Circulating tumor-derived biomarkers in lung cancer

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The NIH Biomarkers Definition Working Group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" (1). In lung cancer, an enormous research effort is underway related to biomarkers in airway epithelial cells, sputum, breath, urine and blood for early diagnosis or prediction of high risk. Here, we will focus on blood as the source of biomarker research and in particular comment on circulating tumor cells (CTCs) and circulating nucleic acids.

Dissemination of tumor cells via the blood circulation is a key step in the progression of solid tumors including lung cancer. While small-cell lung cancer (SCLC) is considered as a systemic disease at the time of diagnosis, non-small cell lung cancer (NSCLC) (if detected at early stages) appears to be a localized disease, which, however, has a high potential to spread to distant organs such as bone marrow, brain and liver. Previous studies using cytokeratins for the detection of disseminated tumor cells in the bone marrow have shown that tumor cell dissemination and homing to bone marrow is frequent in NSCLC patients with no clinical or imaging signs of overt metastases and even detectable in stage I patients (2).

Thus, blood-borne dissemination of tumor cells is an early event in both SCLC and NSCLC. However, bone marrow sampling is an invasive procedure and bloodborne dissemination of tumor cells can be more easily assessed by sampling of peripheral blood. Blood serum/plasma samples are easy to collect and to store in biobanks for many years.

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CTCs can now be detected in the peripheral blood at the single cell level using sensitive methods for enrichment and detection (3). Most CTC studies on lung cancer have been conducted with the CellSearch® system, the Isolation by Size of Epithelial Tumour Cells (ISET) filter device, or CTC chips. Both, the CellSearch® system and the CTC-chips, use the epithelial cell specific adhesion molecule EpCAM for CTC capture (4). The CTC detection rate with the CellSearch® system ranges from 23-85% of patients with NSCLC depending on the disease stage with 0-17% of stage I and II patients showing >2 CTCs (5,6). In general, the number of CTCs detected with this system was low in NSCLC (e.g., only 25% had 3 or more CTCs/7.5 mL blood in stage IV patients), whereas the CTC count in SCLC patients was significantly higher ranging from 60-86% of patients with limited or extensive disease states with more than 3 CTCs/7.5 mL blood (7,8). This led to the hypothesis that a substantial fraction of CTCs in NSCLC patients may have undergone an epithelial-mesenchymal transition (EMT), which is associated with the downregulation of the expression of epithelial marker proteins such as EpCAM. These (semi)-mesenchymal CTCs are missed by EpCAM-dependent CTC assays such as the CellSearch® system. Therefore, EpCAM-independent technologies might have a higher sensitivity for the detection of CTCs in NSCLC patients. This assumption is supported by the results obtained with the ISET filter technology; CTCs were already detected in approximately 37% of stage I/II patients and in more than 80% of stage III/IV patients (9). In addition, clusters of CTCs (and other cell types) called CTM (CTC microemboli) were captured with the filter device (9,10). CTMs are heterogeneous in their cellular composition and their biological significance remains subject of future investigations.

Besides CTC analysis, the detection/characterization of tumor derived cell-free nucleic acids (cfNA) such as DNA and microRNA (miR), which are released into the blood by necrotic/apoptotic tumor cells and by viable tumor cells via packaging into exosomes, has gained considerable attention over the past years. Depending on the disease stage cfNA can

be derived from the primary tumor and/or (micro) metastases and/or even CTCs (11). As cfNA harbor tumor-specific aberrations this might represent a complementary approach to unravel genomic aberrations relevant to the screening for lung cancer (12). Moreover, recent studies in lung cancer have shown that mutations in targets (e.g., EGF receptor) or genes of important pathways (e.g., KRAS) can be revealed on cfNA and this information may guide targeted therapy in the future (13).

More recently, circulating miRs (i.e., small noncoding RNAs with multiple regulatory functions) have gained attention as additional blood-based biomarkers. In lung cancer, various circulating miRs are increased or decreased as compared to healthy individuals or patients with benign lung diseases (14). E.g., Roth *et al.* reported that the levels of miR10b, miR141 and miR155 were significantly higher in lung cancer patients than those in patients with benign disease (15). These changes may reflect tumor-associated pathophysiological processes relevant to the development and progression of lung cancer. To further validate the clinical utility of circulating miRs as promising biomarkers in lung cancer, large-scale prospective studies are needed.

The detection and molecular characterization of CTCs and cfNA is currently one of the most active areas of translational cancer research. Aims of research on CTCs and cfNA as biomarker include: (I) screening for lung cancer, (II) estimation of the risk for metastatic relapse or metastatic progression, (III) stratification and real-time monitoring of therapies and (IV) identification of therapeutic targets and resistance mechanisms. In lung cancer, a considerable number of promising studies on these blood-based biomarkers have been reported during recent years. These biomarkers have to be validated in multi-centre clinical studies with defined end points such as disease-free or overall survival.

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