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Liquid biopsies for solid tumors: Understanding tumor heterogeneity and real time monitoring of early resistance to targeted therapies

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ABSTRACT

In the era of personalized medicine detection of the molecular drivers of tumors and of specific DNA mutations predicting response or resistance to targeted agents has become routine practice in clinical oncology. The tumor biopsy depicts only a single timeframe from a single site, and might be inadequate to characterize a tumor because of intratumoral and intermetastatic heterogeneity. Circulating tumor DNA offers a "real time" tool for serially monitoring tumor genomes in a non-invasive manner providing accessible genetic biomarkers for cancer diagnosis, prognosis, and response to therapy. The liquid biopsy can be used for a variety of clinical and investigational applications. Future development will have to provide a cost effective analysis mainly identifying the genes known to be recurrently mutated in each tumor. Therefore, developing standardized methodologies for DNA analyses and validation in large prospective clinical studies is mandatory to implement the 'liquid biopsy' approach in the clinical management of cancer patients. In our review, we will focus on the clinical applications of liquid biopsies and on the recent findings in this field.

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Contents

1. Introduction

The spread of personalized medicine for cancer patients relies on the recognition of the molecular drivers of the disease. This approach aims at improving the clinical outcome by giving patients drugs tailored to the genomic makeup of their tumor. Biomarkers predicting therapy response are frequently evaluated on tumor biopsy samples. However, the biopsy depicts only a snapshot from a single metastatic site in a given moment. Therefore, it might be inadequate to characterize a tumor because of intratumoral and intermetastatic heterogeneity. Tumor heterogeneity is described in both 'space and time' (Swanton, 2012) — with anatomically different areas of the same primary tumor and metastases showing different genomic profiles (Gerlinger et al, 2012). Therefore, more comprehensive tumor genome information is needed to provide an accurate portrait of the whole tumor than those that can be offered by a single biopsy. Moreover, acquired drug resistance to targeted agents is common during the course of the disease, thus there is an urgent need to monitor tumor evolution and ideally predict the onset of resistance to targeted therapies. Circulating tumor DNA (ctDNA) offers a unique opportunity for serially monitoring tumor genomes in a non-invasive manner. As ctDNA is a potential surrogate for

Abbreviations: ctDNA, circulating tumor DNA; MPS, massive parallel sequencing; MRD, minimal residual disease; NGS, Next Generation Sequencing; PCR, polymerase chain reaction.

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the tumor itself, it is often referred to as 'liquid biopsy'. In our review, we focus on the clinical applications of liquid biopsies and on the recent findings in this field.

2. Biology of circulating tumor DNA

Data available about the origin, mechanism, and release of ctDNA in the circulation, are often conflicting. Some seem to derive from nucleated blood cells while some others seem to origin from the apoptosis and necrosis of cancer cells in the tumor microenvironment (Stroun et al., 2000). According to other data, ctDNA could derive from the lyses of circulating cancer cells or micrometastases shed by the tumor (Stroun et al., 2000). Also, it has been supposed that the tumor actively releases DNA into the bloodstream (Stroun et al., 2000). The amount of ctDNA deriving from tumor cells changes owing to the size and the state of the tumor. The proportion of ctDNA is also influenced by clearance, degradation and other physiological filtering events of the blood and lymphatic circulation (Schwarzenbach et al., 2011). The levels of ctDNA might also reflect physiological and pathological processes that are not tumor-specific. In addition, increased levels of ctDNA may be found in patients with benign lesions, inflammatory diseases and tissue trauma (Diehl et al., 2006). However, the concentration of ctDNA in the serum of cancer patients is about 4 times that of healthy controls (Shapiro et al., 1983). The amount of DNA released from dead cancer cells varies between small fragments of 70 to 200 base pairs and large fragments of about 21 kb and it is longer than that of non-neoplastic DNA (Jahr et al., 2001). The presence of specific somatic mutations allows to discriminate ctDNA from normal circulating cell free DNA. These mutations are detectable only in the genome of cancer cells and not in the DNA of normal cells of the same individual. Highly sensitive technologies allow the detection of small amount of tumor DNA within the large substratum of normal circulating DNA, thus making feasible the clinical application of ctDNA characterization.

Techniques like digital polymerase chain reaction (PCR) (Taly et al., 2012), beads, emulsion, amplification, and magnetics (BEAMing) (Diehl et al., 2006),tagged-amplicon deep sequencing (TAM-seq) (Forshew et al., 2012) or pyrophosphorolysis-activated polymerization (PAP) (Liu & Sommer, 2000), seem suitable for analysis of tumor specific aberrations such as somatic single-nucleotide variants, chromosomal rearrangements and epigenetic alterations at very low concentrations (McBride et al., 2010; Leary et al., 2012; Schwarzenbach et al., 2012; Chan et al., 2013; Murtaza et al., 2013).

3. Minimal residual disease monitoring and early detection

Predicting whether a cancer patient will relapse remains a challenge in modern medicine. ctDNA can be counted in the plasma and serum of patients with advanced cancer (Leon et al., 1977; Kinde et al, 2011; Forshew et al., 2012; Dawson et al, 2013; Murtaza et al., 2013), but very few data are available for the early setting (Bettegowda et al., 2014). The detection of micrometastatic disease following surgical resection of a localized cancer requires the use of an alternative molecular assay to quantify the risk of relapse and to drive the selection therapy. Currently, the TNM system and the histopathological features of the tumor are the criteria used to foresee the risk of recurrence and possible benefit from adjuvant therapy. At the time being, we do not have any biological markers able to identify possible residual tumor after surgery. In this scenario, ctDNA could be used as a biomarker, after potentially curative treatment, to recognize individuals at risk of relapse, since it is often measurable at a very low level in plasma DNA (Diehl et al., 2008; Reinert et al., 2015). Previous studies have demonstrated that by monitoring tumor-specific mutations in plasma following surgical resection, it is possible to identify individuals with residual disease (Beaver et al., 2014) and to detect early disease recurrence (Diehl et al., 2008; Chen et al., 2009). Potentially, ctDNA analysis could detect occult metastatic disease after surgery and defines which patients will recur. Diehl et al. measured the amount of ctDNA in 18 metastatic colorectal cancer (CRC) patients who underwent surgical resection of their metastases and observed that the measure of the circulating mutant DNA levels after surgery was highly predictive of disease recurrence (Diehl et al., 2008). The ability to precisely detect the level of ctDNA, rather than to simply determine whether or not ctDNA was detectable, was the crucial feature of this study but — due to the small sample size — further evaluations are required. Another interesting study provided some data on the potential utility of ctDNA measurements to detect tumors in patients with various cancers (Bettegowda et al, 2014). The purpose of this study was to measure levels of ctDNA with structural changes or tumor-specific DNA mutations in a broad cohort of tumor tissue samples and matched human plasma. Using digital PCR-based technologies, ctDNA was detected in 75% of a total of 640 patients with advanced melanoma, ovarian, colorectal, bladder, gastroesophageal, pancreatic, breast, hepatocellular, head and neck cancers. Among 223 patients with localized cancer and without clinical or radiographic evidence of distant metastases, 55% had measurable ctDNA even in the early stage of disease. Differences in the fraction of patients with detectable levels of ctDNA also correlated with stage: 47% of patients with stage I cancer of any type had detectable ctDNA, whereas the fraction of patients with detectable ctDNA was 55, 69, and 82% for patients with stage II, III, and IV cancers, respectively. Similarly, the concentration of ctDNA in the plasma increased with stage. In a recent study the utility of assessing ctDNA in early breast cancer in order to predict early recurrence was investigated. Using a non-invasive ctDNA analysis, Isaac Garcia-Murillas and colleagues tracked breast tumor-specific mutations in 55 patients who had undergone surgery and chemotherapy as a potentially curative treatment (Garcia-Murillas et al., 2015). The results of the prospective study hint that patients at risk of relapse may be identified earlier. The presence of ctDNA predicted the relapse in 12 out of the 15 patients who relapsed on study. Among patients who did not relapse, 96% had no measurable ctDNA in either the post-surgery sample (24 of 25; $P = .0038$) or during temporal tracking of tumor mutations (27 of 28; $P < .0001$). One patient, with triple-negative disease, had detectable ctDNA after surgery but did not relapse on study. All metastatic tumors were detectable by ctDNA except for three patients who had recurrence in the brain. ctDNA detected at baseline, prior to any therapy, was not associated with early relapse. ctDNA detected at 2–4 weeks after surgery was predictive of early relapse: those who had detectable ctDNA (19%; 7 of 37 patients) had a median disease-free survival (DFS) of 6.5 months; median DFS among patients with no detectable ctDNA was not reached. In addition, the blood test was able to detect cancer recurrence on average 7.9 months before any signs became visible. In addition to these analyses, the authors, sequenced DNA from the primary cancer of 5 patients, from the residual primary tumor resected after chemotherapy, from the plasma DNA taken before relapse, and from the subsequent metastasis when biopsied. They showed that high-depth targeted capture massively parallel sequencing of ctDNA before relapse has the potential to identify the genetic characteristics of the minimal residual disease (MRD) and the lethal clone that may differ in its somatic mutations from the dominant clone in the primary cancer.

Therefore, the analysis of ctDNA could define the genetic events of MRD and of subsequent metastatic relapse more accurately than sequencing of the primary cancer. This study has two salient limitations: first the brief follow-up that allowed to identify only the proportion of women who relapsed during the study; second the women tested for ctDNA were at high risk of relapse because all of them received neoadjuvant chemotherapy (Sundaresan & Haber, 2015). Therefore a much longer follow-up and further studies in patients with low-risk primary tumors are required to determine whether this approach could be equally effective for late relapses and for patients with low-risk tumors. The potential use of ctDNA as a biomarker for cancer screening is the most challenging future application of ctDNA assessment; it could be useful for early diagnosis at a time when disease burden is still minimal,

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