Analytica Chimica Acta xxx (2017) 1–9

Contents lists available at ScienceDirect

Analytica Chimica Acta

journal homepage: www.elsevier.com/locate/aca

Review

Review of recent developments in determining volatile organic compounds in exhaled breath as biomarkers for lung cancer diagnosis

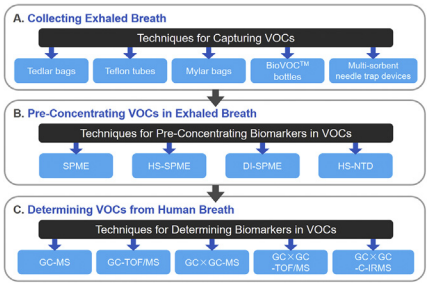
Jiemin Zhou [a, 1], Zi-Ao Huang [b, 1], Ujendra Kumar [a], David D.Y. Chen [b, *]

[a] Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC V6T 1Z4, Canada
[b] Department of Chemistry, University of British Columbia, Vancouver, BC V6T 1Z1, Canada

HIGHLIGHTS

- Methods for determination of volatile organic compounds (VOC).
- VOC as potential markers for early diagnosis of lung cancer.
- Review of sample pretreatment and analytical methods used.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 23 August 2016
Received in revised form
8 September 2017
Accepted 9 September 2017
Available online xxx

Keywords:
Volatile organic compounds
Exhaled breath
Lung cancer
Early diagnosis
Biomarker

ABSTRACT

Lung cancer is the most common cause of cancer deaths, its global incidence is rising, and continuing rises are predicted. The potential to diagnose lung cancers based on the determination of volatile organic compounds (VOCs) in human breath has been attracting increasing attention with the development of new techniques and methodologies. However, despite many reports of VOC profiling in lung cancer patients, little is known about how specific biomarkers relate to the biochemical pathways involved in lung cancer development, and there is still no reliable method for diagnosing lung cancer at the early stages. This review summarizes some of the latest methods used for monitoring biomarkers in lung cancer patients, which could be applicable for clinical diagnosis. Techniques for capturing and pre-concentrating biomarkers, and the technologies used for subsequently determining them, are also discussed.

Contents

* Corresponding author.
E-mail address: chen@chem.ubc.ca (D.D.Y. Chen).
[1] These two authors contributed equally to this paper.

http://dx.doi.org/10.1016/j.aca.2017.09.021
0003-2670/

1. Introduction

1.1. Significance of diagnosing lung cancer at early stages

Due to its high, and rising, morbidity and mortality, lung cancer has become the leading cause of cancer deaths globally [1–3]. Approximately 14.1 million people were diagnosed with cancer in 2012, with 8.2 million deaths worldwide [4,5]. Of these 14.1 million cases, 1.8 million (13%) were lung cancer. Increases in various environmental risk factors are expected to induce rises in annual numbers of new cancer cases and associated deaths to 24 and 14.6 million, respectively, by 2035 [6]. Therefore, there is a clear need to develop new methods for preventing, detecting, and treating cancer [7].

Cancer screening is important for detecting the disease at early stages, to avoid metastatic spread, thereby increasing the rate of successful treatment. New screening methods that are highly sensitive, specific, and fast are needed for early diagnosis, prognosis, monitoring pathogenesis, and targeted therapy [8–12]. The search for new diagnostic methods and tools that can meet these needs is increasingly attracting the attention of researchers in interdisciplinary fields, such as biomedicine, biophysics, and analytical chemistry [13].

1.2. Current techniques for diagnosing lung cancer at early stages

Lung cancers are usually categorized as one of two types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with the latter representing a large majority (85–90%) of cases [14]. Regardless of histopathological subtype, 88% of lung cancer patients die within 5 years of diagnosis, suggesting that delayed diagnosis is a significant problem [15]. Currently, various combinations of multiple techniques, including radiology, endoscopy, and molecular biotechnology, are used to detect lung cancer at early stages [6]. These techniques, and their diagnostic applications, are briefly listed and described in Table 1.

All these methods are useful at various stages of diagnosis and have specific merits. However, in early stages of the disease it remains difficult to distinguish lung cancer from benign nodules based purely on morphological criteria. This results in frequent false positives and unnecessary surgical resection [10,11,17,20,21]. Detecting volatile organic compounds (VOCs) in the exhaled breath of patients may offer a rapid, noninvasive, inexpensive and more specific alternative [37]. However, the success of VOC-based diagnosis depends on the identification and validation of one or more chemical species that can serve as accurate biomarkers of lung cancer [38,39].

Recent developments in sampling techniques and detection methods have been discussed extensively in review articles written by Sun et al. and Saalberg et al. [40,41]. Techniques for determining VOCs, including gas chromatography (GC) or mass spectrometry (MS) based and sensor-based techniques, have been described in detail [40]. In contrast, this review primarily addresses the identification of VOCs, and we aim to highlight research focused on the discovery of biomarkers for early screening and diagnosis of lung cancer. Literature published up to the end of May 2017 is included, and the main compounds considered relevant to lung cancer diagnosis are listed. The reported sensitivity and specificity of these compounds are also summarized.

2. Diagnosing lung cancer via determination of voc in exhaled breath

2.1. Determination of VOC as a tool for disease diagnosis

The smell of human breath has been for used for diagnostic purposes since ancient times. The possibility of using it for detecting lung cancer has also been investigated for many years, and greatly boosted by rapid recent developments in metabolomics as a new branch (together with genomics, transcriptomics, and proteomics) of systems biology [38]. Metabolomic analysis of exhaled breath generally focuses on the quantitative determination of metabolites with low molecular weights (less than 1000 amu) [42]. Increases in levels of these molecules are induced by diverse pathophysiological stimuli, genetic modifications, or environmental factors acting on living systems [42]. The metabolites detected include amino acids, fatty acids, lipids, and carbohydrates, which are usually the end products of biochemical pathways that have significant roles in controlling cellular structure and signaling [43].

Changes in the levels of some metabolites in exhaled breath may be warning signs for diseases such as lung cancer. Thus, detection of these changes has potential utility for diagnosing, screening, and characterizing the biological pathways of these diseases [11,15]. Exhaled breath contains over 3500 substances, most of which are VOCs in trace quantities (from ppm to less than ppb levels) [11,15,38,42–45]. Therefore, determination of VOCs in exhaled breath is a challenging task, requiring excellent sensitivity and selectivity to detect trace metabolites with the presence of those at higher concentrations.

2.2. Determination of VOC of lung cancer patients' breath

2.2.1. Identification of VOCs produced by biochemical pathways relevant to lung cancers

Numerous VOC metabolites with potential utility as biomarkers

Please cite this article in press as: J. Zhou, et al., Review of recent developments in determining volatile organic compounds in exhaled breath as biomarkers for lung cancer diagnosis, Analytica Chimica Acta (2017), http://dx.doi.org/10.1016/j.aca.2017.09.021