LIQUID BIOPSY: THERANOSTICS AND PERSONALIZED ONCOLOGY

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ABSTRACT

Cancer is linked with mutated genes, and the study of tumor-associated genetic alterations is gradually used for diagnostic and treatment purposes. The solid tumors are now obtained from biopsy and/or surgical or biopsy specimens. Tumor cells release circulating free DNA into the blood, but the majority of circulating DNA are often not of cancerous origin, and the detection of cancer-associated alleles in the blood has long been unbearable to achieve. Modern science has overwhelmed these restrictions, making it possible to identify both genetic and epigenetic aberrations. A liquid biopsy (LB) or blood sample can provide the genetic landscape of all cancerous lesions (primary and metastases) as well as offering the opportunity to systematically track genomic evolution. This communication will explore how LB is associated with personalized oncology to predict response to treatments and the development of acquired resistance.

Keywords: Oncology, Liquid biopsy, Theranostic, Cancer.

INTRODUCTION

GLOBOCAN 2018 estimates that the incidence and mortality from cancer worldwide were 18.1 million and 9.6 million deaths, respectively [1]. The following critical pathway is required for cancer development: Maintenance of proliferative signaling, evasion of growth suppressors, resistance to cell death, replicative immortality, angiogenic induction, inflammation, invasion, development of metastases, and reprogramming of the energy metabolism makes immunological protection impossible, generated by genome instability.

Morphologically, tumors contain a group of apparently normal cells, which create the "tumor microenvironment." Therefore, obtaining the DNA sequence enables molecular diagnosis and cancer monitoring and will provide a complete overview of tumor development [2,3]. The identification of the variations of the tumor genotype demonstrates that the heterogeneity parameter that predicts the therapeutic response, subpopulations of cancer cells, and unique genomes can exist within the same tumor and evolve (intratumor heterogeneity), which is used for characterization, monitoring of clonal dynamics, and identification of therapeutic resistance [4]. The current diagnosis of tumors is studied with a tissue biopsy, it is considered the gold standard; however, it has many limitations to have an accurate diagnosis, it determines its origin and genetic profile, although it only allows studying a static and limited sample, and eventually, it is difficult to obtain, it has low sensitivity and precision, it does not allow determining heterogeneity or invasiveness, it is incompatible with longitudinal clinical follow-up, and it does not detect an early-stage tumor or residual tumors [5,6]. The coexistence of cells of different origins and populations with different genomic and epigenomic profiles represents the tumor genetic perspective that determines the molecular profile that allows monitoring, detecting resistance to therapy, this knowledge gives rise to the new paradigm of "Oncology and Precision," where clinical, anatomopathological, molecular, genomic, and proteomic and metabolomic data are integrated, which aim to apply more precise and effective personalized treatments according to the genetic profile of each tumor. The US National Cancer Institute defines that the liquid biopsy (LB) as "a blood test, which studies the free nucleic acids of circulating cancer tumor cells (CTC), DNA fragments of tumor cells," represents is a complementary alternative to detect genomic alterations, predicts early relapse and response to treatment, using rapid sampling non-invasive and repeatable. It allows to dynamically identify tumor genomes in body fluids such as blood, saliva, stool, urine, pleural, cerebrospinal and ascitic fluids, allows early screening, evaluates tumor progress, therapeutic response and detects recurrences through analysis of circulating tumor DNA (ctDNA), circulating tumor cells (CTC), which are the only components for clinical application approved by the FDA. Extracellular vesicles (EV), circulating tumor RNA (ctRNA), and platelets formed by tumors (tumor-educated platelets) members of the tumor circuloma are biomarkers still under study [7-9].

The innovative studies on ctDNA and CTC investigated by the Human Genome Project and Cancer Genome Project demonstrate that they can be the biomarkers that provide genomic, proteomic, and metabolomic information for the diagnosis and detection of cancer patients, the DNA fragments are discharged into the bloodstream by cells as a product of apoptosis or necrosis, by the secretion of vesicles and exosomes. It is correlated with tumor staging and prognosis, DNA analyzes related to sensitivity and precision that are essential for the study of somatic genomic alterations, mutations, deletions, or amplification, the analysis must be complemented with tissue biopsies for real-time molecular monitoring, resistance to treatment, and detection of recurrence, the test is useful when tumor tissue is not available or insufficient [10,11]. During the disease, other tumors and metastatic sites may appear and/or develop resistance to therapy, requiring treatment modification. BL can show the appearance of new mutations [12,13].

Several studies show that DNA contains the mutations of the original tumor, it has been shown that it can be the guide that directs the routine treatment of lung cancer, allows to monitor the evolution, and identifies resistance to treatment. The FDA approved the first LB to diagnose EGFR mutations in patients with non-small cell lung carcinoma with the Cobas v2 EGFR mutation test and for the detection of colorectal cancer [14,15]. Other biomarkers in BL are microRNAs (miRNAs) which are small non-coding endogenous RNA molecules, released, and secreted into the circulation by multiple immune and tumor cells, participate in proliferation, differentiation, replication, apoptosis, metabolism, neoplastic transformation, invasion, metastasis, and resistance to therapy are directly related to miRNA dysregulation and aberrant expression in cancer [16].

Genotyping in BL shows molecular heterogeneity in biomolecules, such as CTC, ctDNA, ctRNA, miRNA, lnRNA, exosomes, and autoantibodies, allows real-time monitoring of evolution, and establishes the diagnosis;

in earlier stages, it evaluates the response and resistance to treatment, quantifies the minimum residual of the disease and bases the therapy individualized, represents a potential for clinical applications as a valuable tool for the clinical management of patients with advanced-stage and difficult-to-treat cancers, predicts response to treatment, and can detect recurrence from early stages and evolution over time. The clinical application of LB is the way to precise theranostics and personalized medicine, due to the possibility of repeated sampling, which allows creating a complete molecular profile and the incorporation of new miniaturized technologies, engineering nanomaterials, and electrochemical detection, develops simpler, lowcost platforms which are suitable for clinical use [17].

The identification of new, highly sensitive, and specific tumor biomarkers is very important. The development of high-performance omic technologies, such as next generation sequencing, is a more efficient methodology that detects and characterizes genetic and molecular mutations, the decoding of genetic information is easier, faster, and less expensive for monitoring in time real of the disease, the objective is to establish the tumor profile for an early diagnosis that guides personalized therapeutic decisions with greater precision [18]. Studying gene panels such as the transcriptome and the whole exome looking for mutations, this technology may be more accessible for clinical application. Potentially useful standards for sharing genomic data, such as HL7 FHIR and mCODE, are in the research and/or development stage, critical for precision oncology [19].

The use of ctDNA, CTC, and exosomes as potential biomarkers for cancer theranostics is an emerging area with potential clinical utility. LB emerges as a minimally invasive, repeatable, and inexpensive method of tumor DNA diagnosis, which investigates tumor heterogeneity, monitors therapeutic effectiveness, prognosis, and acquired resistance to therapy in cancer.

CONFLICTS OF INTEREST

Authors do not have any conflicts of interest

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