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Expression of E26 Transformation Specific-1 (ETS-1) in Tumor-Infiltrating Lymphocytes (TIL's) is Adverse Prognostic Factor in Invasive Breast Cancer: A Commentary

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About the Study

One of the transcription factors that have a role in breast cancer biology is E26 Transformation Specific-1 (ETS-1). It has also been shown that ETS-1 is involved in lymphoid cells activation and differentiation. We analysed its immunohistochemical expression in Tumor Infiltrating Lymphocytes (TILs) in invasive breast cancer and correlated its Immunohistochemical Score (IHS) to traditional predictive and prognostic factors in breast cancer and survival (OS, DFS). The sample contains data of 121 patients with invasive breast cancer, Not Otherwise Specified (NOS). Three representative areas of every tumor sample were chosen and arranged on a recipient paraffin block for the simultaneous analysis of multiple tissue samples (tissue microarray, TMA). In almost all patients (95%), some expression of ETS-1 in TILs was found. A moderate/high score of ETS-1 correlated with larger tumor size, higher histological grade, high proliferation index and low progesterone receptors. In the follow-up period (average 80.6 months, range 9-124 months), 31 patients died of breast cancer-related death. The patients with moderate/high ETS-1 expression in TILs had shorter OS (Kaplan-Meier) and DFS (Univariate logistic regression) than patients with weak/negative ETS-1 expression. We conclude that in invasive breast cancer, expression of ETS-1 in TILs is an adverse prognostic factor.

The microenvironment depicts the relationship between tumor cells and immune response, and every insight into stromal lymphocytes could contribute to explaining their role and activity. In the context of immunotherapy today, the interest in the tumor microenvironment, especially stromal lymphocytes has grown. There is also evidence that TILs present in breast cancer before treatment can predict response to therapy and lead to a better prognosis[1,2]. The prognostic significance of the various Tumor Infiltrating Lymphocytes (TIL) subpopulations, density, and location may vary according to tumor type and stage. In invasive breast carcinoma, there is no consensus about TILs, therefore, additional research is required in the field of TILs and the molecules they express [3-6].

One of the transcription factors that play a role in breast cancer biology is E26 Transformation Specific-1 (ETS-1), whose altered expression is found in different human tumors [7-9]. Also, many authors reported ETS-1 to be an important factor in lymphoid cells activation and differentiation, including T, B and NK cells [10-14].

The study aimed to analyse the expression of ETS-1 protein in stromal TILs in the tumor tissue of 121 breast cancer patients (NST, NOS), without further analysis of the lymphocyte subpopulation. Three representative areas from each tumor paraffin block were taken and arranged on a recipient paraffin block with predefined coordinates for the simultaneous analysis of multiple tissue samples (tissue microarray, TMA). After the immunohistochemical analysis, we correlated its Immunohistochemical Score (IHS) to traditional predictive and prognostic factors of breast cancer and survival (OS and DFS) in a 124-month follow-up period.

We found ETS-1 expression in the majority of analyzed cases (95%), and negative/weak expression in 6(5%) cases which is explained by the unique phenotypic characteristics of TILs in invasive breast cancer. The study suggests that ETS-1 is down-regulated in TILs of less aggressive tumors and activated in more aggressive and larger tumors, thus contributing to the aggressiveness of the disease. ETS-1 is an important factor in the differentiation of lymphatic cells in physiological conditions, but in TILs, the expression of ETS-1 of the wild or mutated type may have a negative effect on the immune cells and their ability to kill the tumor cells. Although TILs have been found to be mainly composed of T lymphocytes, and the majority expresses a cytotoxic effector phenotype, it is possible that the population with negative or weak expression of ETS-1 had a significantly different composition of lymphoid cells. There are reports which suggest that expression of ETS-1 is down-regulated in B cells so it is also possible that in tumors with negative or low ETS-1 expression, lymphocytic infiltration had increased number of B cells whose presence is also, according to some authors, a positive prognostic factor in breast cancer [15,16].

Conclusion

This study suggests that patients with moderate/stronger expression of ETS-1 in breast cancer TILs have shorter OS and DFS than patients with negative/weak expression. Immunohistochemical expression of ETS-1 in TILs also correlated with traditionally poor prognostic factors in breast cancer patients: older age, larger tumors, higher histological grade, negative PR and higher proliferation index. We conclude that the analysis of genes and their products of the entire TIL population, such as ETS-1, could give us important information on breast cancer biology and survival. Of course, for understanding the complete mechanism of interaction between TILs, ETS-1 and breast cancer, future studies are needed which may provide new insights into breast cancer prognosis and therapy.

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