

Longtime Recirculating Tumor Cells in Breast Cancer Patients

To the Editor: In their article (Clin Cancer Res 2004;10, 8152–62), Meng et al. report on the detection of circulating tumor cells in blood of breast cancer patients even in long-term remission. In a somewhat different approach (1),¹ using only RBC lysis and no other enrichment apart from a single step of centrifugation, we detect considerable numbers of circulating epithelial cells in 92% of patients with breast or lung cancer and none in 97% of normal controls. Among 16 patients with complete continuous remission, 13 had detectable numbers of circulating epithelial cells which were significantly lower ($P = 0.005$) than in patients with metastatic disease. Meng et al. speculate that, due to the rapid turnover of circulating tumor cells with a half-life of 1 to 2.5 hours after surgery of the primary tumor, there must be remote tumors, feeding these cells into the circulation. In breast cancer patients, we observe an up to 1,000-fold increase in epithelial cells during the first 3 days after surgery (Fig. 1; 2 out of the now >50 cases). A considerable part of these cells then disappears after another 2 to 4 days, consistent with a rapid turnover of these initially appearing cells. Subsequently, however, the number of epithelial cells remains stable over long periods of time (>1 year, as shown below). The same is true for remnant circulating epithelial cells after completion of adjuvant therapy and after completion of neoadjuvant therapy and surgery (Fig. 2). Others have shown (3) that dormant tumor cells can be long-lived. This agrees with our observations that the number of circulating cells remains at identically high levels for long times without any indication of relapse in the absence of additional

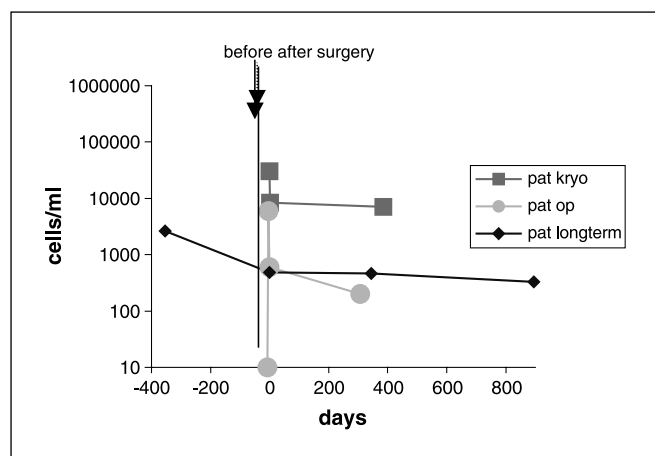


Fig. 1. Epithelial cells 3 days after surgery.

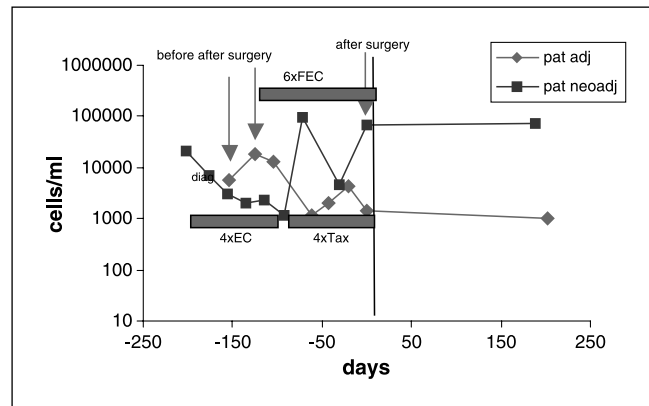


Fig. 2. Circulating epithelial cells after completion of adjuvant therapy and after completion of neoadjuvant therapy and surgery.

interventions. We therefore favor the hypothesis that part of the tumor cells detected in the blood belong to a population of resting, longtime recirculating dormant breast cancer (stem) cells.

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In Response: We are pleased that experienced investigators like Dr. Pachmann are interested in tumor dormancy, a relatively neglected field. Her provocative hypothesis is that breast cancer dormancy is caused by long-lived breast cancer stem cells. We agree that stem cells may play a major role but neither Pachmann nor ourselves have definitive evidence about this issue. The disagreement is whether circulating tumor cells (CTCs) in dormancy are derived from replicating tumor cells in the tissues or whether CTCs are long lived. Her results indicating maintenance of a high level of epithelial cells in clinically tumor-free patients does not distinguish between our “balance” conclusion and her hypothesis. Our conclusion that replication and cell death are balanced arises from the following evidence: (a) Epithelial cells detached from their underlying stroma and neighboring cells enter an apoptotic program (1). (b) The

¹Pachmann et al., submitted for publication.

half-life of CTCs in patients after mastectomy is 1 to 2.4 hours. Hence, CTCs are not exempt from the rapid turnover of normal epithelial cells. (c) CTCs released from breast carcinomas have distorted nuclei, shrink in size if incubated, and, occasionally, display classical apoptotic features. (d) Patients can have CTCs as long as 22 years after mastectomy. This period of time for circulation of long-lived CTCs appears unlikely. (e) In a mouse lymphoma model of dormancy, we proved that there was a balance between replication and cell death of lymphoma cells in the spleen, the major organ site of the tumor (2). However, in human breast cancer dormancy, we lack the formal proof necessary to exclude Pachmann's alternative hypothesis.

However, her studies raise significant questions. The enormous numbers of epithelial cells observed in the blood of breast cancer patients 6 months after surgery (as many as 7×10^4 CTCs/ml blood) is several logs more than any other researcher has reported even in actively growing breast cancer. In our studies of dormancy patients, we used cytomorphology, immunophenotype and aneusomy to unambiguously identify the malignant nature of the epithelial cells. Pachmann presents no proof that the observed epithelial cells are malignant tumor cells (TCs). Therefore, it is possible that almost all of these cells are hematopoietic in origin. Pachmann also refers to a mouse model in which solitary TCs persisting in tissue were shown to be resistant to chemotherapy presumably because they were not dividing (3). Their persistence may not represent the population of TCs that retains the capacity to cause a relapse in patients with cancer dormancy.

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References

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