Chapter 24

Immune Regulation in Breast Cancer Metastasis and Immunotherapy

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Abstract

There are significant alterations in the tumor surrounding stromal cells in addition to the cancer cells in tumor microenvironment. Tumor cells can metastasize by acquiring the ability to escape immune control and surveillance. A decline in the ability of the immune cells to recognize and kill the tumor leads to tumor relapse or metastasis after primary treatment. Comprehensive review in this chapter will be conducted to further investigate into the mechanism of immune evasion in metastatic tumor microenvironment. The immune cells, stromal cells, extracellular matrix protein/component, and their interaction will be reviewed and summarized. Breast cancer has not been previously viewed as a particularly immunogenic type of tumor. Nevertheless, immune parameters have been increasingly studied in breast cancer, and accumulating data show that they are relevant for the development and progression of this tumor type. Consequently, immunotherapies of breast cancer are now tested in different clinical trials. The prospect of immunotherapy in metastatic breast cancer will be introduced. The importance of host-targeted modulation/therapy will be increased in addition to cancer-targeted strategies. We have to better define subpopulations of breast cancer patients to optimize the immunological way to overcome the cancer metastasis.

Keywords: oncology, breast cancer, immunotherapy, microenvironment, stroma

1. Introduction

The innate and adaptive immune responses are crucial for combating pathogen infection, repairing damaged tissue, and maintaining immune homeostasis. The immune system is composed mainly of macrophages and lymphocytes, including B-cells, CD4+ T-cells, CD8+ cells, and natural killer (NK) cells [1, 2]. The innate immune response is a nonspecific general response to infection used mainly by macrophages and natural killer cells, while the adaptive

immune system is a more developed system in which certain lymphocytes "recall" specific pathogen-antigenic patterns and alert the immune system when activated. The macrophage plays an important role in the innate immune system to help the adaptive immune system. In the lung alveoli, these macrophages phagocytize apoptotic cells and debris and digest them in lysosomes [1]. Binding of antigens presented by major histocompatibility complex (MHC-I/II) to antigen-presenting cells' (APCs') Toll-like receptors can help to avoid an autoimmune response by having a system for recognizing cells that are native to the host body. The APCs then express the MHC/antigen complex and a co-stimulatory molecule to the naïve T-cells to suppress their activation against the normal tissue cells, preventing autoimmune damage [3]. An essential factor in the adaptive immune system is the recognition of antigens. All microbes, cells, cancer cells, and other pathogens possess antigens. As explained earlier, MHC complexes present cell antigens for APCs to copy and express themselves. The APCs then present this MHC/antigen complex with a co-stimulatory molecule to activate or suppress naïve T-cells, depending on the nature of the antigens [3]. Although derived from normal cells, cancer cells have significant mutations to alter their antigenic peptide sequences and become immunogenic [4]. If the antigen can be recognized as pathogenic, the T-cells release cytokines to allow themselves to differentiate into cytotoxic phenotypes and then secrete chemokines to recruit more immune cells from the circulation. B-cells also produce complementary antibodies to help target the pathogen for destruction if its antigens are previously recognized from past infections [5]. Many of the antigen-presenting functions are dysregulated in cancer environment. Tumor cells secrete factors that induce immunological tolerance (e.g., lactic acid, indoleamine 2,3-dioxygenase (IDO), and various cytokines), recruit immunosuppressive immune cells such as M2 macrophages, alter their cell attributes to avoid recognition (e.g., by suppressing antigen presentation or becoming elusive mesenchymal-like cells), and skew immune cell function by triggering immunosuppressive pathways. Additionally, they constitutively proliferate by activating signaling pathways that promote growth (e.g., the estrogen-induced growth pathway in breast cancer). Consequently, there are many interacting factors that have to be considered in breast cancer therapy in order to better improve tumor treatment response and survival.

The tumor microenvironment consists of not only a stroma composed of fibroblasts, adipocytes, endothelial, and resident immune cells but also an insoluble extracellular matrix (ECM). The ECM itself is composed by a complex mixture of components, including proteins, glycoproteins, proteoglycans, and polysaccharides [6, 7]. Breast cancer-associated alterations in the amount and organization of extracellular components have been demonstrated in previous studies. These changes lead to tumor metastasis progression and treatment resistance through dysregulated biochemical and physical properties of tumor-associated ECM and subsequently affecting peri-tumoral stromal cells, including immune, endothelial, and other stromal cells in promoting oncogenesis (e.g., evolution of ductal carcinoma in situ to invasive disease). Although many ECM components have been identified as relevant factors in breast cancer progression, evaluation and targeting of a single molecule appears to have limited usefulness in predicting therapeutic response. This might attribute to the large number of ECM components, which, even if likely redundant, collectively contribute to distinctive physical, biochemical, and biomechanical properties of the tumor microenvironment [8]. In gene

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expression, profiles of breast cancer-associated fibroblasts identify distinct stromal patterns with prognostic implication, and the expression profiles of some extracellular matrix genes provide prognostic information of patients at risk of clinical progression and/or predictive significance for treatment efficacy. It needs to define function and composition of the distinct stromal components, and integrated by proteomic studies to compose and clarify the complex interactions between tumor cells and their surrounding microenvironment.

2. Tumor-associated immune stroma and immunosuppressive cells in the tumor microenvironment

Immune cells can functionally suppress cancer or become dysregulated with immune suppression in the tumor-associated microenvironment. Dendritic cells, macrophages, natural killer cells, regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs) all have been demonstrated to participate in the tumor-promoting microenvironment because of their functional characteristics within the tumor niche. Especially, M2-polarized macrophage populations in the tumor-associated macrophages (TAMs) promote pro-angiogenesis, immune suppression/evasion, and tumor cell migration and invasion [9]. TAMs-targeted strategy may lead to reduced angiogenesis, tumor cell invasion, and metastasis, as well as enhance the antitumor activity of chemotherapeutics [10]. Upon tumor progression, MDSCs could differentiate into dendritic cells and TAMs and lead to tumor immune suppression/evasion, extracellular matrix remodeling, and epithelial-mesenchymal transition (EMT) [11]. Dysfunctional dendritic cell activity within cancer leads to lower number of mature dendritic cells. Inefficient maturation of dendritic cell may contribute to tolerogenic effect and immunosuppression [12]. Two specific NK subpopulations have been demonstrated in tumor microenvironment: tumor-infiltrating natural killer cells (TINKs) and tumor-associated natural killer cells (TANKs) [13]. These NK subpopulations represent distinct cytokine profiles leading to enhanced angiogenesis and tumor progression [14]. Additionally, Tregs have been shown to play a crucial role in tumor progression via infiltration of tumor tissue and mitigation of the antitumor immune response [15]. Furthermore, it is reported that Tregs may enhance angiogenesis in a mouse model of ovarian cancer [16]. Taken together, this evidence suggests that contextual responses of immune cells within the tumor stroma help to modulate tumor progression. Given the complicated crosstalk between tumor cells, local endogenous stroma, and tumor-associated stroma, personalized multimodal therapeutic strategies should be developed that target not only the tumor bulk but also the tumor-associated immunosuppressive stromal compartment and associated cell-derived factors.

3. Overcoming the immunosuppression

Proper T-cell activation will require two signals regulating T-cell survival, proliferation, and/or responsiveness to antigens. The first signal is initiated by the T-cell receptor (TCR) through antigen recognition, while the second one is mediated by an interaction between receptors and

ligands of co-stimulatory and/or co-inhibitory signals, also known as immune checkpoints, in particular the B7 family [17, 18]. Under physiologic conditions, there exists a counterbalance between co-inhibitory and co-stimulatory signals, which is essential for the maintenance of self-tolerance and immune homeostasis, thereby protecting the host from unnecessary damage upon the clearance of the pathogen by the immune system [19]. In tumors following oncogenic transformation, immune inhibitory molecules are overexpressed resulting in the attenuation of adapted immune reactions and immune resistance. T-cells are able to control diverse effector responses by integrating both adaptive and innate immune mechanisms. Therefore, agonists of co-stimulatory receptors or antagonists of inhibitory receptors might enhance antigen-specific T-cell response [20]. The blockade of immune checkpoints monoclonal antibodies has been demonstrated to trigger effective antitumor responses not only in classical "immunogenic" tumor types, such as melanoma and renal cell carcinoma [21, 22], but also in many other solid cancers, such as lung [23], colorectal [24], ovarian [25], gastric [26], esophageal [27], bladder [28], and more recently breast cancer [29]. In addition to anti-CTLA4, mAbs directed against PD1 and PD-L1 are emerging as important therapeutic strategies in the treatment of cancer patients. These drugs are characterized by a better safety profile and more effective antitumor activity. PD1 is an immune inhibitory receptor mainly expressed on activated T-cells, B-cells, and monocytes, but also on Tregs. Following interaction with its ligands (i.e., PD-L1 and/or PD-L2), PD1 induces T-cell anergy, leading to immune escape [30–32]. PD-L1 is the best characterized of the two known PD1 ligands and can be expressed by tumor cells as well as by T- and B-cells, macrophages, and dendritic cells [33, 34]. Food and Drug Administration (FDA) has approved the use of anti-PD1 mAbs nivolumab and pembrolizumab in metastatic melanoma (in 2014) and non-small cell lung cancer (in 2015), while anti-PD-L1 has demonstrated similar antitumor activities and is currently in a glowing stage of development [35, 36].

In breast cancer, PD-L1 transcript expression positively correlates with that of interferon (IFN)-γ and other inflammatory genes [37] and in 12 of 41 triple-negative breast cancer (TNBC) found the same chromosomal amplification, which is associated with higher expression of PD1 ligands compared to estrogen receptor (ER)-positive or human epidermal growth factor receptor 2 (HER2)-positive breast cancer tissues [38]. The largest immunohistochemical evaluation evaluating almost 4000 breast cancer tissues detected PD-L1 expression (cutoff at 1%) in 1.7% of all tumors and in 19% of the 302 TNBC samples [39]. However, among the tumor-infiltrating lymphocytes (TILs), PD-L1 expression was present in 6% overall and in 39% of TNBCs. Luminal A and luminal B subtypes are the major breast cancer tumors. However, PD-L1 expression is rather less common in luminal subtypes given their high prevalence, they still represent a considerable proportion of PD-L1-positive tumors (i.e., 44% of all PD-L1-positive tumors in the study by Ali et al. [39]). This subgroup of luminal PD-L1-expressed patients might benefit from immunotherapy [40]. A transcriptomic meta-analysis of 5454 breast cancer tissues demonstrated a highly variable frequency of PD-L1 mRNA expression [39]. Expression was most prevalent in basal tumors, followed by HER2, and then luminal subtypes. High PD-L1 expression levels were associated with poor clinical prognostic factor such as larger tumor size, higher grade, triple negative, and higher proliferative activity [39]. Recently, PD-L1 expression was detected in circulating tumor cells (CTCs) in the blood

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of hormone receptor-positive, HER2-negative breast cancer patients [41]. Thus, PD-L1 expression of circulating tumors cells or soluble form detection can be plausible for stratification and monitoring of tumor patients undergoing immune checkpoint blockade. The influence of confounding variables is less strong in the therapeutic setting where the expression of PD-L1, which is in turn associated with the expression of ICR genes, is correlated with responsiveness to neoadjuvant breast cancer chemotherapy [42, 43]. The predictive role of PD-L1 in the metastatic setting is completely unknown.

4. Immunotherapy in breast cancer

Breast cancer has been considered as non-immunogenic tumor, and therefore immunotherapies play a limited role in breast cancer patients. In the metastatic setting, vaccination therapies have shown some signs of activity [44, 45], but results have been overall disappointing with lower objective response (OR) and clinical benefit. NeuVax, which is composed of the human epidermal growth factor receptor 2 (HER2)-derived peptide E75 (nelipepimut-S) combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) as an immunoadjuvant, appears to have clinical efficacy in early phase I/II trials [46, 47]. It is now the only breast cancer vaccine being evaluated in a phase III trial [48, 49]. Adoptive therapy with TILs is relatively active in melanoma patients [50]. However, this approach has not yet been applied in breast cancer due to the difficulty to generate sufficiently effective TIL cultures against the original tumor [51]. A phase I/IIa study in metastatic breast cancer by Domschke et al. [52] and Stefanovic et al. [53] demonstrated promising results in terms of immunological response, disease control, and survival by using bone marrow-derived tumor-reactive memory T-cells. An intriguing median overall survival (OS) of 34 months was achieved with three (20%) patients alive at last follow-up and more than 7 years after treatment. Interestingly, the survival rate correlates with the immunological response in the peripheral blood. They are now testing this approach in combination with cyclophosphamide to counteract the response to Tregs in a phase II study [54].

The first study employing checkpoint inhibitors tested the anti-CTLA4 mAb tremelimumab in combination with endocrine therapy (examestane) in metastatic ER-positive breast cancer patients. No significant clinical response was observed by treatment although 42% of patients achieved stable disease for more than 3 months [55]. The anti-CTLA4 mAb ipilimumab is now being tested in patients with earlier stage or lower tumor burden. Based on the predictive and/or prognostic role of TILs [56, 57] and immune signatures [37] in breast cancers, and in view of the encouraging activity of PD1 blockade among multiple tumors, this strategy is now actively studied in breast cancer.

In general, TNBCs have a higher density of TILs, more active expression of inflammatory-related genes, and considering that the prognostic role of TILs is more prominent in TNBC than in other subtypes, the efficacy of PD1 inhibition has so far been evaluated in this setting [58, 59]. Results from two studies assessing the anti-PD1 mAb pembrolizumab and the anti-PDL1 atezolizumab were recently presented. The pembrolizumab phase Ib KEYNOTE-012

trial recruited 32 metastatic TNBC patients, most of whom had previously received at least three lines of chemotherapy for metastatic disease [60]. Only patients with PD-L1 staining in the stroma or in ≥1% of tumor cells (evaluated by IHC) in archived samples were eligible. Satisfactory response rate of 19% was obtained with one complete and four partial responders. The atezolizumab phase Ia expansion trial enrolled 54 TNBC patients [61]. Even with previous chemotherapy heavily pretreated patients (85% had received four or more lines of chemotherapy), a similar overall response rate of 24% was reported with three partial and two complete responses in the 21 studied patients [62]. The efficacy of single-agent immunotherapy soon led to combination strategies and showed better efficacies with the combination of anti-PD1 mAb nivolumab and ipilimumab in melanoma [63]. Some combinatorial trials have been initiated to evaluate the activity of these and other anti-PD1/PD-L1 mAbs in multiple tumors, including breast cancer. These trials include combinations with co-stimulatory molecules, different checkpoint inhibitors, p53 vaccine, HER2-targeted monoclonal antibodies, histone deacetylase inhibitors, less cytotoxic chemotherapy or tyrosine kinase inhibitor (nab-paclitaxel, eribulin, PLX3397), poly I:C (a Toll-like receptor agonist), bevacizumab (an anti-angiogenic mAb), and radiotherapy [29].

5. Conclusions/perspectives

Over the last 20 years, we have learned more about the correlation of solid tumors and the immune system. By understanding the interactions has come a renaissance in cancer therapy, as immunotherapeutic interventions, which augment tumor-specific responses and inhibit the suppressive pathways maintaining cancer cells' immune privilege, have shown increasing efficacy in the clinical practice. However, despite the advancement we have made in understanding these mechanisms, we have just started to translate this knowledge into therapeutic implications.

Trastuzumab was the first antibody that could induce an antigen-specific antitumor immune response [64]. It remains to be investigated whether the main effect of trastuzumab is related to immunological mechanisms or to synergistic activity with chemotherapy [65]. Meanwhile, many antibodies have been approved for treating solid tumors including breast cancer. However, tumor-targeted antibodies represent only a small part of the immunotherapeutic strategies.

The treatment or prevention of metastatic breast cancer remains challenging. Targeting the immune checkpoint molecules in the tumor microenvironment, to modulate antitumor immune response with manageable toxicity, is an attractive and promising therapeutic strategy for breast cancer. Nevertheless, only the minority of breast cancer patients with metastatic disease has responded to an anti-PD-1 therapy (18% with the antibody pembrolizumab). Future in-depth research is urgently needed to identify the predictive biomarkers in those responders before starting the treatment. These therapies may represent the future standards of care but "one size doesn't fit all" is a dictum reflecting the wide range of immune treatments. We need to define the susceptible subpopulations (with predictive biomarkers) and to apply those treatments as monotherapy, combined with standard therapies, in a more optimized sequence of therapy, or at the optimal timing of therapy (adjuvant vs. metastatic setting).

Understanding the pathological mechanisms of different checkpoint molecules involved in cancer progression, immune-related toxicities, and the mechanisms of immunologic resistance to checkpoint modulation may further enhance the efficacy of cancer immunotherapies with its potential clinical applications.

Conflict of interest

The author declares no financial or commercial conflict of interest.

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