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Hot Topic

The immune system and hormone-receptor positive breast cancer: Is it really a dead end?

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ABSTRACT

Even if breast cancer has not been traditionally considered an immunogenic tumor, recent data suggest that immunity, and its interaction with tumor cells and tumor microenvironment, might play an important role in this malignancy, in particular in triple negative and HER2+ subtypes. As no consistent data on the potential clinical relevance of tumor infiltrating lymphocytes have been produced in hormone receptor positive (HR+) HER2− breast cancer, the interest in studying immune aspects in this subtype has become less appealing. Nevertheless, some scattered evidence indicates that immunity and inflammation may be implicated in the biology of this subtype as well. In HR+ breast cancer, the interaction between tumor cells and the immune milieu might rely on different mechanisms than in other BC subtypes, involving the modulation of the tumor microenvironment by mutual interplays of endocrine factors, pro-inflammatory status and immune cells. These subtle mechanisms may require more refined methods of evaluation, such as the assessment of tumor infiltrating lymphocytes subpopulations or gene signatures.

In this paper we aim to perform a comprehensive review of pre-clinical and clinical data on the interplay between the immune system and breast cancer in the HR+ subtype, to guide further research in the field.

Introduction

Recently, thanks to increased knowledge, to the development of immune drugs and their successful application in various neoplastic diseases, the field of oncoimmunology has gained renewed interest across multiple cancers. Indeed, the tumor-immune interface may represent a universal therapeutic target to circumvent cancer heterogeneity.

Breast cancer (BC) has not traditionally been considered an immunogenic tumor. More recently, an increasing amount of observations has revealed that the presence of tumor infiltrating lymphocytes (TILs, as evaluated on hematoxylin and eosin stained slides according to consensus guidelines), may play a prognostic [1–8] and sometimes even a predictive [2] role in particular in estrogen receptor (ER)-negative BCs.

The largest corpus of data regards triple-negative BC (TNBC), which is characterized by a high level of genetic instability and mutational load leading to generation of huge amount of neoantigens. In addition, chemotherapy can induce immunogenic cell death which increases the release of neoantigens and activates the immune system. Several data in TNBC report that the presence of high TILs is associated with a better outcome in patients diagnosed with early BC treated with neoadjuvant or adjuvant chemotherapy [1,2,5–7,9–11]. HER2-positive disease is also a highly proliferating BC subtype, characterized by an increased level of genomic instability. Moreover, the overexpression of HER2 itself acts as a tumor-associated antigen, triggering the immune system. Therefore, mechanisms of immune escape are an important prerequisite for HER2-positive tumor cells in order to escape the control by the immune system and allow tumor growth. Furthermore, anti-HER2 antibodies like trastuzumab are known to activate immunity through ADCC (antibody-dependent cell-mediated cytotoxicity) [12]. Available data in this BC subtype suggest an implication of the immune system in the modulation of prognosis and sensitivity to treatments; however, the role of TILs is more controversial than in TNBC, particularly in relation to the prediction of benefit from anti-HER2 drugs.

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To date, no consistent data on the potential clinical relevance of TILs or other immune biomarkers have been produced in the hormone receptor positive (HR+), HER2− BC. Studies that evaluated general TILs in early BC patients have failed to demonstrate any prognostic or predictive role in this subtype. Therefore, the interest in studying immune aspects in HR+ BC has become less appealing than in other subtypes. However, although scattered, some data suggest that immunity and inflammation may be somehow implicated in the biology of HR+ BC. Intuitively, the mechanisms at the basis of this possible interaction are likely to differ from those involved in TNBC and HER2+ BC. Generally, HR+/HER2− BC does not present a high proliferation rate and a high degree of genetic instability (except a subset of Luminal B tumors), therefore it is not prone to the generation of large amounts of neo-antigens. The interaction between HR+ tumor cells and the immune milieu might rely on subtler mechanisms involving the modulation of the tumor microenvironment by mutual interplays between endocrine factors, a pro-inflammatory status and immune cells. It is arguable that the methods so far applied to the study of the relation of immune system and HR+ BC in large patients cohorts have not been refined enough and that a deeper focus on the crosstalk between the immune system and HR+ BC might highlight a more complex interaction than in HER2+ and TN subtypes.

In this paper we aim to perform a comprehensive review of preclinical and clinical studies evaluating the interplay between the immune system and BC in the HR+ subtype, to guide further research in the field.

The tumor immune microenvironment and its players

The immunoediting process proceeds sequentially through three phases: elimination, equilibrium and escape [13,14]. During the elimination phase an intact immune system can detect and eventually destroy emerging transformed cells. If not all transformed cells are cleared during the elimination phase, the immune system maintains residual tumor cells in a state of dormancy (equilibrium). During this phase, the immune system sculpts tumor immunogenicity exerting a selective pressure which promotes the outgrowth of tumor cells that have acquired immune-evasive abilities. Tumor escape can occur through reduced immune recognition but may also result from the establishment of an immunosuppressive state in the tumor microenvironment.

Multiple effectors and modulators are involved in the homeostasis and balance of the tumor-directed immune response. Generally, CD8+, CD4+ Th1 (T-helper1) and NK (natural killer) cells favor a tumor-suppressive response, whereas CD4+ Th2 (T-helper 2), FOXP3+ T-reg (T-regulatory) and dendritic cells favor a pro-tumorigenic response. [15,16]. While CD8+ cytotoxic T lymphocytes constitute, together with NK cells, the primary immune effectors that eliminate cancer cells, FOXP3+ T-regs act as mediators of immune tolerance by suppressing the activation of several other immune cells, such as CD4+ and CD8+ T-cells, NK cells and antigen presenting cells (APC) [13].

Tumor associated macrophages (TAMs) arise from circulating monocytes that migrate into tumor tissues and differentiate into macrophages. The tumor immune microenvironment may guide macrophages differentiation into two major subsets usually referred as pro-inflammatory M1 type and anti-inflammatory M2 type. M2-like TAMs are capable of promoting angiogenesis and enhancing tumor metastatic potential [17–19]. The polarization of the tumor microenvironment also depends on the balance between immune-suppressive (e.g. IL6, IL10, TGFβ) and tumor-suppressive (e.g. IL-12, IFN-γ, TNFα) soluble factors. Moreover, both tumor cells and immune cells can activate immune-suppressive pathways triggered by the CTLA-4/B74 and PD-1/PD-L1 checkpoint axis, which negatively control the activation of the antitumor immune response [14].

Systemic and local inflammation in HR+ BC carcinogenesis

Some BC risk factors, such as menopause and older age, are well known for being associated with systemic inflammation characterized by increased levels of circulating pro-inflammatory cytokines [17,20]. Other BC risk factors, such as pregnancy and obesity, can promote an inflammatory microenvironment locally in the breast [17,21,22].

BC risk among post-menopausal women increases with increasing body mass index BMI [23,24]. This might be the result of an increase in serum estradiol due to an augmented production of estrogens by aromatase in the adipose tissue [25]. Moreover, obesity is characterized not only by an increase in adipose tissue, but also by an alteration of its biology. White adipose tissue from obese individuals exhibits inflammation with the presence of crown-like structures consisting of macrophages encircling necrotic adipocytes (Fig. 1) [17,26]. Some studies showed that obesity-mediated breast inflammation is associated with elevated aromatase activity, probably through an increase in cyclooxygenase 2 (COX-2) derived prostaglandin-E2 that induces CYP19 transcription. For this reason, NSAID-dependent COX-2 inhibition has been evaluated as a potential protective factor against HR+ BC in obese post-menopausal women. In this context, retrospective studies have shown encouraging results [27,28].

In addition, also some pro-inflammatory cytokines, such as TNFα and IL6, have been associated with aromatase expression [29,30]. This ultimately may enhance estrogen synthesis in the inflammated microenvironment potentially favoring the growth of HR+ BC [21,31].

Relation of inflammation and immunity with HR+ tumor aggressiveness: preclinical evidences

In addition to contributing to tumorigenesis, the tumor immune/inflammation milieu can have a number of direct effects on BC cells, promoting a more aggressive, endocrine-resistant HR + tumor phenotype.

Numerous inflammation mediators have been implicated in tumor progression and aggressiveness, such as IL6, CCL5, TGFβ and TNFα.

IL6 is a pro-inflammatory cytokine known to promote proliferation and increase invasiveness of in vitro HR+ BC cells by inducing epithelial mesenchymal transition [32]. An in vitro study revealed that BC cell lines can produce IL6 themselves, but HR+ BC cells usually secrete lower levels of IL6 than HR− BC cells. However, breast fibroblasts in the primary tumor site as well as bone mesenchymal stem cells in metastatic sites produce IL6 which may act as a paracrine stimulus on HR+ BC cells [33,34]. Immune cells can represent an additional source of IL6 [17].

Among chemokines, one of the most widely investigated for its association with BC progression is CCL5, also known as RANTES (regulated on activation, normal T cell expressed and secreted). Recently, CCL5 expression appeared to be positively associated with disease progression in a mouse model of luminal BC. The analysis of the expression of specific transcriptional factors by CD4+ TILs revealed that high tumoral CCL5 levels facilitated the polarization of CD4+ T cells toward a protumorigenic Th2 phenotype. This has been confirmed by the observation that in mice bearing the null CCL5 phenotype, Th2 polarization was dramatically decreased, overall altering tumor microenvironment balance in favor of an antitumorigenic polarization, ultimately leading to the inhibition of luminal breast tumorigenesis and metastasis [35].