Review paper

Metabolome-based biomarkers: their potential role in the early detection of lung cancer

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Lung cancer is the leading cause of cancer-related death worldwide, and a major problem affecting its mortality is the late diagnosis of the majority of cases, where treatment options are limited and overall prognosis is very bad. Currently, a low-dose computed tomography (LD-CT) screening in the high-risk group is the only available diagnostic strategy that could reduce mortality due to this malignancy. However, the LD-CT screening test suffers from a high false positive rate. Hence, complementation of LD-CT examination with blood-based biomarkers is a rational approach to increase efficacy and reduce the cost of early lung cancer screening programs. Several molecular signatures that discriminate between patients with early lung cancer and healthy individuals have been proposed in recent years, which are based on components of serum/plasma metabolome. However, none of these signatures has been validated by independent studies based on material collected during real lung cancer screening. Therefore, the validation of the real diagnostic value of these otherwise promising candidates remains a critical step in this challenging field of cancer diagnostics.

Key words: lung cancer screening, mass spectrometry, nuclear magnetic resonance, blood metabolomics.

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide for both men and women [1]. Late diagnosis is a critical public health problem related to this malignancy. Currently, about 15% of cases are diagnosed at an early stage (stage I–II), where effective treatment is possible and the probability of five-year survival is above 60% [2, 3]. On the other hand, nearly 60% of cases are diagnosed in the metastatic stage (stage IV) with very poor prognosis, where the probability of five-year survival is below 5%.

The main aetiological factor of lung cancer is tobacco use, and a large proportion of all pulmonary carcinomas are attributable to the effects of cigarette smoking [4, 5]. Regardless of the indispensable efforts to diminish tobacco usage (i.e. primary prevention), another leading strategy to reduce mortality from lung cancer is to introduce screening in a high-risk group that would allow early detection of this disease (i.e. secondary prevention). Currently, a low-dose computed tomography (LD-CT) screening in the high-risk smoking population is the only available tool. In 2011, the results of the National Lung Screening (NLST) were published, according to which LD-CT screening enabled a 20% reduction in mortality due to lung cancer when compared to the standard RTG [6]. Since then, other studies have also confirmed the usefulness of LD-CT for the early detection of lung cancer (reviewed in [7]). The disadvantage of this test, however, is a large number of false-positive results: in the high-risk group, any types of nodules and other suspicious changes are usually detected in 30–50% of participants, while actual malignancy is confirmed by further diagnostics in 1–2% of participants. Moreover, it is estimated that the majority (even above 75%) of screening participants who have pulmonary changes detected by LD-CT are subjected to unnecessary diagnostic procedures, including 25% of patients subjected to further invasive procedures [8]. This problem, known as a high false positive rate of diagnosis, next to the economic issues, is the main source of doubt regarding the feasibility and legitimacy of the widespread introduction of this screening approach. Hence, it is generally accepted that a combination of LD-CT with an additional test based on biomarkers would be a favourable strategy for increasing the effectiveness and reduction of the real cost of lung cancer screening programs [9].

A hypothetical biomarker used for supporting early detection of lung cancer could be used at different stages of a diagnostic strategy (Fig. 1). On the one hand, it could be utilised to pre-select the candidates within the high-risk group before CT examination (option 1). On the other hand, it can be used to estimate the risk of malignancy in case of doubtful changes detected by LD-CT examination before further invasive procedures (option 2). In both cases, the most important feature of such a hypothetical biomarker should be a high negative predictive value (NPV) that would reliably exclude the presence of disease in the case of a negative test result. Positive predictive value (PPV) is less critical because individuals with a positive test result

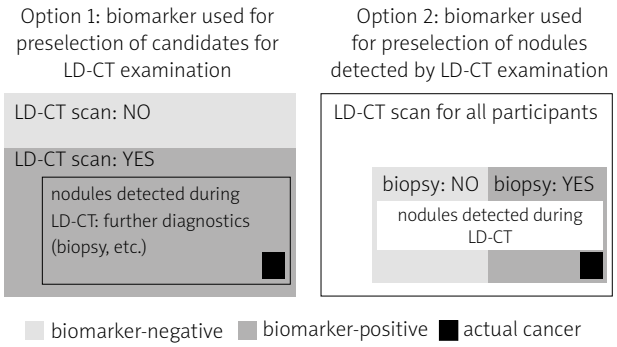

Fig. 1. Hypothetical biomarker used at different stages of a diagnostic strategy

would already be subjected to further diagnostics. Currently, a few "classical" cancer biomarkers are proposed for detection of lung cancer, but most of them have a low specificity. In the blood of non-small cell lung cancer patients, the CYFRA 21-1 (cytokeratin-19 fragment) and carcinoembryonic antigens (CEA) are assessed, whereas NSE (neuron-specific enolase) is considered to be the marker for small cell carcinoma. However, levels of these markers usually increase at advanced stages of lung cancer. In the case of NSE, the diagnostic sensitivity is between 40 and 60% in patients with an early stage of cancer, but its diagnostic specificity is very low [10]. Therefore, it is necessary to search for new reliable lung cancer markers that are useful in the diagnosis of early stages of a disease.

Hypothetical lung cancer biomarkers with possible applicability in early detection should be detected in body fluids, primarily in the blood, or exhaled breath. In the last decades intensive research has been conducted in numerous research centres focusing on identification of early lung cancer biomarker candidates. These studies focused on different components of blood, which included circulating tumour cells, cell-free DNA (cfDNA), auto-antibodies, and proteome, peptide, and miRNA components [11–15]. Such studies have enabled the development of several promising biomarker candidates, which primarily involved panels of plasma/serum components. These biomarkers make it possible to differentiate healthy people from patients with lung cancer, achieving high sensitivity and specificity values. An example of such research is the work of Patz *et al.* [16]. In this study a panel composed of four proteins: carcinoembryonic antigen, retinol binding protein, α-1-antitrypsin, and squamous cell carcinoma antigen was selected. The classifier based on the proposed panel was able to distinguish groups of healthy people from the cancer patients (in different cancer stages). Sensitivity and specificity in the training set were 89.3% and 84.7%, respectively, while in the independent validation set 77.8% and 75.4%. Similarly, high indices were obtained for cancer signature composed of leucine-rich α-2-glycoprotein 1 (LRG1), α-1 anti-chymotrypsin (ACT), complement factor 9 (C9), and haptoglobin [17]. Promising results have also been obtained in several other studies. The following proteins were considered as potential biomarkers of lung cancer: connective tissue-activating peptide III (CTAP III)/neutrophil activating protein-2 (NAP-2) and haptoglobin [18], osteopontin [19], complement activation product c4d [20]. and panel of thirteen proteins (LRP1, BGH3, COIA1, TETN, TSP1, ALDOA, GRP78, ISLR, FRIL, LG3BP, PRDX1, FIBA, GSLG1) that allowed differentiation of benign from malignant changes [21]. However, the majority of these studies were not designed in association with early lung cancer screening programs, hence their practical applicability has not been validated yet. Nevertheless, a panel of endogenous serum peptides was described more recently that discriminated early lung cancer cases from healthy participants of a lung cancer screening program, which showed NPV of 100% and 88% in training and validation cohorts, respectively [22]. Other types of blood components were also tested, which includes a panel of 24 plasma-based microRNAs that was capable of increasing the specificity of LD-CT in a lung cancer screening trial [23]. Moreover, in addition to works based on blood-derived material, a few promising examples of lung cancer biomarkers with high diagnostic potential were proposed recently using other types of bio-specimens. This includes Epi proLung test, which investigates the status of hypermethylation of SHOX2 in bronchial aspirates collected during bronchoscopy (the test already gained the CE-IVD certificate) [24].

Metabolomics – a new source of cancer biomarkers

Metabolomics is a science that deals with the quantitative and qualitative analysis and identification of metabolites that constitute the metabolome of a cell or tissue [25, 26]. The term "metabolite(s)" usually refers to various biomolecules with a molecular mass below 1500 Da. These molecules are both building components of cells and mediators involved in intracellular signalling. In general, metabolomics focuses on substrates and products of metabolism, including carbohydrates, amino acids, nucleotides, carboxylic acids, and lipids. The typical metabolic process is a combination of evolutionary conserved biochemical reactions shared by many organisms. The complexity of metabolome is much lower than that of genome or proteome; the quantity of human genes, proteins, and metabolites is estimated at 20,000–25,000, 250,000–1,000,000 (including posttranslational modifications), and 2000–2500, respectively. On the other hand, in comparison to other "omes", metabolome the most closely reflects the current status of phenotype and tells us what exactly has happened in the organisms [27]. Furthermore, metabolome reliably mirrors the environmental influence, because it is the endpoint of gene-environment interaction. However, there is no simple relationship between mRNA/protein levels and actual metabolism because of numerous ways of transcripts' and proteins' "maturation" and modification. Therefore, metabolome should be addressed directly on its own [28]. Nevertheless, metabolomics has enormous application potential in the search for reliable markers of different disease states, including cancer [29].

Two of the most common metabolomics approaches are based on nuclear magnetic resonance (NMR) spectroscopy or mass spectrometry (MS) techniques, each with their

specific advantages and limitations. NMR, in contrast to MS, does not require laborious steps for sample preparation, such as extraction, separation or derivatisation, that can cause metabolite losses as well as lower reproducibility. However, the weakest point of NMR is sensitivity. On the other hand, metabolomics based on MS provides an analytical platform combining sensitivity and selectivity. Additionally, different MS approaches such as diverse ionisation techniques and mass analyser technology can be used in order to extend the number of metabolites that can be detected. In recent years several studies have been published based on the use of NMR or MS techniques to create profiles of serum/plasma metabolites that would allow differentiation between samples of lung cancer patients and healthy individuals, or between samples of individuals with benign and malignant lung diseases; the information provided in these works is summarised in Table 1. A few of them specifically addressed the problem of low advanced cancer and appeared relevant in the issue of early detection of this malignancy.

Metabolome biomarkers in early lung cancer

A study based on NMR analysis showed statistically significant differences in levels of various amino acids and carboxylic acids when plasma samples of 85 patients with early lung cancer (i.e. stage I or II) and 78 healthy controls were compared [30]. In this study, higher levels of lactic and pyruvic acid were observed in plasma samples of patients, as well as decreased levels of amino acids (alanine, valine, lysine, glutamine, tyrosine, histidine), acetic acid, acetoacetic acid, lemon acid and formic acid. Another NMR-based study of serum metabolites compared 48 lung cancer samples (including 50% of early cases) and 12 samples from patients with chronic obstructive pulmonary disease (COPD) [31]. Cancer patients in all progression stages had increased levels of N-acetylated glycoproteins, leucine, lysine, mannose, choline, and lipids, but reduced levels of acetate, citrate, and methanol. Additionally, samples with early lung cancer had also increased levels of isoleucine, valine, 3-methyl-2-oxovalerate, 3-hydroxybutyrate,

Table 1. Studies pursuing the blood metabolome biomarkers in early lung cancer

Number of study subjects	Sample type	Analytical technique	Major findings	Reference
85 eLC and 78 CTR	Plasma	NMR	LC samples had significantly: • higher levels of lactic and pyruvic acid, • decreased levels of amino acids (alanine, valine, lysine, glutamine, tyrosine, histidine), acetic acid, acetoacetic acid, lemon acid, and formic acid	Rocha 2011 [30]
48 LC (24 eLC) and 12 COPD	Serum	NMR	LC samples (in comparison to COPD samples) had significantly: • higher levels of isoleucine, valine, 3-methyl-2-oxovalerate, 3-hydroxybutyrate, acetone, acetoacetate, isobutyrate, lactate, creatinine, α-glucose, and lipids, • decreased levels of glutamine and trimethylamine	Deja 2014 [31]
142 LC (72 eLC) and 87 CTR	Serum	NMR	18 metabolites significantly changed between LC and CTR samples, including amino acids, carboxylic acids, and alcohols	Puchades-Carrasco 2016 [32]
101 LC (54 eLC) and 62 CTR	Plasma and serum	GC-MS	80 metabolites significantly changed between LC and CTR samples, including LC-upregulated glutamate, aspartate, and Bin_225393, as well as LC-downregulated xylose	Fahrman 2015 [36]
30 LC (22 eLC) and 30 CTR	Serum	GC-MS and LC-MS/MS	LC samples had significantly: • higher levels of phosphorylcholine, glycerophospho-N-arachidonoyl ethanolamine, γ-linolenic acid, α-hydroxyisobutyric acid, and 9,12-octadecadienoic acid, • decreased levels of prasterone sulphate, sphingosine, serine, and 2,3,4-trihydroxybutyric acids	Chen 2015 [33]
94 LC (57 eLC) and 190 CTR	Serum	GC-MS and LC-MS/MS	79 metabolites significantly increased and 70 metabolites decreased in LC samples	Mazzone 2016 [34]
50 eLC and 25 CTR	Serum	LC-MS/MS	36 metabolites significantly changed between LC and CTR samples, including carnitine, acylcarnitines, malic acid, pyroglutamic acid, histidine, and histamine	Klupczynska 2017 [35]
31 eLC and 92 CTR	Serum	GC-MS	Benzaldehyde significantly increased, while 16 metabolites (including several amino acids, carboxylic acids, and tocopherols) decreased in LC samples	Ros-Mazurczyk 2017 [37]
199 eLC and 147 CTR	Plasma	ESI-MS/MS	Top significant discriminatory lipid species included LC-upregulated LPE (18:1) and ePE (40:4) as well as LC-downregulated C(18:2)CE and SM(22:0)	Yu 2017 [40]
100 eLC and 300 CTR	Serum	MALDI-MS/MS and LC-MS/MS	Discriminatory phospholipid component included LC-increased PCs, diacylophospholipids and SM as well as LC-decreased LPCs (including LPC18:2, LPC18:1 and LPC18:0)	Ros-Mazurczyk 2017 [41]

COPD – chronic obstructive pulmonary disease; CTR – control; eLC – early lung cancer; ePE – ether phosphatidylethanolamine; LC – lung cancer; LPC – lysophosphatidylcholine; LPE – lysophosphatidylethanolamine; MS – mass spectrometry; NMR – nuclear magnetic resonance; PC – phosphatidylcholines; SM – sphingomyelins

acetone, acetoacetate, isobutyrate, lactate, creatinine, α-glucose, and lipids, and reduced levels of glutamine and trimethylamine in comparison to COPD. More recently, a larger NMR-based study compared serum samples of 142 lung cancer patients (including 51% of early cases) and 87 healthy volunteers [32]. Statistically significant differences between cancers and controls were found in levels of 18 metabolites representing different amino acids, carboxylic acids, and alcohols, as well as molecules involved in lipid metabolism. Moreover, levels of 17 serum metabolite discriminated early and advanced cancer cases.

There are also a few studies based on a combination of different MS platforms. A study that utilised gas chromatography coupled with MS (GC-MS) and liquid chromatography coupled with tandem MS (LC-MS/MS) compared serum metabolites in 30 cancer samples (including 73% of early cases) and 30 healthy controls [33]. This study revealed increased levels of phosphorylcholine, glycerophospho-N-arachidonoyl ethanolamine (GpAEA), γ-linolenic acid, α-hydroxyisobutyric acid, and 9,12-octadecadienoic acid in cancer samples, and decreased levels of prasterone sulphate, sphingosine, serine, and 2,3,4-trihydroxybutyric acids. Interestingly, this study revealed higher sensitivity and specificity of GpAEA and sphingosine in the ossification of cancer samples than CEA and CYFRA21-1. A larger study that utilised a combination of GC/MS and LC-MS/MS compared serum metabolites in 94 lung cancer samples (including 61% of early cases) and 190 controls [34]. This study revealed increased levels of 79 compounds and decreased levels of 70 compounds in cancer samples; different multicomponent signatures were built based on this data with classification accuracy ranging from 0.75 to 0.86 at the cross-validation phase. Another study that was based on a high-resolution LC-MS/MS compared serum samples from 50 early lung cancer cases and 25 controls [35]. This analysis revealed 36 compounds with significantly different levels between cancer and control samples, which included carnitine, acylcarnitines, malic acid, pyroglutamic acid, histidine, and histamine. Moreover, a signature composed of 12 compounds allowed to build a cancer classifier characterized by an area under ROC curve (AUC) equal 0.836. Another study based only on GC-MS analysis examined both plasma and serum samples from 101 lung cancer patients (including 53% of early cases) and 62 controls [36]. This work revealed four metabolites (xylose, glutamate, aspartate, and Bin_225393) that significantly discriminated cancer samples and allowed construction of a cancer classifier that was validated by an independent set of samples. Interestingly, the authors concluded that even though the two blood matrices yielded similar performances, the serum had higher sensitivity for low-abundant compounds. Yet another GC-MS study was based solely on cancer cases detected during early lung cancer screening (31 samples) and matched controls from participants of the same screening program (92 samples) [37]. This pilot study revealed 17 serum metabolites with significantly different levels between both groups, including increased benzaldehyde in cancer samples and several amino acids and carboxylic acids, and decreased tocopherols in cancer samples.

Lipidome biomarkers in early lung cancer

Lipids, especially phospholipids and sphingolipids, are a particularly interesting class of metabolites because they play a key structural and regulatory role as building blocks of cellular membranes as well as mediators in intra- and inter-cellular communication. Therefore, this fraction of metabolome, frequently termed lipidome, is a potent source of biomarkers of different human diseases including cancer [38, 39]. Lipid research primarily relies on mass spectrometry techniques that are based on soft ionisation, such as electrospray ionisation (ESI) and matrix-assisted laser desorption/ionisation (MALDI). In a study based on ESI-MS/MS technique plasma samples from 199 early lung cancer cases and 147 healthy individuals were compared [40]. Among identified lipids with the highest discrimination power were: lysophosphatidylethanolamine LPE(18:1), phosphatidylethanolamine ePE(40:4), cholesterol ester C(18:2)CE, and sphingomyelin SM(22:0). The cancer classifier built of these four lipids was characterised by AUC equal to 82.3% and 80.8% at the training and validation step, respectively. Another study used a combination of MALDI-ToF profiling and UPLC-ESI-IT to analyse components of serum lipid fraction from 100 early lung cancer patients (including 31 cases detected during lung cancer screening) and 300 matched controls selected from high-risk participants of the lung screening program [41]. Results obtained by MALDI-ToF profiling allowed construction of a cancer classifier composed of seven components, which was characterised by an AUC equal to 0.88 and 98% NPV. Moreover, complementary analysis by LC-MS confirmed the lower level of several lysophosphatidylcholines in serum samples of cancer patients. Particularly interesting was LPC18:2, which itself classified cancer samples with a total weighted error below 25%. Nevertheless, this promising result remains to be validated using an independent group of individuals participating in a new lung cancer screening program.

Conclusions

Complementation of LD-CT examination with blood-based biomarkers is a rational approach to increase the efficacy and reduce the cost of the early lung cancer screening program. Such markers may be found within genome, transcriptome, proteome, and metabolome. The metabolome, however, contains the final downstream product of the other "omes". Concentrations of metabolites directly reflect the current biochemical activity of the tissues/cells, so the metabolome is nearest to the molecular phenotype of the examined organism. In recent years a few capable serum/plasma metabolome signatures that discriminate patients with early lung cancer from healthy individuals were proposed. However, none of these signatures has been validated by independent studies based on material collected during real lung cancer screening. Therefore, the validation of the real diagnostic value of these otherwise promising candidates remains a critical step in this challenging field of cancer diagnostics. Moreover, the presented results focused mostly on the qualitative but not quantitative approach, which also limits the clinical appli-

cation of these markers. Nevertheless, the story of potential application of metabolomics in the early diagnosis of lung cancer has just started. This approach has emerging potential either on its own or in combination with other more mature "omics" technologies.

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References

1. Wong MCS, Lao XQ, Ho KF, Goggins WB, Tse SLA. Incidence and mortality of lung cancer: global trends and association with socioeconomic status. Sci Rep 2017; 7: 14300.
2. Blandin Knight S, Crosbie PA, Balata H, Chudziak J, Hussell T, Dive C. Progress and prospects of early detection in lung cancer. Open Biol 2017; 7: 170070.
3. Eggert JA, Palavanzadeh M, Blanton A. Screening and Early Detection of Lung Cancer. Seminars in Oncol Nurs 2017; 33: 129-140.
4. Furrukh M. Tobacco Smoking and Lung Cancer: Perception-changing facts. Sultan Qaboos University Med J 2013; 13: 345-358.
5. Hecht SS. Cigarette smoking and lung cancer: chemical mechanisms and approaches to prevention. Lancet Oncol 2002; 3: 461-469.
6. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365: 395-409.
7. Midthun DE. Early detection of lung cancer. F1000Res 2016; 5.
8. Rzyman W, Jelitto-Gorska M, Dziedzic R, Biadacz I, Ksiazek J, Chwirot P, Marjanski T. Diagnostic work-up and surgery in participants of the Gdansk lung cancer screening programme: the incidence of surgery for non-malignant conditions. Interact Cardiovasc Thorac Surg 2013; 17: 969-973.
9. Chu GCW, Lazare K, Sullivan F. Serum and blood based biomarkers for lung cancer screening: a systematic review. BMC Cancer 2018; 18: 181.
10. Wójcik E, Sas-Korczyńska B, Tarapacz J, Rychlik U, Stasik Z, Kulpa JK. Możliwości wykorzystania markerów ProGRP, NSE i CYFRA 21-1 w diagnostyce raka płuca. NOWOTWORY J Oncol 2008; 58: 231-237.
11. Sozzi G, Boeri M. Potential biomarkers for lung cancer screening. Transl Lung Cancer Res 2014; 3: 139-148.
12. Mazzone PJ, Sears CR, Arenberg DA, et al. Evaluating Molecular Biomarkers for the Early Detection of Lung Cancer: When Is a Biomarker Ready for Clinical Use? An Official American Thoracic Society Policy Statement. Am J Respir Crit Care Med 2017; 196: e15-e29.
13. Gedvilaitė V, Schveigert D, Cicėnas S. Cell-free DNA in non-small cell lung cancer. Acta Med Litu 2017; 24: 138-144.
14. Moretti F, D'Antona P, Finardi E, et al. Systematic review and critique of circulating miRNAs as biomarkers of stage I-II non-small cell lung cancer. Oncotarget 2017; 8: 94980-94996.
15. Sullivan FM, Farmer E, Mair FS, et al. Detection in blood of autoantibodies to tumour antigens as a case-finding method in lung cancer using the EarlyCDT®-Lung Test (ECLS): study protocol for a randomized controlled trial. BMC Cancer 2017; 17: 187.
16. Patz EF, Jr., Campa MJ, Gottlin EB, Kusmartseva I, Guan XR, Herndon JE 2nd. Panel of serum biomarkers for the diagnosis of lung cancer. J Clin Oncol 2007; 25: 5578-5583.
17. Guergova-Kuras M, Kurucz I, Hempel W, et al. Discovery of lung cancer biomarkers by profiling the plasma proteome with monoclonal antibody libraries. Mol Cell Proteomics 2011; 10: M111.010298.
18. Yee J, Sadar MD, Sin DD, et al. Connective tissue-activating peptide III: a novel blood biomarker for early lung cancer detection. J Clin Oncol 2009; 27: 2787-2792.
19. Joseph S, Harrington R, Walter D, et al. Plasma osteopontin velocity differentiates lung cancers from controls in a CT screening population. Cancer Biomark 2012; 12: 177-184.
20. Ajona D, Pajares MJ, Corrales L, et al. Investigation of complement activation product c4d as a diagnostic and prognostic biomarker for lung cancer. J Natl Cancer Inst 2013; 105: 1385-1393.
21. Li XJ, Hayward C, Fong PY, et al. A blood-based proteomic classifier for the molecular characterization of pulmonary nodules. Sci Transl Med 2013; 5: 207ra142.
22. Widlak P, Pietrowska M, Polanska J, Marczyk M, Ros-Mazurczyk M, Dziadziuszko R, Jassem J, Rzyman W. Serum mass profile signature as a biomarker of early lung cancer. Lung Cancer 2016; 99: 46-52.
23. Sestini S, Boeri M, Marchiano A, et al. Circulating microRNA signature as liquid-biopsy to monitor lung cancer in low-dose computed tomography screening. Oncotarget 2015; 6: 32868-32877.
24. Schmidt B, Liebenberg V, Dietrich D, et al. SHOX2 DNA Methylation is a Biomarker for the diagnosis of lung cancer based on bronchial aspirates. BMC Cancer 2010; 10: 600-600.
25. German JB, Hammock BD, Watkins SM. Metabolomics: building on a century of biochemistry to guide human health. Metabolomics 2005; 1: 3-9.
26. Clish CB. Metabolomics: an emerging but powerful tool for precision medicine. Cold Spring Harb Mol Case Stud 2015; 1: a000588.
27. Fukusaki E. Application of Metabolomics for High Resolution Phenotype Analysis. Mass Spectrometry 2014; 3: S0045.
28. Wishart DS. Emerging applications of metabolomics in drug discovery and precision medicine. Nat Rev Drug Discov 2016; 15: 473-484.
29. Spratlin JL, Serkova NJ, Eckhardt SG. Clinical applications of metabolomics in oncology: a review. Clin Cancer Res 2009; 15: 431-440.
30. Rocha CM, Carrola J, Barros AS, et al. Metabolic signatures of lung cancer in biofluids: NMR-based metabonomics of blood plasma. J Proteome Res 2011; 10: 4314-4324.
31. Deja S, Porebska I, Kowal A, et al. Metabolomics provide new insights on lung cancer staging and discrimination from chronic obstructive pulmonary disease. J Pharm Biomed Anal 2014; 100: 369-380.
32. Puchades-Carrasco L, Jantus-Lewintre E, Perez-Rambla C, et al. Serum metabolomic profiling facilitates the non-invasive identification of metabolic biomarkers associated with the onset and progression of non-small cell lung cancer. Oncotarget 2016; 7: 12904-12916.
33. Chen Y, Ma Z, Min L, Li H, Wang B, Zhong J, Dai L. Biomarker identification and pathway analysis by serum metabolomics of lung cancer. Biomed Res Int 2015; 2015: 183624.
34. Mazzone PJ, Wang XF, Beukemann M, Zhang Q, Seeley M, Mohney R, Holt T, Pappan KL. Metabolite Profiles of the Serum of Patients with Non-Small Cell Carcinoma. J Thorac Oncol 2016; 11: 72-78.
35. Klupczynska A, Derezinski P, Garrett TJ, Rubio VY, Dyszkiewicz W, Kasprzyk M, Kokot ZJ. Study of early stage non-small-cell lung cancer using Orbitrap-based global serum metabolomics. J Cancer Res Clin Oncol 2017; 143: 649-659.
36. Fahrmann JF, Kim K, DeFelice BC, et al. Investigation of metabolomic blood biomarkers for detection of adenocarcinoma lung cancer. Cancer Epidemiol Biomarkers Prev 2015; 24: 1716-1723.
37. Ros-Mazurczyk M, Wojakowska A, Marczak L, et al. Panel of serum metabolites discriminates cancer patients and healthy participants of lung cancer screening – a pilot study. Acta Biochim Pol 2017; 64: 513-518.
38. Santos CR, Schulze A. Lipid metabolism in cancer. FEBS J 2012; 279: 2610-2623.
39. Jelonek K, Ros M, Pietrowska M, Widlak P. Cancer biomarkers and mass spectrometry-based analyses of phospholipids in body fluids. Clin Lipidol 2013; 8: 137-150.

40. Yu Z, Chen H, Ai J, et al. Global lipidomics identified plasma lipids as novel biomarkers for early detection of lung cancer. Oncotarget 2017; 8: 107899-107906.
41. Ros-Mazurczyk M, Jelonek K, Marczyk M, et al. Serum lipid profile discriminates patients with early lung cancer from healthy controls. Lung Cancer 2017; 112: 69-74.

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