induction of the anti-breast tumor immune response (Sinha *et al.*, 2005; Morales *et al.*, 2009; Steding *et al.*, 2011; Thakur *et al.*, 2012). These studies further demonstrate that MDSCs negatively regulate the antitumor immune response, and that MDSC suppression may enhance immunosurveillance against breast cancer cells.

2.4 Th17 cells

Based on the cytokines they produce, $CD4^+$ T helper cells are classically divided into either Th1 or Th2 cells. Th17 is a recently discovered type of $CD4^+$

T helper cell, characterized by the production of IL-17 (Korn *et al.*, 2009). The Th17 cell is well recognized for its role in autoimmunity (Harrington *et al.*, 2005; Dong, 2006). The role of Th17 cells in the microenvironment of various tumors has been studied in recent years. Both antitumor and tumor-promoting functions have been identified in Th17 cells, depending on the tumor type (Zou and Restifo, 2010). Breast cancer-produced PGE2 was shown to induce the expression of IL-23, which then promotes Th17 cell survival and expansion (Qian *et al.*, 2013). Chen *et al.* (2013) showed that a high number of IL-17 producing cells in breast tumors correlate with high histological grade, negative ER/PR status, and triple-negative phenotype. Moreover, patients with high IL-17 have shorter disease-free survival. Novitskiy *et al.* (2011) demonstrated a strong association between IL-17 expression and poor outcomes in lymph node-positive, ER-negative, and luminal B subtype breast cancers. A positive correlation between $FOXP3^+$ Treg cells and IL-17-producing Th17 cells was shown in human breast tumors. It was suggested that Th17 cells promote breast cancer progression through the induction of angiogenic factors such as VEGF, MMP9, and IL-8 (Benevides *et al.*, 2013). IL-17 may also promote breast cancer progression by enhancing the protumorigenic functions of MDSCs and TAMs. Interestingly, treatment with an anti-IL17 antibody decreased tumor growth and metastatic burden (Novitskiy *et al.*, 2011). Although these data strongly suggest that IL-17-producing Th17 cells may act as tumor-promoting T helper cells in breast cancer, Yang *et al.* (2012) showed that the Th17 cell is associated with a favorable prognosis and may display antitumor activity. This suggests plasticity of Th17 cells in breast cancer progression (Coussens *et al.*, 2013). In summary, the Th17 cell likely acts as a tumor-promoting $CD4^+$ T helper cell in breast cancer, but in some clinical settings, it may act as a tumor suppressor. More research is needed to further identify the role that Th17 cells play in different stages of breast cancer development, and only then may Th17 cells be considered a promising therapeutic target.

3 Proinflammatory cytokines and chemokines

The role of proinflammatory cytokines and chemokines, such as IL-6, IL-1, IL-8, TNF-α, monocyte chemotactic protein-1 (MCP-1), CCL5, and chemokine (C-X-C motif) ligand (CXCL12), in breast cancer has been extensively studied and reviewed (Ben-Baruch, 2003; Goldberg and Schwertfeger, 2010; Baumgarten and Frasor, 2012). Here, only the most recent findings will be discussed.

IL-6 is a key inflammatory cytokine in a number of diseases. Circulating IL-6 levels are positively associated with clinical tumor stage, lymph node infiltration, and number of distant metastases in breast cancer patients (Salgado *et al.*, 2003; Dethlefsen *et al.*, 2013). However, no correlation between breast cancer risk and the functional polymorphism of the IL-6 gene promoter was observed in a meta-analysis (Yu *et al.*, 2010). Rokavec *et al.* (2012) showed that the transient induction of IL-6 by monocyte-derived MCP-1 drives a feed-forward inflammatory signaling pathway that leads to constitutive IL-6 production and breast cancer cell transformation and tumorigenesis, revealing a novel mechanistic link between IL-6 and breast cancer initiation. *In vitro* IL-6 can either promote or inhibit breast cancer cell growth depending on hormone receptor status (Dethlefsen *et al.*, 2013). In TNBC, autocrine expressions of IL-6 and IL-8 are critical for their anchorage-independent growth and resistance to apoptosis (Hartman *et al.*, 2013). IL-6 not only regulates breast CSC self-renewal (Marotta *et al.*, 2011), but also promotes CSC survival and proliferation through the activation of Notch, Wnt, Hedgehog, and TGF-β signaling pathways (Dethlefsen *et al.*, 2013). IL-6 also promotes breast cancer metastasis through the induction of epithelial to mesenchymal transition (EMT) (Korkaya *et al.*, 2012; Xie *et al.*, 2012; Hwang *et al.*, 2013). These studies suggest that IL-6 may promote breast cancer progression, metastasis, and resistance to treatment by acting on the CSC population and initiating EMT.

IL-8 is highly expressed in ER− breast cancers and increases the invasiveness and metastatic potential of both ER+ and ER− breast cancer cells (Todorović-Raković and Milovanović, 2013). IL-8 promotes CSC self-renewal and invasion by binding to its cognate receptor CXCR1 on CSCs (Charafe-Jauffret *et al.*, 2009). It also affects breast CSC activity measured *ex vivo* using patient-derived breast cancer samples, through a CXCR1/2-dependent but HER2-independent pathway (Singh *et al.*, 2013). Upregulation of IL-8 through leukotriene B4 receptor 2 (BLT2) activation also promotes breast cancer cell invasiveness (Kim

et al., 2012). HER2/HER3 co-expression induced IL-8 autocrine signaling is responsible for breast cancer cell invasiveness (Aceto *et al.*, 2012). Li S. *et al.* (2012) showed that TWIST1-induced IL-8 also promotes breast cancer cell invasion. Targeting both the JAK2 and STAT5 signaling pathways diminishes IL-8 expression, which in turn decreases tumor metastasis and improves survival (Britschgi *et al.*, 2012). These studies suggest that inhibition of the IL-8 signaling pathway may diminish breast cancer invasiveness and metastasis by acting on breast cancer cells and CSCs.

A recent preclinical study showed that chemotherapy-induced inflammation is one of the main contributors to chemo-resistance and metastasis (Acharyya *et al.*, 2012). Profiles of cytokines and chemokines in the tumor microenvironment showed that chemotherapy strikingly induces endothelial cell production of TNF-α. This enhances tumor cell CXCL1/2 production, which in turn facilitates recruitment of $CD11b^{+}Gr1^{+}$ MDSCs. These cells release S100A8/9, an inflammatory modulator that activates the p70S6K and ERK1/2 signaling pathways and provides a survival advantage for both primary and metastatic tumor cells (Acharyya *et al.*, 2012). TNF-α also promotes breast cancer metastasis by inducing EMT through the NF-κB-mediated transcriptional activation of TWIST1 (Li C.W. *et al.*, 2012). It was recently shown that targeting transmembrane TNF-α was effective in delaying tumor growth and inhibiting tumor metastasis (Yu M. *et al.*, 2013). TNF-α inhibition may synergize with anti-HER2 therapy to improve treatment outcomes (Ceran *et al.*, 2012). These studies suggest that TNF-α may play a significant role in breast tumor progression not only by directly acting on breast cancer cells, but also by recruiting and activating suppressive immune cells.

CXCL12 is a chemokine that has been shown to be associated with breast cancer metastasis (Boimel *et al.*, 2012; Wendel *et al.*, 2012; Mukherjee and Zhao, 2013). Targeting CXCL12/CXCR4 signaling by using the oncolytic virus therapy strategy inhibits breast cancer metastasis (Gil *et al.*, 2013). It was recently shown that a pair of microRNAs, miR-126 and miR-126*, suppresses breast cancer metastasis by inhibiting the recruitment of tumor promoting mesenchymal stem cells (MSCs). CXCL12 was identified as a target gene of miR-126 and miR-126* (Zhang Y. *et al.*, 2013b). These two studies suggest a role for the CXCL12/CXCR4 axis in breast cancer metastasis. However, Williams *et al.* (2010) showed that CXCL12 expression in the primary tumor site may prevent or attenuate breast cancer metastasis by recruiting antitumor immune cells. This suggests that a differential targeting strategy for CXCL12 in the primary tumor site compared to metastatic sites might be needed for the best clinical outcome.

It was recently shown that hypoxia inducible factor (HIF)-1α-mediated paracrine signaling pathways (i.e., CXCL10/CXCR3 and CCL5/CCR5) between MSCs and breast cancer cells promoted metastasis (Chaturvedi *et al.*, 2013). This suggests that hypoxia of the tumor microenvironment may promote metastasis through the synergistic effect of HIF-1α and proinflammatory mediators. In addition to proinflammatory cytokines and chemokines, immunosuppressive molecules such as TGF-β, IL-10, and PGE2 are often present in abundant levels in the tumor microenvironment (Wrzesinski *et al.*, 2007; Chen and Smyth, 2011; Hamidullah *et al.*, 2012; Basu *et al.*, 2013). Other suppressive factors produced by breast cancer cells, such as soluble forms of the ligand, soluble major histocompatibility complex class I-related-chain A (sMICA) and IDO, have also been shown to suppress antitumor NK cells and $CD8^{+}$ T cells (Groh *et al.*, 2002; Uyttenhove *et al.*, 2003; Muller *et al.*, 2005).

Taken together, tumorigenic cytokines, chemokines, and immunosuppressive soluble factors produced by cancer cells or stromal cells promote chronic inflammation in the breast tumor microenvironment. These molecules, in turn, enhance tumor growth and metastasis by directly acting on tumor cells, facilitating recruitment and activation of suppressive immune cells, and suppressing antitumor effector cells.

4 Immunotherapeutic strategies

Escape of tumor cells from immunosurveillance often results from diminished effector cell function and the immune suppressive tumor microenvironment (Schreiber *et al.*, 2011; Vesely *et al.*, 2011). Therefore, the goal of an effective immunotherapy is to boost the antitumor immunity of effector cells and to neutralize tumor-promoting chronic inflammation

(Coussens *et al.*, 2013). The proinflammatory cytokines and chemokines and suppressive immune cells present in the breast tumor microenvironment are potential therapeutic targets, as discussed above. Several other immunotherapeutic strategies have been successfully tested in preclinical and/or clinical studies and will be discussed here (Fig. 2).

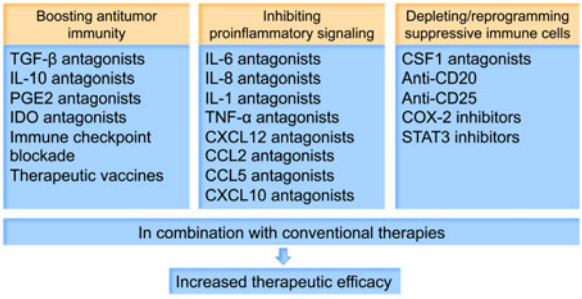

Fig. 2 Scheme of immunotherapeutic strategies
Antitumor immunity can be boosted by antagonizing suppressive factors, such as TGF-β, IL-10, IDO, and PGE2, inhibition of immune checkpoints, and therapeutic vaccines. Proinflammatory mediators, such as IL-6, IL-8, IL-1, TNF-α, CCL5, CCL2, CXCL10 and CXCL12, can also be targeted. Moreover, depleting or reprogramming suppressive immune cells, such as Treg cells, TAM, or B cells, can also indirectly boost antitumor immunity. Immunotherapy combined with conventional therapies will likely improve the overall therapeutic efficacy. Abbreviations: TGF, transforming growth factor; IL, interleukin; PG, prostaglandin; IDO, indoleamine-pyrrole 2,3-dioxygenase; TNF, tumor necrosis factor; CXCL, chemokine (C-X-C motif) ligand; CCL, CC chemokine ligand; CSF, colony stimulating factor; COX-2, cyclooxygenase-2; STAT3, signal transducer and activator of transcription 3

4.1 Immune checkpoint blockade

The $CD8^+$ T cell is a major antitumor effector cell in breast cancer (Jiang and Shapiro, 2014). $CD8^+$ T cell infiltration is associated with better overall patient outcomes, independent of other prognostic factors such as tumor grade, lymph node stage, size, vascular invasion, and HER2 status (Mahmoud *et al.*, 2011). However, the net effect of $CD8^+$ T cell mediated cytotoxicity is regulated by the balance between co-stimulatory and inhibitory signals (i.e., immune checkpoints) (Greenwald *et al.*, 2005; Zou and Chen, 2008). One of the most extensively studied immune checkpoint receptors is cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) (Pardoll, 2012). Ipilimumab is a humanized monoclonal antibody that suppresses CTLA4 signaling and was approved by the US Food and Drug Administration (FDA) to treat melanoma in 2011 (Emens, 2012). Peripheral blood mononuclear cells (PBMCs) from breast cancer patients express higher levels of CTLA4, are less responsive to phytohaemagglutinin (PHA) stimulation, and produce lower levels of IL-2, suggesting that CTLA4 expression in immune cells may be responsible for immune evasion of breast cancer cells (Mao *et al.*, 2010). CTLA4 polymorphisms may also be associated with breast cancer susceptibility and progression in Chinese women (Wang *et al.*, 2007). Fractionated radiotherapy was shown to synergize with anti-CTLA4 therapy to induce antitumor T cell immunity and inhibit the growth of tumors outside the radiation field (i.e., an abscopal effect) (Dewan *et al.*, 2009). This suggests that the anti-CTLA4 antibody may be effective in breast cancer treatment when combined with conventional therapies.

Another well characterized immune checkpoint receptor is programmed cell death protein 1 (PD-1). A recently completed phase I trial showed that treatment with an anti-PD-1 antibody was safe and produced durable tumor regression in 6%–17% of patients with melanoma, non-small cell lung cancer, or renal cancer (Brahmer *et al.*, 2012). Programmed death-1-ligand 1 (PD-L1) expression on breast cancer cells has been shown to inhibit T cell proliferation and induce their apoptosis (Zhang *et al.*, 2008). The presence of PD-1+ tumor infiltrating lymphocytes (TILs) is associated with a significantly worse overall survival, and further subtype analysis showed that this is associated with worse survival in luminal B and basal-like subtypes (Muenst *et al.*, 2013). A very recent preclinical study showed that COX-2 deficient breast cancer cells express lower levels of PD-L1, which leads to suppression of tumor growth in immune competent mice (Markosyan *et al.*, 2013). Anti-PD-1 antibody therapy has been shown to enhance the response to radiotherapy and DC vaccines in established breast cancers (Verbrugge *et al.*, 2012; Ge *et al.*, 2013). Anti-PD-1 antibody also significantly improves the effectiveness of the anti-HER2 monoclonal antibody in immunocompetent mice (Stagg *et al.*, 2011). Together, these studies suggest that anti-PD-1 may be used in combination with other therapies to improve the overall treatment efficacy in breast cancer.

4.2 Therapeutic vaccines

Therapeutic cancer vaccine is another strategy to boost the host immune system to suppress tumor growth. The principle is to utilize tumor-associated antigens (TAAs) to induce targeted immune attack against tumor cells. Numerous preclinical and clinical studies have shown that cancer vaccines are safe and have extremely low levels of toxicity (i.e., mostly limited to grade I and grade II). The most effective outcome is often observed when patients are treated with vaccines in combination with other therapeutic regimens (Schlom, 2012). A large number of early phase breast cancer vaccine clinical trials have been carried out with HER2 TAAs (Emens, 2012; Wiedermann *et al.*, 2013). Miles *et al.* (2011) showed that the therapeutic vaccine, sialyl-TN-keyhole limpet hemocyanin (STn-KLH), alone did not affect time to progression (TTP) or overall survival. However, a very recent multicenter, double blinded, randomized phase III clinical trial showed that patients with metastatic breast cancer receiving STn-KLH plus endocrine therapy had significantly longer TTP and overall survival (Ibrahim *et al.*, 2013). Another small clinical trial showed that metastatic breast cancer patients treated with a vaccine comprising human telomerase reverse transcriptase (hTERT) peptide plus anti-CD25 antibody had much higher OS than those treated with hTERT vaccine alone (Rech *et al.*, 2012). This suggests that the efficacy of breast cancer vaccines can be enhanced by depleting suppressive components of the tumor microenvironment, such as Treg cells. Antigen-loaded DC vaccines, engineered to produce antibodies against CTLA-4 and glucocorticoid-induced TNFR-related protein (GITR), induced stronger $CD8^+$ T cell immunity against breast cancer cells (Pruitt *et al.*, 2011), suggesting that breast cancer vaccines combined with immune checkpoint inhibition may produce stronger antitumor immunity *in vivo*. Enhanced HER2/neu-specific immune responses were achieved when breast cancer patients received both the vaccine and the HER2/neu inhibiting monoclonal antibody, trastuzumab (Disis *et al.*, 2009). Low-dose paclitaxel was also able to enhance DC function in preclinical studies (Pfannenstiel *et al.*, 2010). Together, these data suggest that breast cancer vaccines may have the highest efficacy when combined with other therapeutic modalities.

Consistent with earlier findings showing an inverse correlation between prior chemotherapy and the efficacy of vaccine treatment (von Mehren *et al.*, 2000; 2001), a recently reported pilot study of a MUC-1/CEA/TRICOM poxviral-based vaccine showed that only 1 of 12 patients with breast cancer had an objective complete response, whereas all the others had rapid progression of disease (Mohebtash *et al.*, 2011). The only responder was a patient who had minimal disease and was not as heavily pretreated as the others, suggesting that breast cancer vaccine monotherapy in patients with heavy tumor burdens or extensive prior treatment with chemotherapy is not likely to produce a significant clinical benefit. This finding also suggests that breast cancer therapeutic vaccines should be used as early as possible to prevent recurrence and dissemination of tumors (Wiedermann *et al.*, 2013).

5 Concluding remarks

Chronic inflammation in the breast cancer microenvironment, comprised of proinflammatory mediators, immunosuppressive factors, and suppressive immune cells, may represent intrinsic negative feedback in response to a tumor-inhibiting acute immune reaction. The studies reviewed above demonstrate that the immune network plays a significant role in the development and progression of breast cancer. In the future, incorporating some of these factors into the traditional classification scheme may be helpful in determining prognosis and treatment options. Identification of genetic variations that affect inflammation and immunity may provide better therapeutic targets for breast cancer patients, which may allow for a more personalized approach to management. Moreover, identification of these variations may also be useful for designing new preventive approaches for populations with a high risk of developing breast cancer. In summary, compelling preclinical and clinical studies have shown that the inflammatory microenvironment not only promotes breast cancer progression and metastasis, but also enhances treatment resistance and accelerates recurrence. This knowledge has identified numerous novel targets for breast cancer immunotherapies that include depletion or reprogramming of suppressive immune cells, neutralization

of proinflammatory mediators, inhibition of immune checkpoints and immunosuppressive factors, and therapeutic vaccines. A combination of these strategies with conventional breast cancer therapies will likely improve overall treatment efficacy.

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Compliance with ethics guidelines

Xinguo JIANG declares that he has no conflict of interest.

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Introducing editorial board member:

Dr. Xinguo JIANG, the author of this invited review, is a new editorial board member of *Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)* in 2014. His main research interests include: (1) the immune system and inflammation in breast cancer, (2) inflammation in pulmonary hypertension, and (3) microvascular health in solid organ transplantation. After he graduated from Zhejiang University, China and finished his residency, he obtained a PhD in Physiology from the University of Illinois at Urbana-Champaign (USA) in 2007. He finished his post-doctoral training at Stanford University (USA), and currently he is a research scientist at Stanford University with a focus on lung diseases.

中文概要：

本文题目：乳腺癌的免疫调节治疗

Harnessing the immune system for the treatment of breast cancer

研究目的：这篇综述主要阐述了免疫系统在乳腺癌发生、发展和转移过程中的双向作用，以及乳腺癌的最新免疫治疗方法。

重要结论：免疫系统能够杀灭肿瘤细胞，但是由于肿瘤导致的慢性炎症反应却可以促进肿瘤生长和转移。因此，乳腺癌免疫调节治疗包括增强抗肿瘤免疫细胞功能、肿瘤疫苗、去除抑制性免疫细胞或者抑制性细胞因子、抑制免疫抑制信号。

关键词组：乳腺癌；慢性炎症反应；促肿瘤发展免疫细胞；肿瘤疫苗；免疫治疗