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Review

Clinical applications of circulating tumor DNA and circulating tumor cells in pancreatic cancer

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is the most frequent pancreatic cancer type and is characterized by a dismal prognosis due to late diagnosis, local tumor invasion, frequent distant metastases and poor sensitivity to current therapy. In this context, circulating tumor cells and circulating tumor DNA constitute easily accessible blood-borne tumor biomarkers that may prove their clinical interest for screening, early diagnosis and metastatic risk assessment of PDAC. Moreover these markers represent a tool to assess PDAC mutational landscape. In this review, together with key biological findings, we summarize the clinical results obtained using "liquid biopsies" at the different stages of the disease, for early and metastatic diagnosis as well as monitoring during therapy.

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a rare tumor that displays a very aggressive behavior. Its annual worldwide incidence is around 1 to 10 cases per 100,000. Pancreatic cancer accounts for only 3% of all cancers, but is responsible of 7% of cancer deaths (Jemal et al., 2011). The American Cancer Society estimates that in 2015 about 49,000 new cases of pancreatic cancer will be diagnosed in the US, causing 40,000 deaths. PDAC is by far the most common type, representing around 80% of all pancreatic cancers (Siegel et al., 2015). PDAC originates from the epithelial cells of the pancreatic duct as well as from the gland-like structures and occurs in the head of the pancreas in approximately 60–70% of cases (Modolell et al., 1999).

Currently, surgery plays a crucial role in the treatment of localized PDAC. Unfortunately, due to the paucity of symptoms, the diagnosis is often delayed and only 10–20% of tumors are amenable to resection at initial diagnosis (Poruk et al., 2013). Another critical point is represented by the complex anatomical relationships that pancreas displays with other organs and major vessels, which may contribute to early dissemination of tumor cells in distant organs. However, patients who underwent a surgical resection have a 20–25% 5-year survival rate (Vincent et al., 2011).

In this context, early diagnosis of PDAC can have a dramatic impact on survival. However, screening methods currently used have not shown to be effective. Among proteomic serum markers, CEA and CA19.9 are used to monitor early recurrences in patients affected by PDAC, but their low sensitivity and specificity prevent any use as a screening tool in healthy people (Goonetilleke and Siriwardena, 2007). In addition, imaging techniques fail to detect early lesions or to distinguish between benign and malignant lesions (Capurso et al., 2015). Besides these screening issues, cytological analysis of pancreatic punctures has a high false negative rate and requires repeated sampling. At metastatic stage, discordant data on predictive value of CA19.9 have been reported, serum tumor marker changes during therapy being marginally associated with survival (Hess et al., 2008; Ishii et al., 1997).

In this context, new effective and reliable biomarkers are necessary not only to improve the early detection and diagnosis of PDAC but also to monitor treatment response and guide therapeutic choices. Circulating tumor cell (CTC) and circulating tumor DNA (ctDNA) could fulfill this need. This review summarizes how non-invasive "liquid biopsy" approaches could improve PDAC diagnosis, monitoring and treatment decisions.

2. Mutational landscape of PDAC

The most common genetic alterations in pancreatic adenocarcinoma are activating mutations of *KRAS* and inactivating mutations of *CDKN2A, TP53, SMAD4* and *BRCA2* (Biankin et al., 2012). A recent study identified other frequent somatic alterations in genes implicated in chromatin regulation or modification (*MLL, ARID1A*), which may be associated to a better prognosis (Sausen et al., 2015).

KRAS mutations are detected in around 90% of PDAC. This detection rate is much higher than in any other tumor type (Almoguera et al., 1988). *KRAS* activating point mutations impair proliferation, differentiation and cell metabolism. Several studies have detected *KRAS* mutations in premalignant pancreatic lesions. More than 90% of pancreatic intraepithelial neoplasms (PanINs) harbor *KRAS* mutations and the mutation rate is directly correlated to the PanIN grade (Kanda et al., 2012). Other mutations, such as *CDKN2A, TP53* and *SMAD4*, occur with increasing frequency in high grade intraepithelial neoplasms (Hustinx et al., 2005). These observations suggest that *KRAS* mutation is an early oncogenic event, while subsequent mutations that contribute to tumor progression might display more intra- and inter-patient heterogeneity.

KRAS mutations are located in recurrent hotspots (e.g., codon 12 and 13) and involve single nucleotide variations. These ubiquitous and recurrent mutations are therefore ideal targets to detect and quantify the presence of tumor DNA in a sample (Croce, 2008; Sinn et al., 2014). *KRAS* mutation detection has thus been investigated in pancreatic juice and stool. Mutation detection was successful in 60–80% of pancreatic juice samples from PDAC patients, but collecting such sample requires uneasy endoscopic procedures (Van Laethem et al., 1998; Watanabe et al., 1999; Wilentz et al., 1998). In the stool, *KRAS* mutations were detected in only 20–55% of PDAC patients; this low sensitivity prevents the use as a screening or diagnostic test in clinics (Caldas et al., 1994; Wenger et al., 1999). Blood-based "liquid biopsies" can outperform these deceiving results, and may prove to be clinically relevant.

3. ctDNA release and detection

3.1. *ctDNA biology*

In 1948, two French biochemists reported that circulating nucleic acids are physiologically present in the serum (Mandel and Metais, 1948). cfDNA primarily originates from apoptotic and necrotic cells (Jahr et al., 2001), but the exact biological mechanisms underlying the release of these 70–200 base pair-long DNA fragments remain to be fully elucidated. A recent study showed that in healthy people most of cfDNA derive from bone-marrow and other organs such as liver (Sun et al., 2015). cfDNA has a short half-life ranging from 15 min to few hours and is cleared away by liver and kidney (Fleischhacker and Schmidt, 2007).

Tumor cells also release fragments of DNA as a result of their high turnover (circulating tumor DNA, ctDNA) and, in cancer patients, ctDNA represents a variable fraction of cfDNA. ctDNA is distinguished from normal cfDNA by the presence of cancer-related mutations, as ctDNA fragments released by the tumor harbor the same genetic alterations. Indeed, several reports showed high concordance between ctDNA mutations, when detectable, and matched tumor mutations (Douillard et al., 2014; Kinugasa et al., 2015; Lebofsky et al., 2015). It is noteworthy that the ctDNA fraction is

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