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Short Communication

Infiltrated T-Cells as Prognosis Marker in Breast Cancer

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Abstract

Breast cancer is one of the most frequent causes of death in women. Several subtypes makes more difficult the diagnosis and treatments of this tumour. Such heterogeneity has made difficult to find a reliable marker useful to predict the outcomes. Lymphocytic infiltration –particularly T-cells- has proved to be valuable as prognostic factor.

Keywords: Breast Cancer; Immune Infiltrated Cells; T-Cell; Prognosis

Abbreviations

APCs: Antigen-Presenting Cells; ER: Estrogen Receptor; HER2+: Human Epidermal Growth Factor Receptor-2; HR+: Hormone Receptor Positive; PR: Progesterone Receptor; T-cell: T Lymphocyte; TIL: Tumour - Infiltrating Lymphocyte; TNBC: Triple-Negative Breast Cancer; Treg: Regulatory T Cells.

Introduction

Breast cancer is the most common and the most frequent cause of cancer death among women worldwide [1] accounting for 25% of cancer cases and 15% of cancer deaths among females [2,3]. With an increasing incidence, breast cancer constitutes one of the most expensive malignancies to treat [4], partly due to its heterogeneity –there are various subtypes with different biological behaviors and clinicopathological and molecular characteristics [5], which makes it a challenging solid tumour to diagnose and treat.

Risk factors for breast cancer include reproductive and endocrine aspects such as a long menstrual history, the use of oral contraceptives, and been nullipara, as well as other individual risk factors such as alcohol consumption, obesity, physical inactivity, and menopausal hormone therapies [6].

Therapeutic treatments for this malignancy generally include surgery, chemotherapy, radiotherapy, endocrinotherapy and molecular targeted therapy. However, despite the progresses in early diagnosis and treatments, multidrug resistance remains the main obstacle in the treatment of metastatic breast cancer and patients' survival [7].

Breast cancer can be classified into three categories: (1) hormone receptor positive (HR+) –which includes estrogen receptor (ER) and/or progesterone receptor (PR)–, (2) human epidermal growth factor receptor-2 overexpressing (HER2+), and (3) triple-negative breast cancer (TNBC) based on histological features.

The HR-positive breast cancer sub-type requires estrogen to grow, and therefore is potentially susceptible to endocrine therapy that blocks the receptors to improve the prognosis [8,9]. The HR-negative sub-type on the other hand, mostly relays on traditional chemotherapy regimens widely used as the first-line scheme [10,11]. Although initially sensitive to chemotherapy treatment [12], tumour recurrence is frequent [13], and drug resistance is believed to be one of the most common causes of tumour recurrence associated with a poor outcome, particularly for HR-negative breast cancer patients [7].

More recently, studies have divided breast cancer into four subtypes according to the combination of these categories. (1) Luminal A (ER+/PR+/HER2–, with either grade 1 or grade 2) –a subtype sensitive to endocrine therapy that has a good prognosis–; (2) Luminal B (ER+/PR+/HER2+, or ER+/PR+/HER2– with grade 3) –as-

sociated with high rate of tumour proliferation–; (3) HER2 overexpression (ER–/PR–/HER2+) –a subtype with a poor prognosis and a rapid progression–; and (4) TNBC (ER–/PR–/HER2–) –with no standard treatment available [14,15].

Such heterogeneity has made difficult to find a reliable marker useful to predict the outcomes. The infiltrate immune component in breast tumours has been used as a prognostic biomarker for treatment, particularly for radiotherapy and chemotherapy [16,17], with special emphasis in lymphocytic infiltration (TILs) as prognostic factors [18,19]. Studies has shown that the presence of CD8+ T-cells infiltrated cells in breast tumours can be linked to better prognosis in ER– and ER+/HER2+ patients, but there is no connection between these cells and prognosis in ER+ cancer patients [20-24], and results of regulatory T cells (Treg) marker are still controversial [20,23].

Growing evidence supports the fact that the immune cells in the tumour microenvironment –mainly T-lymphocytes but also B-cells, natural killer cells and antigen-presenting cells (APCs)– can promote or inhibit tumour growth, used as a prognostic indicator for breast cancer [25].

The presence of immune cells in the tumour microenvironment –most prevalent in TNBC and HER2-positive and less infiltration in the highly proliferative positive estrogen receptor (ER+) cancers– has long been considered as a good prognostic indicator for breast cancer [26].

The levels of immune infiltration, particularly TIL –both stromal lymphocytes without direct contact with cancer cells, and intratumoral lymphocytes in direct contact with tumoral cells [27]–, have a prognostic function [28,29], and are especially useful for predicting cancer-free survival in TNBC patients who received adjuvant chemotherapy [16,30].

Increased number of stromal TILs has been significantly associated with improved overall survival in patients with HER2-positive metastatic breast cancer [31], showing lower TIL values in metastasis samples [31]. Thus, the number of TILs from metastatic lesions has been reported to be lower than primary lesions [32]. However, TILs in the advanced setting will be similar to those in primary disease, in that they represent an activated T-cell response [33]. It has also been suggested that TIL cutoff value might help to define a subgroup that could be enriched for patients who respond to checkpoint blockade [34], serving as selecting factor to decide treatments.

Conclusion

Innate and adaptive immune cell are interrelated in cancer. One of the aims of immunotherapies is to reactivate T-cell in order to fight against cancer cells. However, when tumours have low TIL infiltration, immunotherapies are not very successful. Thus, the amount and composition of infiltrated cells has proved to be a reliable prognostic marker in breast cancer and might have a role in choosing treatments.

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