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Liquid Biopsy For Cancer Detection

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Abstract

Cancer is associated with mutated genes, and analysis of tumor-linked genetic alterations is increasingly used for diagnostic, prognostic and treatment purposes. These genomic alterations can be characterized and monitored by highly sensitive mutation detection techniques. As tumors shed parts of themselves into the circulation, analyses of circulating tumor cells, circulating tumor (ct) DNA, and tumor-derived exosomes, can be done by one such newer technique referred to as “Liquid Biopsy”. It can provide the genetic landscape of all cancerous lesions (primary and metastatic) as well as offering the opportunity to systematically track genomic evolution. Current paper aims to provide a brief review on how tumor-associated mutations detectable in the blood can be used in the clinical practice, including the assessment of prognosis, early detection of disease recurrence, and as surrogates for traditional biopsies with the purpose of predicting response to treatments and the development of acquired resistance.

Keywords: mutation, genome, metastasis, tumor, DNA

Introduction

Detection and determination of tumor biomarkers are made from tissue and blood collection. During the last decade new biological sources are feasible including circulating tumor cells and circulating nucleic acids. [1] The availability of next-generation sequencing and Digital-PCR among other techniques, led to the possibility of getting the most out of this “circulating material” that would mirror the genetic and epigenetic features of the tumor. They are composing a new field named as Liquid Biopsy. [2] The U.S. National Cancer Institute (NCI) defines liquid biopsy (LB) as “a test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood”.[1]

History of Liquid Based Diagnostics

CTCs were noted in blood by Thomas Ashworth in 1869. Following this another invention was made by Mandel and Metais in 1948 when they identified tumor nucleic acid in plasma. Fetal cfDNA was detected in blood by Lo YM in 1997 and was later detected incidentally in early cancers. In 2004, study conducted by Miller MC, Doyle DG for FDA

approved assay to detect CTCs in blood for patients with breast cancer for prognosis and was later expanded to prostate and colon cancers. Comprehensive NGS blood based tumor cfDNA testing was first offered commercially in 2014 by Guardant. In 2016, FDA approved cfDNA test for EGFR mutation in blood from patients with lung cancer was done.[3]

Methods of liquid biopsy:

1. Circulating tumor cells

CTCs have been discovered by autopsy of a metastatic cancer patient in 1869 by Asworth. These cancer cells are present in circulation after detaching from a primary or metastatic tumor site. 1-10 CTCs/ ml blood are noted in patients with metastasis compared to healthy people where they are rarely seen. CTCs have been detected in different cancers like head and neck, melanoma, breast, ovarian, prostate, lung, colorectal, pancreatic and hepatocellular.[4,5] Most CTCs are 'accidental CTCs' which are passively pushed by external forces like tumor growth, mechanical forces during surgical operation or friction. Although these CTCs enter the vasculature by any of these mechanisms, but mostly are eliminated via bloodstream. The natural obstacle to survival of CTCs includes aniokis, shearing forces by blood flow and attack by body's immune system. Also, it is recently discovered that platelets also facilitate the CTCs in distant metastasis by promoting epithelial mesenchymal transition by attaching them to distant organs and increasing the metastatic potential. There are commercial systems available for detection and isolation of CTCs; most commonly used is CellSearch system, an automated detection system for CTCs that uses anti-E CAM antibodies, anti-CK antibodies, and anti-CD45 antibodies.[6]

2. Circulating tumor DNA (ctDNA)

DNA is continuously released into the circulation through processes such as apoptosis and necrosis by both normal and cancerous cells. When released irrespective of cell of origin, it is typically referred to as cfDNA (cell-free DNA); but when released specifically by cancer cells, it is mostly referred to as ctDNA (circulating tumor DNA). Mainly found in serum and plasma. Other sources are ascites, breast milk, lymphatics, bone marrow aspirate and sputum. ctDNA are removed from blood by liver and kidney with half lives ranging from 15 minutes to several hours. ctDNA in patients with cancer range from 0 to 1000 ng/ml of blood, with an average of 180 ng/ml. In contrast, cfDNA in healthy subjects ranges from 0 to 100 ng/ml of blood, with an average of 30 ng/ml. [1,4,5,6]

3. Exosomes

Exosomes are small round vesicles, 30–120 nm in diameter, and of endosomal origin carrying RNA, miRNAs, DNA, and proteins that are released by multiple cell types (including tumor cells) into the extracellular environment. Sources include blood, urine, saliva, pleural effusions, amniotic fluid, nasal secretions, bronchoalveolar lavages, cerebrospinal fluid, breast milk, and ascites. At first they were considered to be only involved with removal of unnecessary molecules, but later studies have shown function of exosomes in tumor progression and metastasis. A number of cell types have been described as releasing exosomes, such as epithelial cells, hematopoietic cells, neuronal cells, fibroblasts, adipocytes and tumor cells.[5,6]

Isolation techniques

CTC's:

Cell surface marker-dependent approaches involve positive selection, which relies on epithelial cell markers, usually EpCAM and cytokeratin. The systems available for isolation include CELLSEARCH system, CTC-chips, ISET system or the ScreenCell approach.[4]

Ct DNA:

Digital PCR technology has commonly been applied to detect targeted DNA aberrations, and approaches involving digital PCR primarily include microfluidic platforms and NGS technologies. [2,3]

Exosomes: exosomes are extracted using techniques like ultrafiltration plus size exclusion chromatography, precipitation with polymers, immunoaffinity purification using magnetic beads and mass spectrometry. [4,6]

Commercially available LB technology in the market

Liquid biopsy technology is available in these brand names like Boreal Genomics, Trovagene , RainDance Technologies, Inivata and Pathway Genomics.

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Illumina's spin-off Grail claims to be future of liquid biopsy technology with Liquid biopsy-based pan-cancer detection tool known as "molecular stethoscope." [3]

Conclusion

Certain Potential limitations of LB could be a lower sensitivity than a standard biopsy. Tracing tumor heterogeneity and detecting which clones dominate which site, may be close to impossible without combining LB with smartly targeted Standard biopsy.

Liquid biospy is at the dawn of a new era of cancer "theranostics", being a non-invasive addition to Standard Biopsy. Important role in the precision medicine field which be molded to an individual's characteristics and biological features.

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