World Journal of Clinical Oncology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5306/wjco.v5.i3.495

World J Clin Oncol 2014 August 10; 5(3): 495-502
ISSN 2218-4333 (online)

TOPIC HIGHLIGHT

WJCO 5th Anniversary Special Issues (2): Breast cancer

Pattern response of dendritic cells in the tumor microenvironment and breast cancer

Alessandra da Cunha, Marcia A Michelin, Eddie FC Murta

Alessandra da Cunha, Marcia A Michelin, Eddie FC Murta, Research Oncology Institute (IPON), Federal University of the Triângulo Mineiro (UFTM), Uberaba, Minas Gerais 38025-440, Brazil
Alessandra da Cunha, Marcia A Michelin, Eddie FC Murta, Discipline of Gynecology, Obstetric and Discipline of Immunology, Uberaba, Minas Gerais 38025-440, Brazil
Author contributions: All authors had idealized and designed the manuscript together; Cunha A had conducted the literature review on the issue and written the manuscript; Michelin MA and Murta EFC had organized the arrangement of ideas in the written material and oriented the manuscript final correction.
Supported by FAPEMIG and CNPq
Correspondence to: Eddie FC Murta, MD, PhD, Research Oncology Institute (IPON), Federal University of the Triângulo Mineiro (UFTM), Av. Getulio Guarita, sn Bairro Abadia, Uberaba, Minas Gerais 38025-440, Brazil. eddiemurta@mednet.com.br
Telephone: +55-34-33185326 Fax: +55-34-33185342
Received: December 29, 2013 Revised: March 7, 2014
Accepted: May 29, 2014
Published online: August 10, 2014

Abstract

Breast cancer (BC) is the most common malignant neoplasm and the cause of death by cancer among women worldwide. Its development, including malignancy grade and patient prognosis, is influenced by various mutations that occur in the tumor cell and by the immune system's status, which has a direct influence on the tumor microenvironment and, consequently, on interactions with non-tumor cells involved in the immunological response. Among the immune response cells, dendritic cells (DCs) play a key role in the induction and maintenance of anti-tumor responses owing to their unique abilities for antigen cross-presentation and promotion of the activation of specific lymphocytes that target neoplasic cells. However, the tumor microenvironment can polarize DCs, transforming them into immunosuppressive regulatory DCs, a tolerogenic phenotype which limits the activity of effector T cells and supports tumor growth and progression. Various factors and signaling pathways have been implicated in the immunosuppressive functioning of DCs in cancer, and researchers are working on resolving processes that can circumvent tumor escape and developing viable therapeutic interventions to prevent or reverse the expression of immunosuppressive DCs in the tumor microenvironment. A better understanding of the pattern of DC response in patients with BC is fundamental to the development of specific therapeutic approaches to enable DCs to function properly. Various studies examining DCs immunotherapy have demonstrated its great potential for inducing immune responses to specific antigens and thereby reversing immunosuppression and related to clinical response in patients with BC. DC-based immunotherapy research has led to immense scientific advances, both in our understanding of the antitumor immune response and for the treatment of these patients.

Key words: Breast cancer; Dendritic cells; Tumor microenvironment

Core tip: Breast cancer is a worldwide major public health problem, and dendritic cells are of crucial importance for activating an effective antitumor immune response. Deepening our understanding of the tumor microenvironment can enable the development of new therapies that will make it possible to induce an efficacious antitumor response. Given the search for effective means with which to induce such a response *via* dendritic cell (DC) immunotherapy, the study of the mechanisms involved in the DC pattern of response in the tumor microenvironment is important.

Cunha A, Michelin MA, Murta EFC. Pattern response of den-

dritic cells in the tumor microenvironment and breast cancer. *World J Clin Oncol* 2014; 5(3): 495-502 Available from: URL: http://www.wjgnet.com/2218-4333/full/v5/i3/495.htm DOI: http://dx.doi.org/10.5306/wjco.v5.i3.495

INTRODUCTION

Breast cancer (BC) is the most common cancer among women and the second most prevalent form of terminal cancer in this population[1]. Cancer is characterized by accelerated and uncontrolled proliferation of normal cells due to specific genetic mutations that alter the cell cycle[2,3]. These genetic changes can culminate in the expression of mutant proteins, that in theory, should be recognized as foreign by the immune system[4]. Within the immune system, dendritic cells (DCs) play a distinct role wherein they are essential both to innate and to acquired immunity[5]. They have the unique ability for antigen cross-presentation for T helper lymphocytes ($CD4^+$) and cytotoxic T lymphocytes ($CD8^+$)[6] in secondary lymphoid organs, a process that activates a sophisticated and specific immunological response[7].

Although they perform the functions of antigen capture and processing in peripheral tissues, DCs are initially immature. They mature when interactions with Toll like Receptors (TLRs) or inflammatory cytokines convert immature DCs into mature DCs that present a specific antigen to naïve T cells, thereby activating them[8]. DCs with differing maturation stimuli upregulate the expression of the cell surface and intracellular molecules required for their journey to secondary lymphoid tissues. However, the activation and maturation of DCs depend on the local microenvironment and can be blocked or polarized by a combination of specific local factors, resulting in the formation of DCs with tolerogenic or immunosuppressive activities[9].

Various types of cells and factors present in tumor microenvironment generate a range of stimuli for DCs, that affect all aspects of their biology and thus control their functionality and longevity[10]. It's known that immunotherapy with CDs is currently being studied and used as therapy for a large variety of tumors, solid or not. We have chosen to study the mechanisms involved in the pattern of response of the CDs in the tumor microenvironment, specifically in the BC because it is considered major public health problem. The knowledge of these cells response will be the basis for developing an effective immunotherapy. In this work, we provide an up-to-date review of the pattern of DC response in the BC tumor microenvironment and the use of immunotherapy with a DC vaccine.

ROLE OF DCs IN TUMOR IMMUNITY

DCs are key regulators of immunity by B and T lymphocytes because of their superior ability to capture, process and present tumor-associated antigens[11]. They are derived from a hematopoietic line with cell subsets that differ in terms of their morphology, phenotype and function depending on the particular conditions and the tissue in which they reside. However, the various DC subsets generally have the ability to stimulate T cells[12]. DCs have different co-stimulatory molecules, such as B7, intercellular adhesion molecule 1 (ICAM-1), lymphocyte function-associated antigen-1 (LFA-1), lymphocyte function-associated antigen-3 (LFA -3) and CD40 on their cell surfaces. As a set, these proteins generate a chain of secondary signals essential to reinforcing the T cell activation, with the resultant immune response initiation, programming and regulation being directed specifically at the tumor[13].

The DC maturation process determines the presentation of processed tumor antigens and the subsequent activation of $CD4^+$ and $CD8^+$ T cells[14]. Their migration from tissues to the lymph nodes is fundamental to this process, since it provides the period during which expression levels of co-stimulatory molecules as class II MHC molecules, adhesion molecules and the C-C motif chemokine receptor (CCR7) are increased. This process is accompanied by a reduction in CCR6[15,16], which coincides with increase in the expression of particular C-C motif chemokine ligands (CCLs)-namely CCL19 (a.k.a. EBI1 ligand chemokine) and CCL21 (a.k.a. secondary lymphoid-tissue chemokine)-within the lymph nodes as well as increased CCR7 binding[17]. The expression of molecules on the DC membrane and the migration of DCs to T-cell populated areas in the lymph nodes, where drainage occurs, during this process are fundamental to specific immune response by the T lymphocytes[7,18]. Nevertheless, depending on microenvironment conditions, which involve the cells present in the tissue as well as the presence of mediators, DCs can present alternative phenotypes that are implicated directly in an immunogenic to tolerogenic change of function[19].

PROGRESSION OF BC, ITS RELATIONSHIP WITH THE TUMOR MICROENVIRONMENT AND THE PROCESS OF DC MATURATION AND ACTIVATION

If found in an early stages, BC has a good cure rate, though the metastatic or recurrent form of the disease has a poor prognosis. BC consists of a heterogeneous group of neoplasms derived from the ductal epithelium. The majority of BCs (80%) are ductal (including medullary, papillary, tubular and mucinous subtypes), and the remaining 20% are lobular cancers. The normal mammary gland consists of a layer of luminal epithelial cells, myoepithelial cells and a continuous basal membrane. The stroma contains fibroblasts, immune system cells (*e.g.*, macrophages, DCs and lymphocytes) and vasculature surrounded by the extracellular matrix and adipocytes, which maintain the structure of normal tissue[20].

The evolution of malignant breast tumors beings with

epithelial hyperproliferation and progressing to *in situ*, invasive ductal and metastatic carcinomas[21]. In *in situ* ductal carcinoma, epigenetically and phenotypically changed myoepithelial cells, which are surrounded by a basal membrane that is still mostly continuous, are incapable of contributing to the polarization and organization of normal cellular processes. In invasive ductal carcinoma, there has been a loss in the continuity of the basal membrane, loss of function of the myoepithelial cells and an invasion of the epithelial cells into the stroma and vasculature. During conversion from *in situ* to invasive carcinoma, there is an increase in the production of extracellular proteases that degrade the stromal matrix and cells[22]. Concomitantly, tumor cells in the stroma produce proteolytic enzymes; while chemokines and cytokines continue to attract leukocytes, modulate tumor remodeling, and facilitate tumor cell invasion of distant organs, leading to metastasis. Infiltrating fibroblasts and leukocytes are induced to increase the secretion of growth factors, cytokines, chemokines and matrix metalloproteinases (MMPs) which produce an immune-evasion mechanism that enables the tumor to progress and achieve angiogenesis[23].

We now know that the tumor microenvironment is the main regulator of carcinogenesis and is responsible for the course of tumor progression, including how tumors respond to various types of treatment[24,25]. The development and progression of a tumor to a malignant phenotype is highly dependent on interactions between the tumor cells and normal cells present in the tumor microenvironment[23,26]. There are extensive changes in genetic expression in all cell types during BC progression. Genetic changes detected in cancerous epithelial cells have been tied to the overexpression of particular C-X-C motif ligand (CXCL) chemokines, namely CXCL14 by myoepithelial cells and CXCL12 by myofibroblasts. These chemokines bind receptors in cancerous epithelial cells, resulting in increases in their proliferation, migration, and invasion, thus favoring tumor remodeling, as well as their ability to migrate to and induce metastasis in distant organs. Chemokines and cytokines produced by tumor cells and infiltrating cells continue to attract more leukocytes, further facilitating tumor progression[27]. Abnormal matrix remodeling in BC tumor progression is attributable to MMPs, which can also activate chemokines, cytokines, adhesion molecules, and growth factors that support tumor progression. Angiogenic factors are activated by MMPs 1, 2, 9 and 14[28].

The tumor microenvironment promotes BC initiation, growth, migration, metastasis, and therapeutic resistance. The mediators and enzymes produced can induce important genetic changes in tumor-associated cells, such as fibroblasts, endothelial cells, adipocytes, and leukocytes. These cells are critical components of the tumor stroma and can damage the microenvironment, enabling malignancy as shown in Figure 1[25]. Tumor occurrence has been shown previously to be associated with DNA methylation and histone modifications in fibroblasts[29]. We also know that germinal mutations in *BRCA1* and *BRCA2* confer increased risk of BC and ovarian cancer and reduced risk of other types of cancer; *TP53* and *PTEN* mutations are also found in BC cells[30-32]. Mature adipocytes influence tumor behavior by producing hormones, growth factors, and cytokines, as well as a heterogeneous group of molecules known as adipokines, which can change the phenotype of the epithelial cell, increasing its mobility. Interestingly, these molecules provide a link between obesity and BC risk[33,34].

The endothelial cells that form tumor neovessels are distinct from normal endothelial progenitor cells[35,36]. Under the influence of proteins in the tumor microenvironment, such as macrophage colony-stimulating factor (M-CSF), monocytes can differentiate into endothelial cells that provide angiogenesis within the tumor[37]. This process, which can also be mediated by components of the extracellular matrix (*e.g.*, fibronectin), leads to the phenomenon of monocyte-epithelial cell differentiation[38].

Tumor-associated macrophages are a major component of the leukocyte infiltrate; when activated, they exercise a tumoricidal action[39]. However, the presence of tumor-associated vascular leukocytes has been shown to be linked directly with tumor growth through increased expression of the cytokine tumor necrosis factor (TNF)-alpha[38]. Release of TNF-alpha in the tumor microenvironment promotes the differentiation of tumor-associated monocytes towards a myeloid-epithelial pro-angiogenic phenotype *via* positive regulation of the fibronectin receptor $\alpha5\beta1$.

In a study of tumors obtained from patients with invasive BC[40], we found that differences in T and B lymphocytes, in terms of peritumor/intratumor infiltrate, were related to tumor size. Specifically, small tumors ($\leqslant$ 2 cm) had relatively lower levels of intratumor B lymphocytes, whereas large tumors (2-6 cm) had relatively low levels of peritumor T lymphocytes. We know that tumor-infiltrating B cells can subserve an antibody response to breast tumors. In a study analyzing the presence of B lymphocytes ($CD20^+$) in 1470 invasive breast carcinomas, Mahmoud and colleagues documented that B lymphocytes were diffuse in areas at a marginal distance from the carcinoma (average distance, 12 cells) compared to their more dense presence within the carcinoma and in stromal compartments adjacent to the tumor. Total B-cell counts correlated with a higher tumor grade and a basal phenotype, as well as with estrogen receptor (ER)/progesterone receptor (PR) negativity[41].

Regulatory T lymphocytes (Tregs) and cytokines have also been implicated in the immune cell infiltration of tumors. Invasive BC tumors have been reported to exhibit elevated levels of intratumoral Tregs, with ER/PR negativity and HER2 overexpression being associated with an unfavorable prognosis[42]. Furthermore, enrichment of Tregs in invasive ductal carcinoma of the breast correlates with upregulation of interleukin (IL)-17A expression and augmented invasive ability[43].

In a letter to the editor about an article entitled "cancer stage and local immune response," the researcher[44]

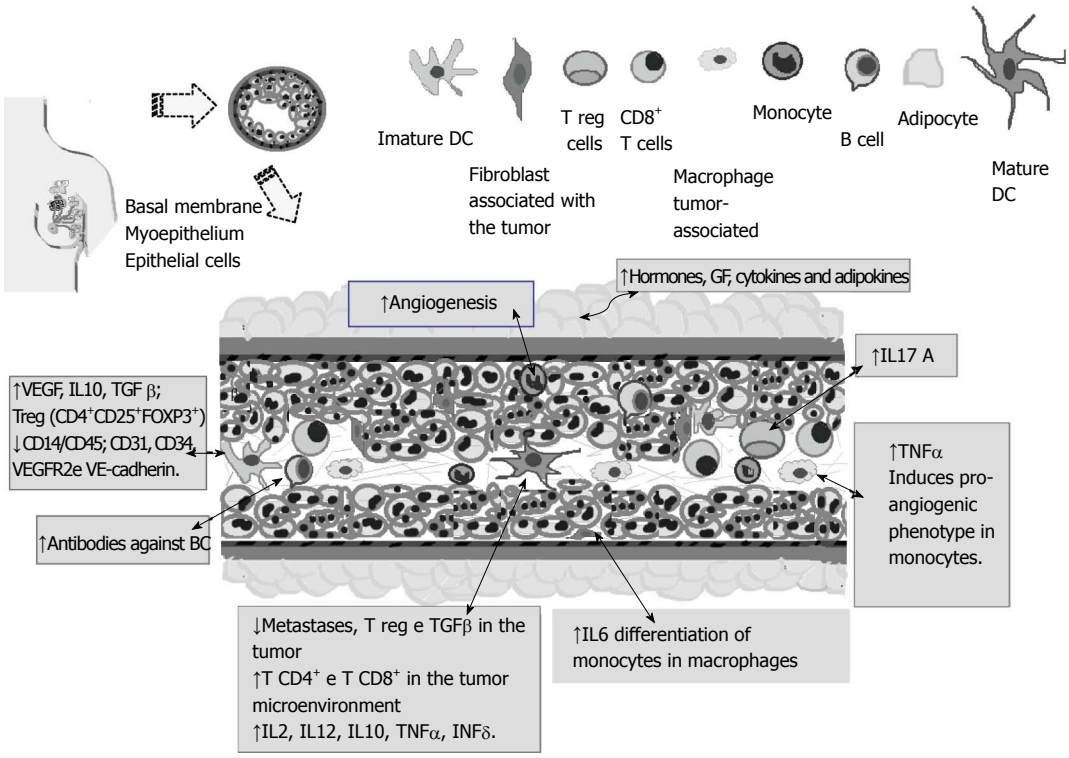

Figure 1 Changes to the tumor microenvironment seen in a mammary gland with breast cancer, consisting of a layer of luminal epithelial cells surrounded by myoepithelial cells, bordered by a continuous basal membrane, with adipocytes external to the mammary gland. In the stroma, there are tumor-associated fibroblasts immune cells surrounded by the extracellular matrix that maintains the tissue structure. In ductal carcinoma, the myoepithelial cells are changed epigenetically and phenotypically. The number of fibroblasts, monocytes and macrophages associated with the tumor are increased in the stroma, elevating secretion of growth factors, cytokines and chemokines, which promotes tumor progression. Dendritic cells (DCs) have plastic characteristics, showing distinct phenotypes depending on their mature state.

Murta reiterated and defended the idea that the BC stroma and peri-or intratumoral lymphocyte infiltrates are important to the development of and prognosis for BC and that immunotherapy for breast cancer is still under investigation. Moreover, the tumor microenvironment has innumerable escape mechanisms and ways to favor tumor progression, even using the cells themselves and mediators of the immune response in its favor.

INFLUENCE OF THE TUMOR MICROENVIRONMENT ON DENDRITIC CELLS

DCs can change their phenotype in response to tumor microenvironmental factors and contribute to angiogenesis. This cellular plasticity characteristic seems to be exploited by tumors that repress DC maturation, thereby inhibiting specific antitumor immune responses[45]. Tumors can induce the generation and accumulation of immunosuppressive cells (*e.g.*, Tregs) in the tumor microenvironment, improving tumor's ability to evade immunological defenses[42]. Tumor-associated cytokines such as vascular endothelial growth factor (VEGF), IL-10, and prostaglandin E 2 (PGE2) can affect the phenotype of DCs[46]. Liu *et al*[47] placed DCs in co-culture with isolated Lewis lung carcinoma cells to simulate the tumor microenvironment. The co-cultured DCs were induced to differentiate into regulatory DCs with a $CD11c^{low}$ $CD11b^{high}$ Ia^{low} phenotype and elevated expression of IL-10, nitric oxide, VEGF, and arginase I. These regulatory DCs inhibited T-cell proliferation both *in vitro* and *in vivo*, with PGE2 being the major inducer of arginase I in the regulatory DCs[47]. Corroborating this idea, several studies have shown that tumor-associated DCs can induce Treg expansion and become not only incapable of inducing specific immune responses but also immunosuppressive[45,48,49]. Furthermore, BC tumors have been reported to promote the differentiation of DCs into a phenotype that expresses IL-10 and tumor growth factor (TGF-beta), which, in turn, induce the expansion of Tregs ($CD4^+CD25^+FOXP3^+$)[50].

Tumor-associated DCs can produce pro-angiogenic factors in the tumor microenvironment. Rapid tumor growth factors are associated with the infiltration of immature DCs that promote angiogenesis and tumor growth, whereas mature DCs are known to suppress angiogenesis[51]. BC cell-secreted IL-6 determines whether monocytes in the tumor stroma will differentiate into DCs or macrophages. *In vitro*, activated monocytes placed in contact with fibroblasts (common in tumor stroma) induce the fibroblasts to release IL-6. IL-6 regulates the expression of M-CSF receptors in functional monocytes and enables them to become reactive to autocrine M-CSF.

Interaction between IL-6 and M-CSF favors monocyte differentiation into macrophages, rather than DCs. Like fibroblasts, Hs578T BC cells modulate monocyte differentiation into macrophages *vs* DCs depending on the presence of IL-6[52].

DCs are a specialized group of antigen-presenting cells with extraordinary functional plasticity. They have the potential to stimulate or suppress immunity, depending on the sequence and combination of microenvironmental stimuli present[12]. DCs cultivated *in vitro* in the presence of tumor factors can have some characteristics of epithelial cells, such as low-density lipoprotein absorption, leptin binding[53], and even suffer a process of endothelialization characterized by loss of CD14/CD45, loss of the endothelial markers CD31 and CD34, and loss of the von Willebrand factor, vascular endothelial growth factor receptor 2 (VEGFR-2), and vascular endothelial (VE)-cadherin[54].

By means of a literature review, Curiel[55] defends the need of a reduction in the function of Treg cells in the microenvironment tumor recurrence in patients with cancer, either individually or in combination with other therapies. According to this study the reduction may be clinically beneficial and potentially effective as an immunotherapy against cancer. In his work, he highlights other studies in which the function of Treg cells can be decreased, as an indirect effect, after the use of other immunotherapeutic agents, as the use of Denileukin diftitox (DAB389IL-2), a fusion protein of interleukin 2 (IL-2) and diphtheria toxin[56], and doses of diftitox denileukin, in combination with a recombinant vaccine poxviral can increase the immune responses in an antigen-specific normal murine model. The authors noted that Treg cells in spleen, peripheral blood and bone marrow of the animals were variously reduced after a single intraperitoneal injection of denileukin diftitox, evident reduction in 24-h effect after around 10 d. Similarly, in another study[57] examined the effects of a single dose of low dose cyclophosphamide (CTX) on immunogenicity of DC vaccines in animals with tumors of the colon and melanoma. As a result there was an increase in IFN-γ produced by lymphocytes in the spleen and significantly reduce $CD4^+$ $CD25^+FoxP3^+$ Treg cells, thus establishing a proposal for an immunotherapy strategy by combining low dose CTX with DC.

In the study[58] an antiangiogenic therapy was used in clinical trials of patients with BC through Sunitinib and Bevacizumab and demonstrated that there is a significant induction of hypoxia in the tumor microenvironment , with increased of stem cell cancer population.

MATURE DCs AND THE TUMOR MICROENVIRONMENT IN BC

As shown in Figure 1, the BC tumor microenvironment is highly immunosuppressive due to the presence of growth factors (*e.g.*, VEGF) and cytokines (*e.g.*, IL-10), and the infiltration of Tregs and immature DCs. Infiltration of mature DCs into primary tumor lesions is associated with prolonged patient survival and reduced risk of metastasis[59]. These findings reinforce the importance of DCs in antitumor immunological oversight, including the migration of DCs into regional lymph nodes where they present specific tumor antigens to naïve T cells.

In 2008, Dieu-Nosjean and colleagues reported a study[60] that indicated that the density of tumor-infiltrating lymphocytes ($CD4^+$, T-bet^+ Th1 T cells, in particular) was reduced in tumors that had weak infiltration by mature DCs. The authors interpreted the findings as indicating that the density of mature DCs was a better predictor of clinical evolution than the other parameters tested.

The therapeutic potential of mature-DC vaccines remains of great interest. Research probing the benefits of DC immunotherapy has demonstrated safety with few averse secondary effects as well as interesting results in terms of efficacy for stimulating immune cells[61,62]. Current strategies to curtail immune evasion by tumors include a combination of DC vaccination with Treg depletion by way of administration of anti-CD25 antibodies[63], and blockade of endothelin receptors in endothelial cells to facilitate the infiltration of cytotoxic T cells into the tumor microenvironment[64]. Stimulation of an immune response by DC immunotherapy has been evidenced by increases in the percentages of IL-2-, TNF-alpha-, and IL-10-expressing T-helper ($CD4^+$) cells. A similar result was observed for IL-2 expression by cytotoxic T ($CD8^+$) cells. The percentage of total T ($CD3^+$) cells remained elevated during immunotherapy. Counts of Treg ($CD25^+$/$FOXP3^+$) cells remained significantly lower than the pretreatment baseline count throughout the treatment period[65].

Vaccines made from DCs pulsed with autologous tumor lysates induced secretion of Th1 cytokines and an increase in natural killer cells and $CD8^+$ IFN-$gamma^+$ T lymphocytes in the peripheral blood of BC patients. This finding suggests that a vaccine of DCs pulsed with tumor lysates may be an effective source of tumor antigens, capable of inducing effective immune responses[66]. In another study, a vaccine of DCs pulsed with HER-2 was reported to be well-tolerated and to attenuate expression of HER-2/neu, enabling an immune response to invasive cancer to be mounted[67]. Finally, in a clinical trial, an antitumor DC vaccine administered together with IL-2 was found to induce specific cellular immunity in patients with BC that was accompanied by a reduction in TGF-beta levels, an increase in IL-12 secretion, and a reduction in $CD4^+$ $CD25^+$ T cells[68]. Based on these promising findings, we believe that DC-based therapies designed to disrupt a tumor-promoting microenvironment should be investigated with the aim of developing more powerful DC vaccines that can generate an intense and long-lasting anti-BC immune response[69].

In conclusion, growing evidence shows that the BC tumor microenvironment is immunosuppressive, at least in part through modification of DCs toward a Treg phenotype, *i.e.,* mature DCs are not functional in the tumor

microenvironment in patients with BC. DC maturation is critical for enabling specific molecular identification of BC antigens and DC vaccine immunotherapies have the potential to induce specific immunity against tumor antigens. Importantly, changes in immunological parameters that favor a specific antigen immune response, together with a reduction in immunosuppression, correlate with a positive clinical response in patients treated with a DC vaccine. Clarification of the microtumor environment, the mediators involved, interactions with immune response cells, and immune-evasive mechanisms may lead to new forms of immunotherapy.

REFERENCES

1 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]
2 **Bertram JS**. The molecular biology of cancer. *Mol Aspects Med* 2000; **21**: 167-223 [PMID: 11173079]
3 **Ueno H**, Klechevsky E, Morita R, Aspord C, Cao T, Matsui T, Di Pucchio T, Connolly J, Fay JW, Pascual V, Palucka AK, Banchereau J. Dendritic cell subsets in health and disease. *Immunol Rev* 2007; **219**: 118-142 [PMID: 17850486 DOI: 10.1111/j.1600-065X.2007.00551.x]
4 **Zitvogel L**, Apetoh L, Ghiringhelli F, André F, Tesniere A, Kroemer G. The anticancer immune response: indispensable for therapeutic success? *J Clin Invest* 2008; **118**: 1991-2001 [PMID: 18523649 DOI: 10.1172/JCI35180]
5 **de Visser KE**, Eichten A, Coussens LM. Paradoxical roles of the immune system during cancer development. *Nat Rev Cancer* 2006; **6**: 24-37 [PMID: 16397525 DOI: 10.1038/nrc1782]
6 **Steinman RM**, Banchereau J. Taking dendritic cells into medicine. *Nature* 2007; **449**: 419-426 [PMID: 17898760 DOI: 10.1038/nature06175]
7 **Banchereau J**, Briere F, Caux C, Davoust J, Lebecque S, Liu YJ, Pulendran B, Palucka K. Immunobiology of dendritic cells. *Annu Rev Immunol* 2000; **18**: 767-811 [PMID: 10837075 DOI: 10.1146/annurev.immunol.18.1.767]
8 **Mellman I**, Steinman RM. Dendritic cells: specialized and regulated antigen processing machines. *Cell* 2001; **106**: 255-258 [PMID: 11509172]
9 **Steinman RM**, Hawiger D, Nussenzweig MC. Tolerogenic dendritic cells. *Annu Rev Immunol* 2003; **21**: 685-711 [PMID: 12615891 DOI: 10.1146/annurev.immunol.21.120601.141040]
10 **Shurin MR**, Shurin GV, Lokshin A, Yurkovetsky ZR, Gutkin DW, Chatta G, Zhong H, Han B, Ferris RL. Intratumoral cytokines/chemokines/growth factors and tumor infiltrating dendritic cells: friends or enemies? *Cancer Metastasis Rev* 2006; **25**: 333-356 [PMID: 17029028]
11 **Banchereau J**, Palucka AK. Dendritic cells as therapeutic vaccines against cancer. *Nat Rev Immunol* 2005; **5**: 296-306 [PMID: 15803149 DOI: 10.1038/nri1592]
12 **Lutz MB,** Schuler G. Immature, semi-mature and fully mature dendritic cells: which signals induce tolerance or immunity? *Trends Immunol* 2002; **23**: 445-449 [PMID: 12200066]
13 **Théry C,** Amigorena S.. The cell biology of antigen presentation in dendritic cells. *Curr Opin Immunol* 2001; **13**: 45-51 [PMID: 11154916]
14 **Koido S**, Hara E, Torii A, Homma S, Toyama Y, Kawahara H, Ogawa M, Watanabe M, Yanaga K, Fujise K, Gong J, Toda G. Induction of antigen-specific CD4- and CD8-mediated T-cell responses by fusions of autologous dendritic cells and metastatic colorectal cancer cells. *Int J Cancer* 2005; **117**: 587-595 [PMID: 15945098 DOI: 10.1002/ijc.21184]
15 **Saeki H**, Moore AM, Brown MJ, Hwang ST. Cutting edge: secondary lymphoid-tissue chemokine (SLC) and CC chemokine receptor 7 (CCR7) participate in the emigration pathway of mature dendritic cells from the skin to regional lymph nodes. *J Immunol* 1999; **162**: 2472-2475 [PMID: 10072485]
16 **Randolph GJ**, Angeli V, Swartz MA. Dendritic-cell trafficking to lymph nodes through lymphatic vessels. *Nat Rev Immunol* 2005; **5**: 617-628 [PMID: 16056255]
17 **Sánchez-Sánchez N**, Riol-Blanco L, de la Rosa G, Puig-Kröger A, García-Bordas J, Martín D, Longo N, Cuadrado A, Cabañas C, Corbí AL, Sánchez-Mateos P, Rodríguez-Fernández JL. Chemokine receptor CCR7 induces intracellular signaling that inhibits apoptosis of mature dendritic cells. *Blood* 2004; **104**: 619-625 [PMID: 15059845]
18 **Kadowaki N**. Dendritic cells: a conductor of T cell differentiation. *Allergol Int* 2007; **56**: 193-199 [PMID: 17646736 DOI: 10.2332/allergolint.R-07-146]
19 **Manicassamy S**, Pulendran B. Dendritic cell control of tolerogenic responses. *Immunol Rev* 2011; **241**: 206-227 [PMID: 21488899 DOI: 10.1111/j.1600-065X.2011.01015.x]
20 **Maller O**, Martinson H, Schedin P. Extracellular matrix composition reveals complex and dynamic stromal-epithelial interactions in the mammary gland. *J Mammary Gland Biol Neoplasia* 2010; **15**: 301-318 [PMID: 20811805 DOI: 10.1007/s10911-010-9189-6]
21 **Gehler S**, Baldassarre M, Lad Y, Leight JL, Wozniak MA, Riching KM, Eliceiri KW, Weaver VM, Calderwood DA, Keely PJ. Filamin A-beta1 integrin complex tunes epithelial cell response to matrix tension. *Mol Biol Cell* 2009; **20**: 3224-3238 [PMID: 19458194]
22 **Hu M**, Yao J, Carroll DK, Weremowicz S, Chen H, Carrasco D, Richardson A, Violette S, Nikolskaya T, Nikolsky Y, Bauerlein EL, Hahn WC, Gelman RS, Allred C, Bissell MJ, Schnitt S, Polyak K. Regulation of in situ to invasive breast carcinoma transition. *Cancer Cell* 2008; **13**: 394-406 [PMID: 18455123]
23 **Artacho-Cordón A**, Artacho-Cordón F, Ríos-Arrabal S, Calvente I, Núñez MI. Tumor microenvironment and breast cancer progression: a complex scenario. *Cancer Biol Ther* 2012; **13**: 14-24 [PMID: 22336584 DOI: 10.4161/cbt.13.1.18869]
24 **Hanahan D**, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646-674 [PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013]
25 **Place AE**, Jin Huh S, Polyak K. The microenvironment in breast cancer progression: biology and implications for treatment. *Breast Cancer Res* 2011; **13**: 227 [PMID: 22078026 DOI: 10.1186/bcr2912]
26 **Allred DC**, Mohsin SK, Fuqua SA. Histological and biological evolution of human premalignant breast disease. *Endocr Relat Cancer* 2001; **8**: 47-61 [PMID: 11350726]
27 **Allinen M**, Beroukhim R, Cai L, Brennan C, Lahti-Domenici J, Huang H, Porter D, Hu M, Chin L, Richardson A, Schnitt S, Sellers WR, Polyak K. Molecular characterization of the tumor microenvironment in breast cancer. *Cancer Cell* 2004; **6**: 17-32 [PMID: 15261139 DOI: 10.1016/j.ccr.2004.06.010]
28 **Chabottaux V**, Noel A. Breast cancer progression: insights into multifaceted matrix metalloproteinases. *Clin Exp Metastasis* 2007; **24**: 647-656 [PMID: 17968664]
29 **Mao Y**, Keller ET, Garfield DH, Shen K, Wang J. Stromal cells in tumor microenvironment and breast cancer. *Cancer Metastasis Rev* 2013; **32**: 303-315 [PMID: 23114846 DOI: 10.1007/s10555-012-9415-3]
30 **Antoniou A**, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjäkoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF. Average risks of breast

and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003; **72**: 1117-1130 [PMID: 12677558 DOI: 10.1086/375033]

31 **Thompson D**, Easton D. The genetic epidemiology of breast cancer genes. *J Mammary Gland Biol Neoplasia* 2004; **9**: 221-236 [PMID: 15557796]

32 **Dite GS**, Jenkins MA, Southey MC, Hocking JS, Giles GG, McCredie MR, Venter DJ, Hopper JL. Familial risks, early-onset breast cancer, and BRCA1 and BRCA2 germline mutations. *J Natl Cancer Inst* 2003; **95**: 448-457 [PMID: 12644538 DOI: 10.1093/jnci/95.6.448]

33 **Bochet L**, Meulle A, Imbert S, Salles B, Valet P, Muller C. Cancer-associated adipocytes promotes breast tumor radioresistance. *Biochem Biophys Res Commun* 2011; **411**: 102-106 [PMID: 21712027 DOI: 10.1016/j.bbrc.2011.06.101]

34 **Carter JC**, Church FC. Mature breast adipocytes promote breast cancer cell motility. *Exp Mol Pathol* 2012; **92**: 312-317 [PMID: 22445926 DOI: 10.1016/j.yexmp]

35 **Bailey AS**, Fleming WH. Converging roads: evidence for an adult hemangioblast. *Exp Hematol* 2003; **31**: 987-993 [PMID: 14585360 DOI: 10.1016/j.exphem.2003.07.001]

36 **Djonov V**, Baum O, Burri PH. Vascular remodeling by intussusceptive angiogenesis. *Cell Tissue Res* 2003; **314**: 107-117 [PMID: 14574551]

37 **Chen H**, Campbell RA, Chang Y, Li M, Wang CS, Li J, Sanchez E, Share M, Steinberg J, Berenson A, Shalitin D, Zeng Z, Gui D, Perez-Pinera P, Berenson RJ, Said J, Bonavida B, Deuel TF, Berenson JR. Pleiotrophin produced by multiple myeloma induces transdifferentiation of monocytes into vascular endothelial cells: a novel mechanism of tumor-induced vasculogenesis. *Blood* 2009; **113**: 1992-2002 [PMID: 19060246]

38 **Li B**, Pozzi A, Young PP. TNFalpha accelerates monocyte to endothelial transdifferentiation in tumors by the induction of integrin alpha5 expression and adhesion to fibronectin. *Mol Cancer Res* 2011; **9**: 702-711 [PMID: 21536688 DOI: 10.1158/1541-7786.MCR-10-0484]

39 **Yu JL**, Rak JW. Host microenvironment in breast cancer development: inflammatory and immune cells in tumour angiogenesis and arteriogenesis. *Breast Cancer Res* 2003; **5**: 83-88 [PMID: 12631386]

40 **Menegaz RA**, Michelin MA, Etchebehere RM, Fernandes PC, Murta EF. Peri- and intratumoral T and B lymphocytic infiltration in breast cancer. *Eur J Gynaecol Oncol* 2008; **29**: 321-326 [PMID: 18714562]

41 **Mahmoud SM**, Lee AH, Paish EC, Macmillan RD, Ellis IO, Green AR. The prognostic significance of B lymphocytes in invasive carcinoma of the breast. *Breast Cancer Res Treat* 2012; **132**: 545-553 [PMID: 21671016 DOI: 10.1007/s10549-011-1620-1]

42 **Liu F**, Lang R, Zhao J, Zhang X, Pringle GA, Fan Y, Yin D, Gu F, Yao Z, Fu L. $CD8^+$ cytotoxic T cell and $FOXP3^+$ regulatory T cell infiltration in relation to breast cancer survival and molecular subtypes. *Breast Cancer Res Treat* 2011; **130**: 645-655 [PMID: 21717105]

43 **Benevides L**, Cardoso CR, Tiezzi DG, Marana HR, Andrade JM, Silva JS. Enrichment of regulatory T cells in invasive breast tumor correlates with the upregulation of IL-17A expression and invasiveness of the tumor. *Eur J Immunol* 2013; **43**: 1518-1528 [PMID: 23529839 DOI: 10.1002/eji.201242951]

44 **Murta EF**. Cancer stage and local immune response. *Immunol Lett* ; **159**: 79 [PMID: 24284374]

45 **Markiewski MM**, DeAngelis RA, Benencia F, Ricklin-Lichtsteiner SK, Koutoulaki A, Gerard C, Coukos G, Lambris JD. Modulation of the antitumor immune response by complement. *Nat Immunol* 2008; **9**: 1225-1235 [PMID: 18820683 DOI: 10.1038/ni.1655]

46 **Korkaya H**, Liu S, Wicha MS. Breast cancer stem cells, cytokine networks, and the tumor microenvironment. *J Clin Invest* 2011; **121**: 3804-3809 [PMID: 21965337 DOI: 10.1172/JCI57099]

47 **Liu Q**, Zhang C, Sun A, Zheng Y, Wang L, Cao X. Tumor-educated CD11bhighIalow regulatory dendritic cells suppress T cell response through arginase I. *J Immunol* 2009; **182**: 6207-6216 [PMID: 19414774 DOI: 10.4049/jimmunol.0803926]

48 **Curiel TJ**, Cheng P, Mottram P, Alvarez X, Moons L, Evdemon-Hogan M, Wei S, Zou L, Kryczek I, Hoyle G, Lackner A, Carmeliet P, Zou W. Dendritic cell subsets differentially regulate angiogenesis in human ovarian cancer. *Cancer Res* 2004; **64**: 5535-5538 [PMID: 15313886 DOI: 10.1158/0008-5472]

49 **Mantovani A**, Sozzani S, Locati M, Schioppa T, Saccani A, Allavena P, Sica A. Infiltration of tumours by macrophages and dendritic cells: tumour-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Novartis Found Symp* 2004; **256**: 137-145; discussion 146-148, 259-269 [PMID: 15027487 DOI: 10.1002/SERIES1767]

50 **Aspord C**, Pedroza-Gonzalez A, Gallegos M, Tindle S, Burton EC, Su D, Marches F, Banchereau J, Palucka AK. Breast cancer instructs dendritic cells to prime interleukin 13-secreting CD4+ T cells that facilitate tumor development. *J Exp Med* 2007; **204**: 1037-1047 [PMID: 17438063 DOI: 10.1084/jem.20061120]

51 **Fainaru O**, Almog N, Yung CW, Nakai K, Montoya-Zavala M, Abdollahi A, D'Amato R, Ingber DE. Tumor growth and angiogenesis are dependent on the presence of immature dendritic cells. *FASEB J* 2010; **24**: 1411-1418 [PMID: 20008545 DOI: 10.1096/fj.09-147025]

52 **Chomarat P**, Banchereau J, Davoust J, Palucka AK. IL-6 switches the differentiation of monocytes from dendritic cells to macrophages. *Nat Immunol* 2000; **1**: 510-514 [PMID: 11101873 DOI: 10.1038/82763]

53 **Gottfried E**, Kreutz M, Haffner S, Holler E, Iacobelli M, Andreesen R, Eissner G. Differentiation of human tumour-associated dendritic cells into endothelial-like cells: an alternative pathway of tumour angiogenesis. *Scand J Immunol* 2007; **65**: 329-335 [PMID: 17386023 DOI: 10.1111/j.1365-3083.2007.01903.x]

54 **Fernandez Pujol B**, Lucibello FC, Zuzarte M, Lütjens P, Müller R, Havemann K. Dendritic cells derived from peripheral monocytes express endothelial markers and in the presence of angiogenic growth factors differentiate into endothelial-like cells. *Eur J Cell Biol* 2001; **80**: 99-110 [PMID: 11211940]

55 **Curiel TJ**. Regulatory T cells and treatment of cancer. *Curr Opin Immunol* 2008; **20**: 241-246 [PMID: 18508251]

56 **Litzinger MT**, Fernando R, Curiel TJ, Grosenbach DW, Schlom J, Palena C. IL-2 immunotoxin denileukin diftitox reduces regulatory T cells and enhances vaccine-mediated T-cell immunity. *Blood* 2007; **110**: 3192-3201 [PMID: 17616639]

57 **Liu JY**, Wu Y, Zhang XS, Yang JL, Li HL, Mao YQ, Wang Y, Cheng X, Li YQ, Xia JC, Masucci M, Zeng YX. Single administration of low dose cyclophosphamide augments the antitumor effect of dendritic cell vaccine. *Cancer Immunol Immunother* 2007; **56**: 1597-1604 [PMID: 17440723]

58 **Conley SJ**, Gheordunescu E, Kakarala P, Newman B, Korkaya H, Heath AN, Clouthier SG, Wicha MS. Antiangiogenic agents increase breast cancer stem cells via the generation of tumor hypoxia. *Proc Natl Acad Sci USA* 2012; **109**: 2784-2789 [PMID: 22308314]

59 **Lotze MT**. Getting to the source: dendritic cells as therapeutic reagents for the treatment of patients with cancer. *Ann Surg* 1997; **226**: 1-5 [PMID: 9242331 DOI: 10.1200/JCO.2007.15.028]

60 **Dieu-Nosjean MC**, Antoine M, Danel C, Heudes D, Wislez M, Poulot V, Rabbe N, Laurans L, Tartour E, de Chaisemartin L, Lebecque S, Fridman WH, Cadranel J. Long-term

survival for patients with non-small-cell lung cancer with intratumoral lymphoid structures. *J Clin Oncol* 2008; **26**: 4410-4417 [PMID: 18802153 DOI: 10.1200/JCO.2007.15.0284]

61 **Barbuto JA**, Ensina LF, Neves AR, Bergami-Santos P, Leite KR, Marques R, Costa F, Martins SC, Camara-Lopes LH, Buzaid AC. Dendritic cell-tumor cell hybrid vaccination for metastatic cancer. *Cancer Immunol Immunother* 2004; **53**: 1111-1118 [PMID: 15185011]

62 **Santin AD**, Bellone S, Palmieri M, Ravaggi A, Romani C, Tassi R, Roman JJ, Burnett A, Pecorelli S, Cannon MJ. HPV16/18 E7-pulsed dendritic cell vaccination in cervical cancer patients with recurrent disease refractory to standard treatment modalities. *Gynecol Oncol* 2006; **100**: 469-478 [PMID: 16249018 DOI: 10.1016/j.ygyno.2005.09.040]

63 **Delluc S**, Hachem P, Rusakiewicz S, Gaston A, Marchiol-Fournigault C, Tourneur L, Babchia N, Fradelizi D, Regnault A, Sang KH, Chiocchia G, Buzyn A. Dramatic efficacy improvement of a DC-based vaccine against AML by CD25 T cell depletion allowing the induction of a long-lasting T cell response. *Cancer Immunol Immunother* 2009; **58**: 1669-1677 [PMID: 19225777]

64 **Buckanovich RJ**, Facciabene A, Kim S, Benencia F, Sasaroli D, Balint K, Katsaros D, O'Brien-Jenkins A, Gimotty PA, Coukos G. Endothelin B receptor mediates the endothelial barrier to T cell homing to tumors and disables immune therapy. *Nat Med* 2008; **14**: 28-36 [PMID: 18157142 DOI: 10.1038/nm1699]

65 **Rodrigues CM**, Matias BF, Murta EF, Michelin MA. The role of T lymphocytes in cancer patients undergoing immunotherapy with autologous dendritic cells. *Clin Med Insights Oncol* 2011; **5**: 107-115 [PMID: 21603246 DOI: 10.4137/CMO.S6927]

66 **Qi CJ**, Ning YL, Han YS, Min HY, Ye H, Zhu YL, Qian KQ. Autologous dendritic cell vaccine for estrogen receptor (ER)/progestin receptor (PR) double-negative breast cancer. *Cancer Immunol Immunother* 2012; **61**: 1415-1424 [PMID: 22290073]

67 **Sharma A**, Koldovsky U, Xu S, Mick R, Roses R, Fitzpatrick E, Weinstein S, Nisenbaum H, Levine BL, Fox K, Zhang P, Koski G, Czerniecki BJ. HER-2 pulsed dendritic cell vaccine can eliminate HER-2 expression and impact ductal carcinoma in situ. *Cancer* 2012; **118**: 4354-4362 [PMID: 22252842]

68 **Baek S**, Kim CS, Kim SB, Kim YM, Kwon SW, Kim Y, Kim H, Lee H. Combination therapy of renal cell carcinoma or breast cancer patients with dendritic cell vaccine and IL-2: results from a phase I/II trial. *J Transl Med* 2011; **9**: 178 [PMID: 22013914 DOI: 10.1186/1479-5876-9-178]

69 **Benencia F**, Sprague L, McGinty J, Pate M, Muccioli M. Dendritic cells the tumor microenvironment and the challenges for an effective antitumor vaccination. *J Biomed Biotechnol* 2012; **2012**: 425476 [PMID: 22505809]

P- Reviewer: Kim SB, Mazzanti R **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com