

Circulating Tumor Cells: Determining Its Number and What It Means

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• Key terms

circulating tumor cells; cancer diagnostics; cancer therapy

WHEN Steven Paget published his theory of “seed and soil” in 1889 (1), the idea of hematogenous tumor cell dissemination was born. In many breast cancer patients, circulating cells with the characteristics of tumor cells can be identified in the peripheral blood that are known as circulating tumor cells (CTCs). These cells are present not only in patients with metastatic disease but also in those whose tumors are apparently localized (2). It has been reported that tumor cells shed into the circulation in response to microinvasive events within the tumor (3). Many of the current research works are therefore focused on the detection of CTCs in the peripheral venous blood.

Techniques used to detect CTCs can be generally divided into cytometric and nucleic acid-based approaches. Cytometric approaches use immunocytochemical methods to identify and characterize individual tumor cells. For instance, Cristofanilli et al. (4) successfully used the CellSearch System to detect CTCs. Since then, this method has been used by many other researchers on breast cancer (5,6). It was also used by the researchers in the other area. Hristov et al. (7) analyzed angiogenic monocytes and endothelial progenitor cells (EPC) for vascular homeostasis in peripheral blood by flow cytometry. Nucleic acid-based approaches detect DNA or RNA sequences that are differentially expressed in tumor cells and in normal blood components (8). In addition, other techniques have been developed to analyze CTCs. For instance, Swennenhuis et al. (9) characterized CTCs by fluorescence in situ hybridization.

The technology of multiparameter flow cytometry described by Hu et al. (10) in their report published in this issue is found interesting, because it represents a significant improvement over the technology that was used by Rehse et al. (11). In their report, Hu et al. isolated the mononucleocytes and labeled them with monoclonal antibodies anti-CD45-PerCP, Ep-CAM-PE, and Cytokeratin 8,18,19-FITC in a similar manner as used by Cristofanilli et al. (4). However, the enrichment procedure was quite different. By now, most researchers use immunomagnetic method to enrich mononucleocytes (12). This method often results in significant losses of target cells. It is expensive, and it involves multiple processes. All these have made its clinical application difficult. Hu's group demonstrated the usefulness and specificity of multiparameter flow cytometry in detecting human breast cancer cells (SKBR-3) in their report. The specificity was significantly higher compared with traditional RT-PCR analyses, and the reported high sensitivity limit of 10^{-5} is sensitive enough to detect the target cells in peripheral blood (12). Hu et al. also investigated the correlation of overall survival (OS) with the number of CTCs detected (advanced breast cancer patients: CTCs ≥ 5 ; limited breast cancer patients: CTCs < 5). The median OS was 95 weeks and 65.5 weeks for patients with CTCs < 5 and CTCs ≥ 5 , respectively. The results of the retrospective study also demonstrated that the OS was independent of clinical pathology and the tumor size but was closely correlated with CTC levels as well as age and metastasis. In addition, this article shows that multiparameter flow cytometry technique is atraumatic and could be used to detect disease progression more accurately than imaging. Together, the results presented in this study using multiparameter flow cytometry to measure CTCs show great promises for its clinical usage and may there-

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Received 21 November 2009; Accepted 4 December 2009

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Published online 23 December 2009 in Wiley InterScience
(www.interscience.wiley.com)

DOI: 10.1002/cyto.a.20842

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fore provide a novel approach of great value to those who are in the areas of cancer diagnostics and/or cancer therapy evaluations.

Very recently, Goodale et al. (13) used flow cytometry method to assess monocyte activation markers and circulating endothelial cells in patients with localized or metastatic breast cancer. EPCs were successfully used as “Trojan horses” in an antiangiogenic gene therapy-mediated anticancer strategy for certain types of malignancies (14). On the basis of its advantages revealed in Hu’s report, multiparameter flow cytometry may be used in the future to detect the metastasis, help to choose the appropriate therapy for patients at different stages and evaluate the prognosis. It is believed that detecting CTCs in breast cancer patients by using multiparameter flow cytometry has a huge potential to become a valuable tool in clinic.

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