Circulating tumor cells as emerging tumor biomarkers in lung cancer

Edward H. Cho

BioNano Genomics, Inc., San Diego, CA 92121, USA

J Thorac Dis 2012;4(5):444-445. DOI: 10.3978/j.issn.2072-1439.2012.08.13

Enumeration of circulating tumor cells (CTCs) has been shown to correlate with poor progression free survival (PFS) and overall survival (OS) in breast, colorectal, and prostate cancers. In lung cancer, there is a large need for more and multiple tumor biomarkers that will allow monitoring of patient progress over the course of therapy. Studies have suggested that the primary treatment for lung cancer, surgery, can lead to an increase of CTCs (1,2). This may lead to a different sort of residual disease even in successful cases of full tumor resection. In CTC studies involving lung cancer, CTC enumeration as a method to monitor patient progress has not been as convincing because CTCs were not found in many study patients, and those patients with CTCs had numbers far lower than other cancer types (3-5). In order for CTCs to become a useful biomarker for lung cancer, there is a need to look beyond enumeration and an understanding of the molecular characteristics of the CTCs and their similarities and differences from their tumor of origin. The ability to quickly define a patient's disease based on molecular signatures as well as identify whether a patient is responding to therapy is potentially a powerful clinical tool for a fast-acting disease.

Initially, various studies demonstrated a correlation between enumerating CTCs from patient blood and worse PFS and OS in breast cancer (6,7). Increasingly, reports of CTC aggregates, or circulating tumor microemboli (CTM), suggest that the increased incidence of venous thromboembolism (VTE) and pulmonary embolism (PE) in cancer patients may be the result of CTMs (8). Again, the correlation between CTM enumeration and patient incidence of VTE/PE is very loose. It is vital to understand if both CTCs and CTMs play a role in metastasis, or if one population correlates significantly with increased morbidity and/or mortality in lung cancer patients more than the other. Studies trying to address this question were performed on late stage cancer patients. This only elucidates a partial portrait of the role of CTCs and CTMs in cancer. To truly understand and deconvolve whether CTCs, CTMs, or both populations are more aggressive will require increased effort on studying early stage patients and following them long-term.

Prevention and early detection have consistently been shown as the best defense against any cancer. The ability to reliably detect and characterize CTCs in healthy patients may avail this early detection that has been so allusive in lung cancer. Other methods for early detection in lung cancer, such as sputum analysis, are promising but the technologies are still underdeveloped. Using CTCs over the course of treatment can be very powerful; however, we have yet to understand what changes in CTC enumeration actually indicates for lung cancer patients. The discovery of several lung cancer associated genetic mutations and structural variations have been identified and may prove to be promising targets for treatment (9). Identifying which patients possess these mutations is not always straight-forward, as lung biopsy material is not always the easiest to obtain. But if CTCs could be obtained from these patients and probed for these mutations, then classifying these patients into molecularly-defined treatment programs would become much more straight-forward. The ability to non-invasively probe and monitor patients throughout the course of the disease can be a powerful tool both for the patient and to the research community to understand the natural and molecular progression of the disease.

Mathematical, computational, and physical measurements modeling how CTCs and CTMs are able to form and traverse the circulatory systems will become extremely important as those will be difficult questions to solve experimentally *in vivo* (10,11). A multi-disciplinary approach to investigate the important questions of cancer biology, including CTCs, has been a major effort by multiple funding agencies including the National Cancer Institute. Verifying these models experimentally will be imperative so we can fully understand the complex variables involved CTC biology and ensure that the models are accurate. Advancements in imaging and image processing techniques will also be vital in understand the molecular and physical characteristics of CTCs and CTMs. The current understanding of CTCs is limited by our molecular vocabulary that has been established through cell line experiments. It becomes increasingly

Corresponding to: Edward H. Cho. BioNano Genomics, Inc., San Diego, CA 92121, USA. Email: echo@bionanogenomics.com.

Submitted Jul 20, 2012. Accepted for publication Aug 21, 2012.
Available at www.jthoracdis.com

ISSN: 2072-1439

important, then, to be able to build up this molecular vocabulary from patient CTCs utilizing multiple downstream parameters, such as genomic structural variation and protein expression, as well as differences in cellular measurements to begin translating between the dialects of cancer cell line biology and patient CTC biology (8,12). Biochemical and cell biological techniques such as PCR/RT-PCR, genetic analysis, and immunocytochemistry will need to evolve to accurately assess very small amounts of biological material, even down to single cell resolution.

There are still several vital questions that are left unanswered surrounding investigation of CTCs. First, are these indeed the seeds for metastasis? Although, logically, it would seem to be a very direct connection, it is important not to obfuscate theory for empirical data. Is the existence of CTCs enough, or are further assays needed to determine if CTCs remain viable during transport? Does filtering these cells out of the blood increase patient survival? Or is it too late already because they already exist? It's commonly believed that even very small, non-palpable, tumors can shed millions of cells into the bloodstream daily. These questions and others surrounding the basic biology of CTCs must be addressed rigorously in order to substantiate the validity of CTC assays.

As CTC biology matures, cautious, more thorough investigation is needed to truly understand the utility of CTCs as tumor biomarkers for lung cancer. CTC enumeration alone may not ultimately become the biomarkers the cancer community has been looking for, but the ability to molecularly characterize CTCs from cancer patients holds much potential for the future of personalized medicine. The future utility of CTCs as tumor biomarkers for lung cancer relies heavily on the ability to sensitively and specifically capture and accurately identify these cells in patients and on the downstream assays that can be used to molecularly define these potential windows into patient tumors.

Acknowledgements

Disclosure: The author declares no conflict of interest.

Cite this article as: Cho EH. Circulating tumor cells as emerging tumor biomarkers in lung cancer. J Thorac Dis 2012;4(5):444-445. DOI: 10.3978/j.issn.2072-1439.2012.08.13

References

1. Goldfarb Y, Ben-Eliyahu S. Surgery as a risk factor for breast cancer recurrence and metastasis: mediating mechanisms and clinical prophylactic approaches. Breast Dis 2006-2007;26:99-114.
2. Momma T, Hamblin MR, Wu HC, et al. Photodynamic therapy of orthotopic prostate cancer with benzoporphyrin derivative: local control and distant metastasis. Cancer Res 1998;58:5425-31.
3. Wendel M, Bazhenova L, Boshuizen R, et al. Fluid biopsy for circulating tumor cell identification in patients with early-and late-stage non-small cell lung cancer: a glimpse into lung cancer biology. Phys Biol 2012;9:016005.
4. Nieva J, Wendel M, Luttgen MS, et al. High-definition imaging of circulating tumor cells and associated cellular events in non-small cell lung cancer patients: a longitudinal analysis. Phys Biol 2012;9:016004.
5. Marrinucci D, Bethel K, Kolatkar A, et al. Fluid biopsy in patients with metastatic prostate, pancreatic and breast cancers. Phys Biol 2012;9:016003.
6. Cristofanilli M, Hayes DF, Budd GT, et al. Circulating tumor cells: a novel prognostic factor for newly diagnosed metastatic breast cancer. J Clin Oncol 2005;23:1420-30.
7. Cristofanilli M, Broglio KR, Guarneri V, et al. Circulating tumor cells in metastatic breast cancer: biologic staging beyond tumor burden. Clin Breast Cancer 2007;7:471-9.
8. Cho EH, Wendel M, Luttgen M, et al. Characterization of circulating tumor cell aggregates identified in patients with epithelial tumors. Phys Biol 2012;9:016001.
9. Schmid K, Oehl N, Wrba F, et al. EGFR/KRAS/BRAF mutations in primary lung adenocarcinomas and corresponding locoregional lymph node metastases. Clin Cancer Res 2009;15:4554-60.
10. Newton PK, Mason J, Bethel K, et al. A stochastic Markov chain model to describe lung cancer growth and metastasis. PLoS One 2012;7:e34637.
11. Phillips KG, Velasco CR, Li J, et al. Optical Quantification of Cellular Mass, Volume, and Density of Circulating Tumor Cells Identified in an Ovarian Cancer Patient. Front Oncol 2012;2:72.
12. Lazar DC, Cho EH, Luttgen MS, et al. Cytometric comparisons between circulating tumor cells from prostate cancer patients and the prostate-tumor-derived LNCaP cell line. Phys Biol 2012;9:016002.