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Liquid biopsy: A new diagnostic concept in oncology

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"Liquid biopsy" was introduced as a new diagnostic concept in 2010 (1) for the analysis of circulating tumor cells (CTCs) and has been now extended to material (in particular DNA) released by tumor cells in the peripheral blood of cancer patients (2, 3). Over the past decade, various methods have been developed to detect CTCs and ctDNA in the peripheral blood of cancer patients (3, 4). While reliable information can be easily obtained in patients with advanced disease, early stage cancer patients usually present with very low concentrations of CTCs and ctDNA. At present, most CTC assays rely on epithelial markers and the majority of CTCs detected are single isolated cells. The clinical relevance of 'mesenchymal' CTCs lacking any epithelial markers as well as CTC clusters are still under investigation. Although most published studies have been performed on patients with carcinomas and melanomas, CTCs have been also detected in the peripheral blood of patients with primary brain tumors (glioblastomas) despite the blood-brain barrier (5). Liquid biopsy assays are currently being validated for early detection of cancer, which is supposed to reduce cancer related mortality. Despite remarkable progress, liquid biopsy-based detection of early stages of cancer remains a challenge, in particular in breast cancer. New blood-based biomarkers for early detection currently validated in clinical trials include miRNAs, exosomes and tumor-educated platelets.

In patients with diagnosed cancer, CTCs and ctDNA analyses can obtain independent information on prognosis in early and advanced stages of disease. In particular, CTC counts at initial diagnosis are able to refine the current risk stratification by TNM staging in early stage breast cancer. Moreover, early detection of relapse by sequential ctDNA (or CTCs) analysis of blood samples obtained post-surgery during the follow up is possible and may be used in future trials to stratify patients to "post-adjuvant" therapies (6).

Another key application of liquid biopsy is to identify therapeutic targets or mechanisms of resistance of metastatic cells in individual patients6. While the analysis of ctDNA focuses on mutations relevant for cancer therapy (e.g., EGFR, KRAS or ESR1 mutations), CTCs offer a wide spectrum of analyses at the DNA, RNA and protein levels (2, 3). Metastatic cells might have unique characteristics that can differ from the bulk of cancer cells in the primary tumor currently used for stratification of patients to systemic therapy. Moreover, monitoring of CTCs and ctDNA before, during and after systemic therapy (e.g., chemotherapy, hormonal therapy, antibody therapy) might provide unique information for the future clinical management of the individual cancer patient and might serve as surrogate marker for response to therapy. In the context of recent success in antibody-mediated blockade of immune checkpoint control molecules, expression of the PD-L1 on

CTCs might be of interest as potential predictive marker. Moreover, the expression of androgen receptor variant 7 in CTCs may predict resistance to anti-androgen therapy in prostate cancer, while mutations in the estrogen receptor gene (ESR1) provides information on resistance to hormone therapy in breast cancer. Additional therapeutic targets detected on CTCs in cancer patients include the estrogen receptor and HER-2 oncogene (3). Single cell RNAseq analysis of CTCs may provide more comprehensive information on relevant pathways.

For functional analysis of CTCs, the development of in vitro and in vivo test systems has started, which might also serve as models for drug testing. In particular, the development of cell lines and xenografts derived from CTCs can provide novel insights into the biology of tumor cell dissemination and may be used to discover new pathways to target specifically metastatic cells.

Besides CTCs and ctDNA the analysis of circulating microRNAs, exosomes or tumor-educated platelets may provide complementary information as "liquid biopsy". E.g., the integrin composition of exosomes seems to determine the organ site of metastatic niches and the RNA expression pattern of blood platelets reveals information on tumors in cancer patients.

Sensitive methods have been also developed to capture disseminated tumor cells (DTCs) in the bone marrow in cancer patients (6), which provide new insights into the process of "cancer dormancy". The nature of dormant breast cancer cells and the mechanisms leading to their outgrowth are poorly understood. Efforts to unravel the nature of cancer dormancy have been hampered by the lack of sensitive methods to detect dormant cells in cancer patients. The development of novel therapies designed to kill dormant residual tumor cells, or maintain them in a quiescent state, represents a highly attractive approach to prevent late recurrence. Such an approach, however, would require a far more detailed understanding of tumor dormancy and recurrence than exists today, as well as biomarkers to enable monitoring of this process and predict recurrence. Analysis of DTCs leads to the discovery of new molecules relevant to the biology of metastasis such as the putative metastasis-suppressor RAI2 (7).

In conclusion, liquid biopsy analysis can be used to obtain new insights into metastasis biology, and as companion diagnostics to improve the stratification of therapies and to obtain insights into therapy-induced selection of cancer cells. Different approaches such as CTC or ctDNA analysis will provide complementary information. Technical and clinical assay validation is very important and can be achieved in international consortia such as the European IMI Cancer-ID network (www.cancer-id.eu).

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