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Commentary

Towards a more sensitive detection of somatic mutations in cell-free DNA

Julie Earl

[a] Medical Oncology research laboratory, Ramón y Cajal Health Research Institute (IRYCIS), Carretera Colmenar Km 9,100, 28034 Madrid, Spain
[b] Biomedical Research Network in Cancer (CIBERONC), C/Monforte de Lemos 3-5, Pabellón 11, 28029 Madrid, Spain

The overall survival rate of adenocarcinoma of the pancreas (PDAC) at 5 years is around 7.2%, with almost equal rates of incidence and mortality [1]. By 2030, it is projected to surpass breast, prostate and colorectal to become one of the leading causes of cancer death. In 2012, the term "liquid biopsy" was coined [2] and is defined as the detection in blood and other bodily fluids of molecules such as protein, DNA, RNA and extracellular vesicles (e.g. exosomes) or cells that originate from the primary tumour. Fresh tissue is scarce in pancreatic cancer (PC) and thus the liquid biopsy is of the upmost importance. As the tumour is constantly changing, liquid biopsy samples can be taken multiple times during disease evolution and dynamic changes in tumour cells can be monitored in real-time. Thus, promoting precision medicine in this disease. PC presents many challenges in the clinic and there are many gaps in PC diagnostics and patient management. Population-wide screening is not feasible in PC due to the low incidence and invasive techniques used for the detection of pancreatic lesions. Therefore, specific, sensitive and minimally invasive biomarkers are needed in order to accurately diagnose PDAC at a potentially curable stage and the identification of effective biomarkers for PC screening is an important unmet clinical need.

The current article describes a single-strand library preparation assay for the sequencing of cell-free DNA (cfDNA) in a clinical cohort of patients with PC or relevant pancreatic lesions and healthy controls [3]. A major pitfall of the cfDNA analysis is the contamination with high molecular weight genomic DNA, which originates from healthy blood cells when the blood is extracted and centrifuged for the retrieval of plasma. The SLHC-seq method enriches short cfDNA fragments of degraded ctDNA, which is of upmost importance in order to remove contaminating high molecular weight genomic DNA. This article is of significance as it describes a new method that can overcome this obstacle and provides quality sequencing data from a low quantity template. This single-strand library preparation approach is much more sensitive than conventional sequencing and PCR approaches. Furthermore, this method may also be applied to non-liquid biopsy sample such paraffin-embedded tissue samples, pancreatic juice or cyst fluid, which suffer from similar pitfalls as liquid biopsy samples in term of degraded, low quantity and quality DNA. A higher efficiency for the detection of mutations was achieved compared to other tumour mutation detection assays using the liquid biopsy. This is particularly important when the level of tumour cfDNA is low, such as in early stage disease or pre-symptomatic disease.

PDAC patients with an early stage pancreatic tumour have a poor prognosis as the disease is often systemic [4]. Furthermore, patients with a localized disease often relapse and progress soon after surgery [5]. Pancreatic cancer is characterized by the presence of KRAS, TP53, CDKN2A and SMAD4 somatic mutations, which can be used as specific markers for tumour cfDNA for the detection of disseminated or residual disease in these patients. Furthermore, the authors showed that small mutant fragments were prevalent in early-stage patients, which may be exploited as a fragment size-based early detection strategy for PC. This could be useful as an early detection marker in high-risk groups such as familial PC, suspicious pancreatic lesions and late onset diabetics [6].

The method described in this article is also applicable to other tumour types where the liquid biopsy serves as an important source of tumour material. Furthermore, the method described provides new insights into the efficient and effective sequencing of cfDNA in liquid biopsy samples. The technique is highly transferable to the clinic and the genomics era means that the majority of large hospital have the appropriate facilities to perform this type of analysis. This would undoubtedly have a positive impact on the clinical management of oncological patients and provide a more personalized medicine approach to pancreatic and other tumour types with a poor prognosis.

Author disclosure

The author declares no conflicts of interest.

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E-mail address: julie.earl@salud.madrid.org.

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