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Review

Current applications of chromatographic methods for diagnosis and identification of potential biomarkers in cancer

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ABSTRACT

Cancer is the leading cause of death worldwide. However, its early diagnosis and treatment improve survival. Due to the asymptomatic properties of almost all types of cancer, some patients are misdiagnosed or the disease is overlooked. Despite the availability of well-known diagnostic tools, such as computed tomography, a wide range of factors can limit a successful application of these techniques. The search for new alternative methods that would be able to diagnose cancer definitively has aroused scientific interest. Many coupled techniques have been employed for this purpose. Nevertheless, chromatographic platforms are considered to be among the most powerful diagnostic tools, which have enabled metabolic profiling, and, as a result, identified cancer biomarkers, which are essential in the treatment process. Rapid advances in technologies have made it possible to introduce new methods of treatment, based on individual predisposition.

Contents

Abbreviations: 2DE, Two-dimensional; BC, Breast cancer; BE, Benign breast cancer; BL, Bladder cancer; BQ, Betel quid; CaP, Prostate cancer; ccRCC, Clear cell renal cell carcinoma; CEC, Capillary electrochromatography; CRC, Colorectal cancer; CT, Computed tomography; ELISA, Enzyme-linked immunosorbent assay; FD-LC-MS/MS, Fluorogenic derivatization-liquid chromatography-tandem mass spectrometry; FFA, Free fatty acid; FIA-ED, Flow-injection analysis-electrochemical detection; FT-IR, Fourier-transform infrared; GC, Gas chromatography; GC-MS, Gas chromatography-mass spectrometry; GC-MS/MS, Gas chromatography-tandem mass spectrometry; GC-TOF-MS, Gas chromatography-time-of-flight-mass spectrometry; GCxGC-TOF-MS, Two-dimensional gas chromatography-time-of-flight-mass spectrometry; HCC, Hepatocellular carcinoma; HILIC, Hydrophilic interaction liquid chromatography; HPLC, High-performance liquid chromatography; HPLC-LIF, High-performance liquid chromatography-laser-induced fluorescence; HPLC-MS, High-performance liquid chromatography-mass spectrometry; HPLC-TOF-MS, High-performance liquid chromatography-time-of-flight-mass spectrometry; IHC, Immunohistochemistry; LC, Liquid chromatography; LC-MS, Liquid chromatography-mass spectrometry; LC-MS/MS, Liquid chromatography-tandem mass spectrometry; LC-TOF-MS, Liquid chromatography-time-of-flight-mass spectrometry; LMC, Low-molecular-weight compound; LOD, Limit of detection; MALDI-MS, Matrix-associated laser-desorption/ionization-mass spectrometry; MALDI-TOF-MS, Matrix-associated laser-desorption/ionization time-of-flight mass spectrometry; MARS14, 14 Multiple Affinity Removal Spin Cartridges; MEKC, Micellar electrokinetic chromatography; MRI, Magnetic resonance imaging; MRM-MS, Multiple reaction monitoring-mass spectrometry; NMR, Nuclear magnetic resonance spectroscopy; NSCLC, Non-small cell lung carcinoma; OLK, Oral leukoplakia; OSSC, Oral squamous cell carcinoma; PCA, Principal-component analysis; PSA, Prostate Specific Antigen; PTR-MS, Proton transfer reaction-mass spectrometry; RCC, Renal cell carcinoma; RP-LC, Reversed-phase-liquid chromatography; RP-UPLC-MS, Reversed-phase-ultra-performance liquid chromatography-mass spectrometry; SCID, Severe combined immune deficiency; SCLC, Small cell lung carcinoma; SELDI-TOF-MS, Surface-enhanced laser-desorption/ionization time-of-flight mass spectrometry; SISCAPA, Stable-isotope standards with capture by anti-peptide antibodies; SPLS-DA, Supervised partial least squares discriminant analysis; SPME, Solid-phase microextraction; TLC, Thin-layer chromatography; UPLC-ESI-TQMS, Ultra-performance liquid chromatography-electrospray ionization-triple quadrupole mass spectrometry; UPLC-MS, Ultra-performance liquid chromatography-mass spectrometry; UPLC-QTOF-MS, Ultra-performance liquid chromatography-quadrupole-time-of-flight mass spectrometry; VOC, Volatile organic compound.

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1. Introduction

Cancer is the most common cause of death in the world. It is reported that more than 11 million people are diagnosed with this disease every year and the number is still increasing. Scientists have recognized 200 forms of cancer and four of them (lung, prostate, breast and colon) are responsible for more than half the deaths [1,2].

Cancer is defined as a disease of DNA deregulation. Both exogenous and endogenous factors contribute to its development. The conversion of normal cells into malignant cells depends on metabolic disturbances. The transformation of a normal cell into a malignant cell can proceed along various paths [3]. Early diagnosis of cancer is thought to play a crucial role in better clinical outcomes. Understanding the metabolism of cancer cells and identifying the metabolic pathways that determine cancer-cell growth pose a huge challenge to scientists.

In cancer research, it is necessary to describe metabolic profiles in normal, precancerous and cancerous tissues, so it is essential to demonstrate whether or not the use of an appropriate technique can determine the concentration of metabolites in samples. Also, it is necessary to identify as many metabolites as possible and to describe a correlation between their levels and the occurrence of tumors.

A large number of techniques, including coupled techniques based on chromatography, have been applied in biochemical research for a long time. GC-MS and LC-MS were described in a review from 1973 and presented as techniques with a wide range of applications [4]. Nowadays, it is well known that they are able to describe the intracellular metabolism of cancer-cell growth.

GC-MS is reported to have many advantages, especially when applied in investigations on human body fluids [5]. This technique has been used in clinical biochemistry and urinary analysis for more than 30 years [6]. In the literature, there are also reports about the application of GC-MS in order to identify potential biomarkers of cancer, to monitor cancer therapies and to determine DNA damage in humans after exposure to cancer-causing agents [7]. GC-MS is characterized by minimal sample requirements, rapid analysis and reduced use of expensive labeled substrates. Despite the lower requirements for cell material, GC-MS helps to obtain measurable results comparable with other techniques, such as NMR [5].

HPLC made it possible to determine polar and thermally-labile compounds. The use of a suitable detector combined with HPLC enables description of the structure, which is essential in identifying unknown compounds. What is more, this technique is characterized by better resolution and reproducibility [8].

Other chromatographic techniques are LC-MS and LC-MS/MS, which are among the most powerful analytical tools for the study of organic compounds. The application of LC-MS in order to analyze urine samples has been known for about 30 years [4]. The development of technology that resulted in monolithic capillary columns and ultra-high-pressure or ultra-performance techniques (e.g., HPLC-MS or UPLC-MS) enabled high chromatographic peak resolution, and reduced time of analysis with simultaneous high-quality mass spectra [9].

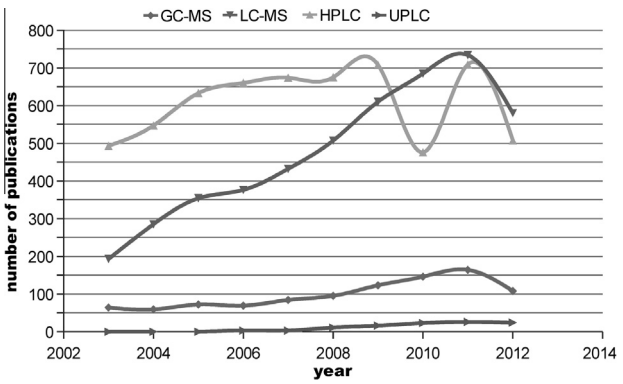

Fig. 1. Number of publications on cancer and chromatographic techniques (2003–12).

The literature also mentions several other coupled techniques based on chromatography (e.g., GC-MS/MS, UPLC-MS, LC-TOF-MS and HPLC-TOF-MS). However, GC-MS, LC-MS, HPLC and UPLC techniques are of particular interest to scientists because they are used in studies related to the human body and its condition, especially in the diagnosis of various types of cancer (Fig. 1). They are widely used in clinical research and biomedical research to validate quantitative analytical assays. Apart from the study of cancer, chromatography-based techniques are used in the diagnosis of metabolic disorders, including various types of acidosis, and in the study of autism [10,11].

A system-suitability test is an essential part of chromatography. The main aim of its application is to verify whether a planned analysis will be performed by a chromatographic system with correct detection sensitivity (checked with test solution), resolution and reproducibility. Resolution refers to separating one eluting compound from the others. Reproducibility shows whether the requirements for precision are met and verified by replicate injections of the analyte. The high quality of results is strongly connected with quality control (QC), which involves activities or techniques performed in order to ensure that quality requirements are met. Fulfilment of analytical requirements is guaranteed by the use of a validated method. A wide range of texts are available (e.g., Good Laboratory Practice, quality-assurance system (ISO 9001) and testing and calibration (ISO 17025) containing general rules) [12].

The lack of specific syndromes and a limited understanding of etiology make it difficult to diagnose cancer in its early stage. Nevertheless, biomarkers turn out to be powerful tools in predicting the development of this disease [2]. Yet, what exactly is a biomarker? The term "biomarker", or more specifically "biological marker", refers to a wide range of medical signs. The National Institute of Health Biomarkers Definitions Working Group [13] described a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention". However, there are also other definitions that present a biomarker as a measurable substance, a structure or even a process that occurs in the body or its products and influences or enables prediction of disease [14]. WHO accepts the definition that a biomarker is "almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological. The measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction" [15].

These definitions raise the question of whether the term "biomarker" is abused by current research. In the literature, we can find the requirements that a potential factor should meet to be called a biomarker [16]. In an analysis of biomarker(s), it is most important to select a proper analytical method, which will be able to detect the value being examined. The detection method must have a larger dynamic range than that of a sample (otherwise a huge amount of potential information may be lost) and resolution (poor resolution of proteins or peptides will obscure important differential details). Linear dynamic range, and subsequent clinical validation and testing of the biomarker in clinical settings are also of some significance.

Cancer biomarkers give information about the physiological state of a cell at a specific time. Early detection of specific biomarkers (before clinical symptoms) enables introduction of adequate