

Tumour-infiltrating CD4 and CD8 T lymphocytes in breast cancer

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SUMMARY

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Lymphocytes are cells circulating between the blood and tissues. It has been stated that a correlation exists between immune infiltrate and breast cancer. These tumours are infiltrated by T cells, B cells, natural killer cells and macrophages. The infiltrating T cells are of helper (CD4⁺) and cytotoxic (CD8⁺) phenotypes. Specific immunity mediated by cytolytic T lymphocytes is suspected of playing an anti-cancer role. It is widely known that regional lymph nodes are an important immunological defence or "barrier" against tumour expansion. Some authors have reported that in cancer patients natural killer (NK) cells and CD8⁺ T cells are diminished in regional lymph nodes, particularly those involved by the tumour.

In the presented study the authors review current knowledge on this problem and the possibility of using successful immunotherapy with monoclonal antibodies for breast cancer.

KEY WORDS: breast cancer, CD4⁺, CD8⁺

Lymphocytes are mobile cells, continuously recirculating between the blood and tissues, returning to the blood via the lymphatic system. It has been stated that peripheral blood contains approximately 2% of all lymphocytes. The rest of these cells can be found in lymphatic organs, namely the tonsils, spleen, young thymus and, especially, lymph nodes [1].

The correlation between immune infiltrate and breast cancer has been widely investigated since the early work of Black [2]. Several studies have stated that these tumours are infiltrated by a heterogeneous population of immune cells, namely T cells, B cells, natural killer (NK) cells and macrophages [3]. Tumour infiltrating lymphocytes (TIL) are of helper (CD4⁺) and cytotoxic (CD8⁺) phenotypes, and express activation markers such as CD25 and the transferrin receptor [4]. Tumour-infiltrating lymphocytes are able to produce and release vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor, which can induce lymphangiogenesis and angiogenesis and consequently could permit the dissemination of cancer cells through lymphatics to regional lymph nodes [5]. An-

tumour effects are mediated through the induction of a CD8⁺ T cell response against a specific antigen. Cytotoxic CD8⁺ lymphocytes and NK cells bind with the Fas ligand and cause tumour cell death. TIL can interact with tumour antigen and cause direct or indirect cell lysis by releasing cytokines such as: interferon γ (INF- γ), tumour necrosis factor α (TNF- α), and granulocyte colony-stimulating factor (GM-CSF).

Functionally T cells lack antibody-dependent cellular cytotoxicity and show no or low natural killer (NK) activity [6]. A quantitative assessment of cell-mediated immunity is the measurement of subpopulations of T-helper and T-suppressor lymphocytes. Impaired cellular immunity can be associated with a depressed CD4/CD8 ratio. The exact relation between the efficacy of T cell-dependent immune mechanisms or between the extent and type of lymphocyte infiltration and tumour progression in carcinoma of the breast is a matter of debate [7,8]. This interrelation is suspected of determining the influence of the immune system on the pathogenesis and progression of breast cancer [9]. Activity of tumour-infiltrating lymphocytes is impaired

by inhibitory cytokines, increased regulatory T lymphocyte reaction, tumour cell MHC molecule alterations, and aberrant Fas ligand expression [10].

Adaptive immunity is mediated by antibodies and by CD4⁺ and CD8⁺ T cells, and it usually exploits an indirect pathway, termed cross-priming, to achieve initial recognition of cancers [11]. Specific immunity mediated by cytolytic T lymphocytes is suspected of playing an anticancer role. Nevertheless, tumours have developed various mechanisms such as downregulation, mutation, or loss of HLA class I molecules to escape from T-cell-based immune surveillance [12]. It is widely known that regional lymph nodes are capable of being an important immunological defence or “barrier” against tumour expansion [13]. Several studies have reported that removal of uninvolved lymph nodes might have a devastating effect on the immunological defence of the host against systemic metastasis or tumour recurrence [14]. Some authors have reported that in cancer patients natural killer (NK) cells and CD8⁺ T cells are diminished in regional lymph nodes, particularly in the lymph nodes with tumour involvement [15, 16]. Nodal status as determined by pathological examination of lymph nodes has been commonly shown to be the single most important predictor of survival in breast cancer [17, 18]. A direct relationship between the risk of distant recurrence and number of involved axillary nodes has been established [19]. Wong et al. [20] demonstrated that the tumour-infiltrating lymphocytes of patients with positive lymph nodes had greater tumoricidal activity.

In an analysis of the peripheral blood and axillary lymph nodes of 40 breast carcinoma patients, Whitfort et al. [15] demonstrated that while there was little difference in the overall proportions of T and B lymphocytes, there was a larger CD4⁺ helper T cell population in regional nodes that had been invaded by cancer. Rubbert et al. [16] also showed a decline of CD8⁺ T cells in regional lymph nodes, particularly in lymph nodes with cancer involvement in breast carcinoma patients. These data indicate that draining lymph nodes of cancer patients may host specific or non-specific suppression of NK cells and CD8⁺ T cells, which seems to be responsible for their

poor immunological activity. Battaglia et al. [21] tried to determine the distribution of a diverse lymphocyte population in normal human lymph nodes in comparison with corresponding peripheral blood. In their study they examined uninvolved lymph nodes in an early stage of cervical or endometrial cancer and benign diseases. The authors found that CD4⁺ lymphocytes were equally represented in both lymph nodes and peripheral blood, whereas CD8⁺ lymphocytes were much less numerous in lymph nodes. Consequently the CD4⁺/CD8⁺ ratio in lymph nodes was almost twice that of peripheral blood. Natural killer cells were <2%.

Georgiannos et al. [22] noted marked variation in intensity of the infiltrate between individual cancers of 60 examined patients with breast cancer with over 90% of tumours having a moderate or intense infiltrate. T-helper (CD4⁺) and cytotoxic T cells (CD8⁺) were found in all primary tumours, but without visible distribution dependency within individual tumours. The infiltrate changed from one that was CD4⁺ predominant to one that was cytotoxic CD8⁺ predominant. Analyzing the association between the characteristics of the immune infiltrate and established markers of prognosis they reached significance only in the intensity of the infiltrate of TIL cells and the number of positive lymph nodes and with ER (oestrogen receptor) expression, but not with PR (progesterone receptor) expression.

Dadmarz et al. [23] separated tumour infiltrating lymphocytes from breast tumours, metastatic lymph nodes and malignant pleural effusions from 34 patients with breast cancer. In addition to screening bulk TIL cultures, cells were separated into CD4⁺ and CD8⁺ subsets and extensively studied. Three CD4⁺ TIL lines were found to secrete significant amounts of GM-CSF and TNF α . In contrast to the CD4⁺ T cells, the CD8⁺ TIL cells did not secrete TNF α , but they did secrete GM-CSF when cultured with autologous tumour without presence of other stimulators. In the study of Kohrt et al. [24] percentage analysis of nodes involved by breast tumour and magnitude of CD4 and CD8 changes did not show a statistically significant relationship. These observations oppose a simple linear relationship between immune alterations and tumour

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