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Commentary

Tumour-Lymphocyte Infiltrator

Zie Liu*

Department of Medical and Surgical Pathology, West China Hospital of Sichuan University, Chengdu, Sichuan, China

DESCRIPTION

Both lymphocytic cell populations that have entered the tumour tissue are made up of tumour infiltrating lymphocytes (TILs). In a number of solid tumours, including breast cancer, TILs have been identified and are emerging as an important biomarker in the prediction of the efficacy and outcome of treatment. TILs in breast cancer consist mainly of cytotoxic T cells (CD8+) and helper T cells (CD4+) and a lower proportion of B- and NK cells. The presence of tertiary lymphoid structures in tumours was associated with large numbers of TILs, which also included follicular helper T cells (Tfh) responsible for producing lymphocytes. The loss of anti-HER2 CD4 + Th1 immune response in breast cancer patients is independently associated with disease recurrence [1]. Stratifying between patients treated with trastuzumab and chemotherapy, our laboratory observed reduced DFS in non-responsive patients with anti-HER2 Th1 relative to responsive patients. This study also noted a decreased proportion of CD4 + T-bet + IFN-γ + cells in recurrence vs. non-recurrence patients. Therefore, Th1 CD4 + TILs can influence anti-tumor immune response in breast cancer along with CD8 + TILs. The progression of breast cancer from DCIS to IDC is related to the loss of CD8+T cells, implying an emerging immune escape mechanism during cancer progression. Advanced tumours with higher infiltrates of CD8+T cells have shown better overall response rates to targeted therapies and chemotherapy, especially in the context of HER2+ and triple negative breast cancers. Increased pathological complete response (pCR) associated with high TIL density has also been seen in several clinical trials, stressing the prognostic importance of TILs as a biomarker of treatment outcome. Increased pathological complete response (pCR) associated with high TIL density has also been seen in several clinical trials, stressing the prognostic importance of TILs as a biomarker of treatment outcome [2]. Lymphodepletive host conditioning regimens are techniques to enhance TIL treatment, leading to major improvements in the length of clinical responses in patients who undergo preparatory lymphodepleting regimens prior to cell infusion. Research in human and murine melanoma models suggests multiple mechanisms by which host conditioning leads to the effectiveness of adoptive cell therapy. Lymphodepletive host conditioning, including regulatory T cells (Tregs) and myeloid-derived suppressor cells, depletes negative regulatory cells (MDSC). Peripheral blood circulating MDSCs have been reported to suppress T cell activation and proliferation in patients with glioma and melanoma. However, studies show that MDSCs present in peripheral blood can inhibit the proliferation of T cells in melanoma patients, but not in tumours. This indicates a role in inhibiting T cell responses in circulating rather than tumor-resident myeloid cells. The elimination by lymphodepletive host conditioning of peripheral MDSCs thus helps in the proliferation of T lymphocytes that are passed adoptively. Regulatory T cells characterized by CD4+CD25+FoxP3+ expression have also been extensively studied in both human and murine systems in tumour bearing hosts. In GBM, accumulation of Tregs inside the tumour bed has been well established, and their depletion in patients and tumor-bearing mice recovering from lymphopenia induced by chemotherapy correlates with increased immunity to the antitumor [3]. There is a negative association between levels of CD4+ Tregs and clinical responses in patients treated with autologous TILs during immune reconstitution in the context of TIL therapy, 56 Small numbers of Tregs in mice can abrogate successful CD8+ T cell-mediated adoptive cell therapy.

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Correspondence to: Zie Liu, Department of Medical and Surgical Pathology, West China Hospital of Sichuan University, Chengdu, Sichuan, China, E-mail: liuzie97281@141.com

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