

## Tumor-Dependent and -Independent Serum/Plasma Biomarkers for Early Diagnosis of Lung Cancer

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### Abstract

Lung cancer continually leads in mortality among cancer patients in the world. In order to reduce the lung cancer mortalities, early treatment is required but early diagnosis is still farfetched because the hopeful serum/plasma biomarkers identified so far lack sufficient sensitivity, specificity, and reproducibility even for diagnosis of lung cancer at late stage. During the past decades, the realization that the genetic mutations are not the only blame and the abnormal lung tissue instigated by aging, cigarette smoking, and environmental toxins plant the “soil” for lung cancer. Such discovery leads to the successful development of novel anti-cancer drugs that target the “soil” by either inhibiting angiogenesis process required for cancer cells to expand or by empowering the immune cells to kill the cancer cells in tumor. Based on the literature search, there have been no reports using the same concept to identify the “soil”-dependent cancer biomarkers. However, in recent years, the “OMICS” technologies including genomics, epigenomics, proteomics, glycomics, lipidomics, and metabolomics have been used to compare the molecular differences between the serum/plasma samples from normal and cancer patients systematically and generated large amounts of data. By reviewing the published data, we picked and discussed 12 lung cancer biomarkers and proposed them to be tumor-dependent and tumor-independent biomarkers released by liver, immune cells, or other organs/tissues. The existence of tumor-independent biomarkers indicates that the “lung cancer soil” is planted beyond the lung. Furthermore, the biomarkers can be proteins/peptides, DNA, RNA, glycans, lipids, metabolites, or any combinations of them.

**Keywords:** Genomics; Epigenomics; Proteomics; Glycomics;

Lipidomics; Metabolomics

**Abbreviations:** AC: Adenocarcinoma; SC: Squamous Cell Cancer; LCC: Large Cell Lung Cancer; SCLC: Small Cell Lung Cancer; CEA: Carcinoembryonic Antigen; CYFRA: 21-1- Cytokeratin 19 Fragment; NSE: Neuron-Specific Enolase; C9: Complement Component 9; MMPs: Matrix Metalloproteinases; CRP: c-Reactive Protein; NOS: Not Otherwise Specified.

### Introduction

Lung cancer is notoriously heterogeneous and comprised of two major types (Figure 1): small cell lung cancer (SCLC, ~15%) and non-small cell lung cancer (NSCLC, ~85%). NSCLC can be further divided histologically into adenocarcinoma (AC, ~40%), squamous carcinoma (SC, ~25%), large cell lung carcinoma (LCC, ~15%), and other (~5%) rare types including glandular tumors, carcinoid tumors, and undifferentiated carcinomas (cancer.org/cancer/lungcancer/index) (Figure 1).

Based on the data published by the National Cancer Institute ([http://seer.cancer.gov/csr/1975\\_2012](http://seer.cancer.gov/csr/1975_2012)) and CA Cancer J Clin (1989-2015) [1-26], we plotted the new cases and deaths from lung cancer in the United States during the past 40 years in Figure 2. As shown in the figure, around 220000 new cases of lung cancer have emerged in the United States annually since 2008 and ~160,000 lung cancer patients die each year in the United States during the past twenty years. Lung cancer still accounts for nearly one-third of all cancer deaths during the past 20 years and remains to be the leading cause of all cancer-related death in the United States [27].

Lung cancer at its early stage is mostly asymptomatic in most cases that make early diagnosis difficult. The current detection and diagnosis for lung cancer include physical and biochemical methods. The physical methods include X-ray, CT (Computed Tomography), and PET (Positron Emission Tomography)/CT that allow the visualization of abnormal grows in the lung [28]. The problems associated with these methods include: 1. a lack of sensitivity for early diagnosis since tumors

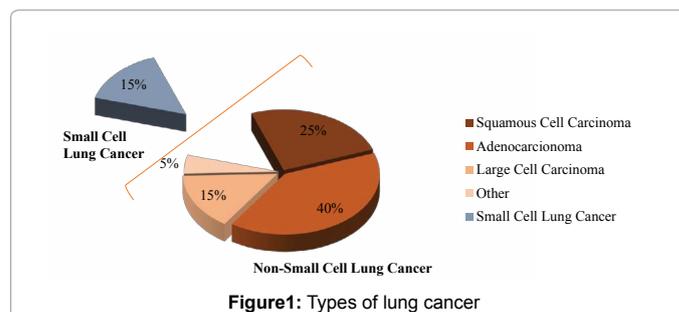


Figure 1: Types of lung cancer

at early stages are usually too small to be detected; 2. high false positive rate since some of visible lumps detected in the lung by these methods are not necessarily tumors; and 3. a high risk of additional cancer from the resulting radiations of these methods [29,30].

As a result, several biochemical methods for the detection of lung cancer are also used clinically by detecting biomarkers released by cancer cells or lung tumors into the serum/plasma [30]. The biochemical methods are less invasive and cost-effective. However, these “cancer cell” or “tumor-released biomarkers” lack sufficient sensitivity, specificity, and reproducibility even for diagnosis of lung cancer at late stage. Despite the advancement in diagnosis and treatment, the overall 5-year survival rate for lung cancer has risen only 4% (from 12% to

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16%) over the past 4 decades [31]. Since survival of patients undergoing tumor resection is greater than 80%, it has been anticipated that early detection and diagnosis of cancers before they progress to an often incurable metastatic stage will greatly improve mortality. Therefore, establishing reliable screening methods for early diagnosis of lung cancer remains to be a major challenge both in theory and in practice.

The vast majority (80–90%) of cases of lung cancer are due to long-term exposure to tobacco smoke and occur at an old age. About 10–15% of cases occur in people who have never smoked [32] and these cases are often caused by a combination of genetic factors and exposure to radon gas, asbestos [33], or other forms of air pollution, including second-hand smoke. [monographs.iarc.fr/ENG/Monographs/vol83.pdf] These causes indicate that damaged or abnormal lung tissue contributes to lung cancer development. Indeed, most of lung cancer cells are derived from epithelial cells of damaged lung tissue. Both lung cancer cells and epithelial cells reside in a microenvironment consisting of the extracellular matrix (ECM), cytokines, and chemokines as well as cellular components such as lymphocytes, bone marrow-derived cells (monocyte/macrophages, mast cells, neutrophils, eosinophils, and basophils), blood vessels (endothelial cells, pericytes, and smooth muscle cells), adipocytes, and tumor-associated fibroblasts [34] (Figure 3).

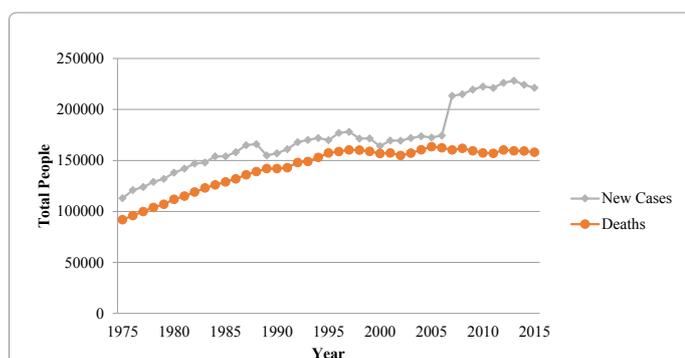


Figure 2: Lung Cancer Statistics in the United States.

The animal studies led by Bissel et al. indicate that it is the microenvironment, (Figure 3) not the accumulated genetic mutations in cancer cells, that determines tumor onset and malignant progression [34,35]. For example, analyses of ‘normal’ epithelial tissue adjacent to tumors have shown that similar patterns of mutations can be found in both, yet tumor growth is restrained by normal microenvironment and promoted by the tumor microenvironment [36,37]. In parallel, studies of large autopsy series have revealed that the majority of middle-aged and older people who die from causes other than cancer have cancer cells throughout their bodies without apparent tumor growth [38]. Therefore, tumor growth only occur when the “cancer soil” is fertile.

The existence of “cancer soil” leads to the successful development of novel anti-cancer drugs that target the abnormal lung environment by either inhibiting angiogenesis process required for cancer cells to expand or by empowering the immune cells to kill the cancer cells in tumor [35]. However, there have been no reports using the same concept to identify the “soil”-dependent cancer biomarkers. Interestingly, even the clinical used and lung cancer/tumor-specific biomarkers overlap with other cancers and inflammatory diseases, suggesting the existence of cancer soil-based common biomarkers [39].

The basic molecular building blocks of human life includes the well-known 20 amino acids that are used to make proteins and the eight nucleosides that compose DNA and RNA along with 9 monosaccharides that make different kinds of glycans and eight kinds of lipids [40]. Unlike the RNAs and proteins, the glycans and the lipids are not directly encoded by DNA but contribute to the pathogenesis and severity of an increasing number of human diseases [41-46]. Therefore, valid serum/plasma-based lung cancer biomarkers could be protein/peptides as well as DNA [47,48], RNA [49], glycans, lipids, and metabolites present in blood circulation.

In recent years, the “OMICS” technologies including genomics [50,51], epigenomics [52], proteomics [53], glycomics [54], lipidomics [55], and metabolomics [56] (Figure 4) have been used to compare the molecular differences between the serum/plasma samples from normal and cancer patients systematically [57]. The data collected so

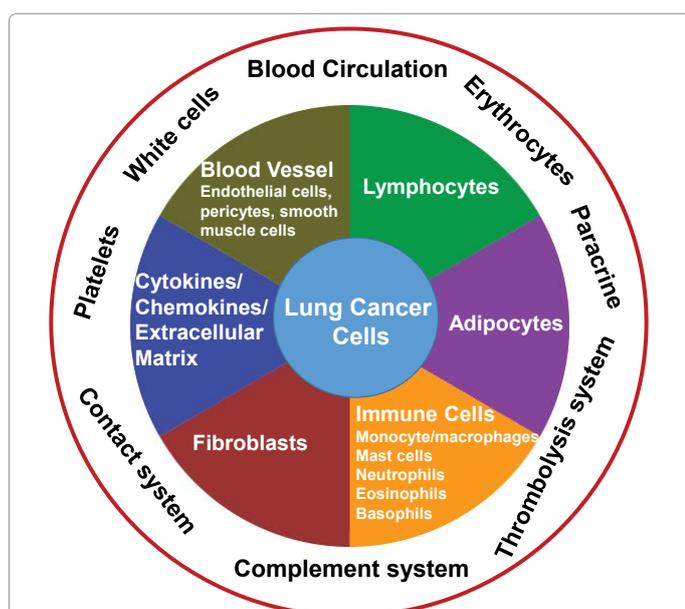


Figure 3: Possible sources of lung cancer biomarkers.

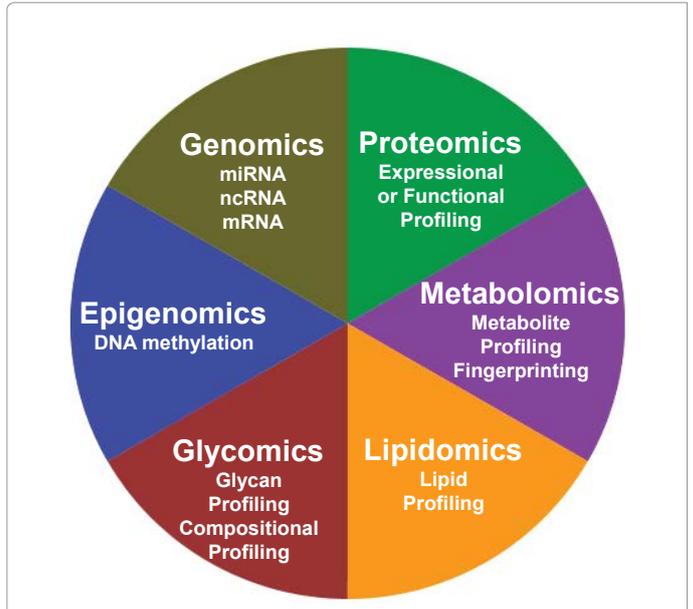


Figure 4: The molecules identified by current OMICS technologies that can be used for lung cancer biomarker discovery.

far indicates that the lung cancer biomarkers can be any kind of the biomolecules. In addition, the biomarkers can be produced by liver, lymphocytes, and other tissue/organs, which suggest that the “lung cancer soil” could be planted beyond the lung. In another word, the tumor microenvironment surrounding cancer cells as shown in Fig. 3 is only part of the “lung cancer soil”. Other “lung cancer soil” resides in abnormal tissues/organs that also support lung tumor growth by releasing signal molecules, functional enzymes, or accumulating “biomarkers” in the blood circulation (Figure 3). Therefore, serum/plasma is a reliable and comprehensive source for biomarker discovery.

### Potential biomarkers for early diagnosis of lung cancer

The use of the term “biomarker” is firstly proposed in 1980 [58]. In 1998, the Working Group of Biomarker Definitions at National Institutes of Health define a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” [59,60].

According to this definition, a measurable factor that provides information on the overall patient outcome irrespective of treatment intervention is classically considered as a prognostic biomarker in literature [60,61]. In contrast, a measurable factor, whether it comes from the cancer cells/tumor tissues or from other tissues/organs, that provides information on the likelihood of treatment efficacy is termed a predictive biomarker [60,61]. During the past, measurable factors in body fluid that can be traced back to cancer cells or tumor tissues are named cancer diagnostic biomarkers. In reality, most of clinically used lung cancer biomarkers do not vanish or still have values much higher than those of normal control patients when the tumor is surgically removed. At present, all clinically approved biomarkers for lung cancer diagnosis are either proteins or peptides and all of them lack sufficient sensitivity, specificity, and reproducibility even for diagnosis of lung cancer at late stage [62] which will be further discussed in the next section.

In our definition, the lung cancer diagnostic biomarkers can be either tumor-dependent or -independent. The tumor-dependent biomarkers are those directly associated with tumors in that their measurable amount in serum/plasma is tumor size-dependent [63], which decreases significantly after tumors being surgically removed or after a course of single or combination of cancer therapy. In contrast, tumor-independent biomarkers are those whose presence in serum/plasma is less affected by the size and the type of the tumor in cancer patients. According to this definition, predictive biomarkers can be either tumor-dependent or -independent whereas prognostic biomarkers could mostly be tumor-independent.

In current review article, in addition to three clinically used lung cancer biomarkers including carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA 21-1), and neuron-specific enolase (NSE), we picked and discussed another 9 different kinds of molecules including miRNAs, glycans, lipids and metabolites identified from serum/plasma of lung cancer patients by OMICS technologies as shown in Table 1.

**CEA and CYFRA21-1:** CEA (carcinoembryonic antigen) and CYFRA21-1 (a 36 kDa fragment of cytokeratin 19 expressed in epithelial cells) are two clinically used diagnosis, prognosis, and predictive biomarkers for lung cancer [64]. The recent advances in proteomics and metabolomics technologies including isotope-based labeling plus mass spectrometry analysis, GC-MS, protein array-based approaches, and protein bioinformatics have enabled researchers to systematically

search for serum/plasma protein biomarkers better than CEA and CYFRA21-1 for lung cancer in terms of selectivity and specificity via side-by-side comparison [65].

CEA is among the earliest elucidated tumor biomarkers [66,67]. It is normally produced in gastrointestinal tissue during fetal development and only present at very low levels in the blood of healthy adults. However, the blood level of CEA in most patients with adenocarcinomas (AC) is significantly increased, which makes CEA an excellent biomarker for detection of adenocarcinomas (AC) in colon, lung, breast, gastric, ovarian, and liver cancers even 50 years after its initial discovery [68]. For lung cancer, the highest serum concentration of CEA is observed in both lung adenocarcinoma (AC) and large cell carcinoma (LCC). However, only 40% of patients with lung adenocarcinoma (AC) show increased CEA level, which means CEA has relatively low sensitivity for lung cancer diagnosis [69]. Furthermore, the increased CEA level are not only observed in other types of cancers but also observed in benign tumors and even in the serum of smokers, which means CEA also lacks required specificity for lung cancer diagnosis. Clinically, CEA is mainly used to evaluate the prognosis and treatment effect of NSCLC and to determine recurrence of lung adenocarcinoma (AC) in patients who had high serum level of CEA. The high CEA level is associated with poor prognosis, high risk of cerebral metastasis, and a poor survival rate in lung cancer patients [70].

CYFRA 21-1 is a 36 kDa fragment of cytokeratin 19 that is expressed in epithelial cells. Pathological studies prove that CYFRA 21-1 is exclusively expressed in lung tissues [71]. At present, CYFRA 21-1 is the best biomarker for squamous carcinoma (SC) with a sensitivity of 59% and a specificity of 94% [72]. Since CYFRA 21-1 is preferentially excreted by the kidney, renal failure will result in elevated serum level. Therefore, patients with kidney diseases are excluded when CYFRA 21-1 is used as a biomarker for cancer diagnosis. Remarkably, CYFRA 21-1 rarely increases in SCLC. CYFRA 21-1 has been used as an independent prognostic biomarker for both early and advanced stages of NSCLC [73]. In addition to lung cancer, a slight CYFRA 21-1 increase can be noted in other lung diseases, such as fibrosis, chronic obstructive pulmonary disease, tuberculosis, and acute infection [74]. Some benign tumors also show increased serum level of CYFRA 21-1, such as in urologic, gastrointestinal, and gynecological tumors [75].

Combining CEA with CYFRA 21-1 increases the sensitivity and specificity for the diagnosis of lung cancer [76]. However, such combination is still far from satisfactory for diagnosis of lung cancer due to unsatisfactory sensitivity and specificity.

**Neuron-Specific Enolase (NSE):** An increased serum NSE level (>25 ng/mL) is observed in 72% of SCLC patients and 8% in other types of lung cancer. Thus, NSE has been a clinically used biomarker for SCLC. NSE is a glycolytic enzyme that is mainly located in the central and peripheral neurons and neuroendocrine tissues. NSE is composed of two polypeptide chains, each has a molecular weight of 39 kDa. It can also be found in smooth muscle, kidney, and some other tissues. NSE is known to be present in lymphocyte, erythrocytes, and platelets as well.

Compared with the patients in early stage SCLC, patients in late stage SCLC have significantly higher level of NSE [77,78]. Thus, NSE also serves as an important diagnostic, predictive, and prognosis biomarker for SCLC [79]. High NSE level (>100 ng/mL) suggests the high probability of SCLC. However, the high levels of NSE can also be observed in patients with benign neuroendocrine tumor, liver tumor, lymphoma, and seminoma [80]. Moderate NSE level in serum is often observed in pancreatic, gastric, colon, and breast cancer patients [81]. These characteristics of NSE make it only use for differential diagnosis,

Serum/plasma Biomarkers	Tumor-dependent?	Lung cancer Classification	Sensitivity & specificity	Serum/plasma biomarkers in other diseases	References
CEA and CYFRA21-1	Partially	AC, SC, LCC	Sensitivity : 77% Specificity : 93%	NOS	[76, 126]
NSE	Partially	SCLC	Sensitivity : 76% Specificity : 92%	Benign neuroendocrine tumor, liver tumor, lymphoma, and seminoma; pancreatic, gastric, colon, and breast cancers	[80, 81, 77, 79, 78]
Autoantibodies against p53, c-myc, HER2, IGFBP-2	No	AC, SC SCLC, LCC	--	Breast, colon, stomach, liver, glioma, colorectal, prostate, ovarian and breast cancer	[83, 85, 88, 84, 87, 86, 82, 89]
C9	No	SC, SCLC	Sensitivity : 53% Specificity : 89%	Cervical, gastric, colorectal and breast cancer	[93]
Fibrinogen	No		--		[96]
MMPs	Partially	AC, SC, SCLC	--	Colorectal, esophageal, pancreatic, gastric, breast cancers, and melanoma	[98, 102, 99, 101, 103]
CRP and IL-6	No	All	--	All cancers and inflammation diseases	[105, 107, 104, 106]
miRNAs	Partially	AC, SC SCLC, NOS	--	All cancers	[109, 108, 110]
Sphingosine	Partially	AC, SC, LCC, SCLC	Sensitivity : 88% Specificity : 88%	NOS	[65]
2,3,4-Trihydroxybutyric acid	No	AC, SC, LCC, SCLC	Sensitivity : 87% Specificity : 83%	NOS	[65]
Glycans	Partially	AC, SC, LCC, SCLC	Sensitivity : 85% Specificity : 86%	NOS	[126]
Monosaccharide compositions	Partially	AC, SC, LCC, SCLC	--	Breast, colon, stomach, liver, glioma, colorectal, prostate, ovarian and breast cancers	[133]

**Table 1:** Selected serum/plasma biomarkers of lung cancer.

particularly in SCLC identification.

**Autoantibodies against p53, c-myc, 14-3-3, and IGFBP-2:** Cancer patients frequently develop autoantibodies [82]. Levels of certain autoantibodies have been found to arise prior tumor formation and before the development of any symptoms, suggesting that autoantibodies might serve as highly effective biomarkers for the early diagnosis of cancers. Advanced proteomics technologies have allowed the demonstration of the appearance of a large number of autoantibodies against tumor antigens in the serum of different cancer patients. The autoantibodies against many autoantigens are found in the sera of lung cancer patients. p53, c-myc, 14-3-3, and IGFBP-2 are part of the detected autoantigens.

p53 is a prominent tumor suppressor. It has been reported that anti-p53 antibodies may develop months to years before the clinical diagnosis of cancer [83]. Remarkably, anti-p53 antibodies have been detected in the sera of heavy smokers who developed lung cancer, making it useful for early diagnosis of lung cancer for heavy smokers [84].

c-Myc is a multifunctional nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation. It is a very strong proto-oncogene and often found to be upregulated in many types of cancers. Detecting a panel of autoantibodies present in the sera of lung cancer patients consisting c-myc, p53, Her-2, NY-ESO-1, MUC1, cancer antigen 1, and TAA GBU4-5 resulted 76% sensitivity and 92% specificity for lung cancer diagnosis [85].

14-3-3 proteins are cytoplasmic proteins and have the ability to bind to more than 200 signaling proteins, including kinases, phosphatases, and transmembrane receptors. 14-3-3 autoantibody was found to be a potential biomarker for the early-stage diagnosis of lung cancer [86]. When used along with autoantibodies to PGP 9.5 and annexin I, the three autoantibodies display a sensitivity of 55% and specificity of 95% for lung cancer patients [87].

Insulin-like growth factor-binding protein-2 [IGFBP-2] is a member of the insulin-like growth factor-binding protein family [IGFBPs]. The main function of IGFBP-2 is to inhibit IGF-mediated growth and development rates. Increased levels of IGFBP-2 have been found in solid tumors and in serum/plasma from patients with different types of cancers [88]. A recent study showed the presence of circulating anti-IGFBP-2 autoantibodies in lung cancer patients. Most importantly, combining anti-IGFBP-2 autoantibody detection and the levels of IGFBP-2 increases the sensitivity (86%) and specificity (58%) for lung cancer diagnosis compared to that of IGFBP-2 alone [89].

**Complement component 9 (C9):**C9 is one of proteins in the complement system, which is a part of the immune system and consists of over 30 proteins mainly synthesized in the liver, released into the blood, and normally circulated as inactive precursors (pro-proteins) [90]. When stimulated, the end-result of the activation cascade is massive amplification of the response and assembles the cell-killing membrane attack complex (MAC-C5b, C6, C7, C8 and C9) where C9 is a critical member and induces pores on cell membranes [91,92]. It has been demonstrated that C9 has a specificity of 89% and a sensitivity of 53% for lung squamous carcinomas (SC) detection [93]. C9 is a glycoprotein that has two potential N-linked glycosylation sites. Serum analysis showed increased fucosylation levels of C9 in squamous carcinomas (SC) lung patients by using a lectin approach. Simultaneously measuring C9 and C9 fucosylation levels further enhances the sensitivity and selectivity of the combined biomarkers for squamous carcinomas (SC) detection of lung patients [93].

**Fibrinogen:** Fibrinogen is a soluble, large, and complex glycoprotein synthesized in the liver by hepatocytes, which is converted by thrombin into fibrin during blood clot formation. Cancer is associated with hypercoagulopathy and has increased risk of thrombosis that negatively influences patient morbidity and mortality [94,95]. The prognostic significance of fibrinogen in patients with early stages of NSCLC has been reported [96]. Patients with higher baseline fibrinogen levels have

lower 3-year progression-free survival (49.2% vs. 63.3%) and lower overall survival rates (66.0% vs. 80.9%) than patients with normal serum fibrinogen concentrations. Higher levels of fibrinogen are also associated with cardiovascular disease, a leading cause of human death. Thus, the plasma levels of fibrinogen and other proteins involved in coagulation cascade in NSCLC should be closely monitored for the biomarker discovery [94].

**Matrix metalloproteinases (MMPs):** MMPs are calcium-dependent zinc-containing endopeptidases that share a similar structure and which collectively have the capacity to degrade virtually every component of the extracellular matrix (ECM). The MMPs play an important role in tissue remodeling associated with various physiological or pathological processes such as morphogenesis, angiogenesis, tissue repair, cirrhosis, arthritis, and metastasis. MMP-1 is a collagenase that cleaves collagen types I, II, III, VII and X [97]. MMP-1 is well known to be overexpressed in various cancer cells during the invasion and metastasis phases [98]. Higher plasma levels of MMP-1 and tumor progression (i.e., tumor size, staging and lymphatic invasion) are associated with a lower patient survival rate [99]. MMP-7, also known as matrilysin, is a member of the MMP family. MMP7 cleaves B chain of insulin and other proteins including a proteoglycan, syndecan-1 [100]. The plasma protein levels of MMP-7 increase in the peripheral blood of lung cancer patients. The sensitivity and specificity as a lung cancer diagnostic biomarker are 62% and 76%, respectively [101]. MMP-9 is a collagenase that cleaves type IV collagen, a major structural protein of basement membranes, including the blood vessel basement membrane. An analysis of 19 independent studies showed that high MMP-9 expression levels are associated with a poor prognosis in patients with NSCLC [102,103]. In summary, the plasma levels of MMPs might be associated with cancer development. MMPs are interesting lung cancer biomarkers.

**CRP and IL-6:** Inflammation has been recognized as an important contributing factor in the development and progression of lung cancer. C-reactive protein (CRP) and interleukin-6 (IL-6) are acute-phase proteins involved in cancer development. CRP is a nonspecific but sensitive biomarker of inflammation synthesized in the liver by hepatocytes and present in blood circulation. IL-6 induces the synthesis of CRP. Increased CRP level is positively correlated with weight loss, anorexia-cachexia syndrome, extent of disease, and recurrence in advanced cancer. The role of CRP as a predictive biomarker of survival has been demonstrated in multiple tumors. Many studies have shown that NSCLC patients with elevated preoperative serum CRP levels experienced worse survival than patients with undetectable CRP levels [104,105]. The concentration of serum IL-6 is associated with tumor progression and overall survival in patients with NSCLC [106]. The combined measurement of both serum CRP and IL-6 levels have better sensitivity and specificity than those of currently used biomarkers, such as CEA and CA19-9 for diagnosis of both gastric and esophagus cancers [107]. However, such studies have not been reported for lung cancer yet.

**miRNAs:** miRNAs are small non-coding RNA molecules (containing about 22 nucleotides), which functions in RNA silencing and post-transcriptional regulation of gene expression and shows tissue-specific signatures. In addition, miRNAs are stable in serum that makes them good candidates for biomarker discovery [108]. Currently, they are the most studied molecules as biomarkers both for cancer and other diseases [49,110]. Several miRNA-based biomarkers for cancer diagnosis are under clinical trials. Based on the results from different studies, possible miRNA-based biomarkers for early diagnosis of lung cancer include miR-25, 141, 155, 223, 629, and 1254. It is also

demonstrated that the levels of miR-652 and miR-660 are significantly elevated in the sera of patients with stage I lung ADC compared with healthy individuals, and the combination of miR-652+miR-660 and Cyfra21-1 give 0.936 AUC for distinguishing patients with stage I lung ADC from health individuals with 90% sensitivity and 87% specificity [110].

**Sphingosine:** Sphingosine (2-amino-4-octadecene-1, 3-diol) is an 18-carbon 2-amino alcohol with an unsaturated hydrocarbon chain, which forms a primary part of sphingolipids. Sphingolipids such as sphingosine and sphingosine-1-phosphate are important cell membrane components. Their role in tumorigenesis has been extensively documented [111]. Sphingosine and sphingosine-1-phosphate are mutually transformative and maintain homeostasis through enzymatic reactions. Sphingosine-1-phosphate is a bioactive compound and inhibits apoptosis and promotes cell proliferation whereas sphingosine is found through metabolomics studies to be a biomarker for lung cancer diagnosis with a sensitivity of 88% and a specificity of 88%. Remarkably, sphingosine alone is as good as the clinically used biomarkers such as CEA (sensitivity 77% and specificity 93%, respectively) and CYFRA 21-1 (sensitivity 57% and specificity 978%, respectively) when the same serum samples from both lung cancer patients and normal controls are used in the same study [65].

**2,3,4-Trihydroxybutyric acid:** 2,3,4-trihydroxybutyric acid is a metabolite with an unknown source of production [112,113]. The levels of 2,3,4-trihydroxybutyric acid in lung cancer patients are decreased 3-fold compared to that of healthy controls. The sensitivity and specificity of 2,3,4-trihydroxybutyric acid as lung cancer biomarker are 87% and 83%, respectively, which makes it a very promising diagnosis biomarker for lung cancer [65]. More strikingly, its levels in lung cancer patient sera are unchanged before and after surgical removal of the tumor, indicating that this unique metabolite is not produced by cancer cells or the tumor and might be associated with system malfunction in lung cancer patients.

**Glycans:** Glycans are most information-dense biomolecules in animal cells [46, 114, 115]. More than 70% proteins in blood circulation are modified by glycans. Two major types (>95%) of glycans are N-linked and O-linked glycans [116-118], which are assembled onto proteins in the Golgi by over two hundred different kinds of glycosyltransferases, nine different types of sugar nucleotides as monosaccharide donors, and many additional regulatory proteins in a protein- cell-, tissue- and environment-sensitive manner [119-122]. Glycans add wide-ranging biological functions to proteins, such as cellular recognition, adhesion, or cellular signaling transduction [123]. Glycans also participate in each steps of oncogenesis, e. g. invasion, metastasis and angiogenesis [44,124,125 118]. Theoretically, glycans might be the most promising biomarkers essential for early diagnosis of cancer and other diseases.

Indeed, side-by-side comparison of N-glycan structures of serum samples from lung cancer patients and normal controls showed significant lung cancer-related glycan structural alterations in that sialyl Lewis X, monoantennary glycans, and highly sialylated glycans are increased whereas the core-fucosylated biantennary glycans are decreased. In addition, there are significant alterations in sialylation with increases in trisialylated glycans and decreases in disialylated glycans in the serum of lung cancer patients. Using receiver operator characteristic (ROC) curves, the total glycan data generate a sensitivity and specificity of 85% and 86%, respectively, combined with an AUC of 0.938 for lung cancer patients compared to controls [126,127]. In addition, a significant increase in the levels of SLe<sup>x</sup> glycan structures in squamous carcinoma (SC) relative to adenocarcinoma (AC) is also

observed, suggesting the levels of SLex glycan structures could be used to distinguish adenocarcinoma (AC) from squamous carcinoma (SC).

Fascinatingly, most of clinically used cancer biomarkers are glycoproteins [128,127]. More importantly, the specificity and sensitivity for cancer detection can be greatly enhanced by simultaneously measuring the levels of the protein and fucose-containing glycans not only for C9 but also for  $\alpha$ -fetoprotein [129,130]. As a result, detecting both protein and glycan levels of  $\alpha$ -fetoprotein in serum for liver cancer diagnosis has been an official procedure used clinically both in Japan and the United States for many years [131].

**Monosaccharide compositions:** Nine monosaccharides including fucose, galactose, glucose, glucuronic acid, mannose, N-acetylglucosamine, N-acetylgalactosamine, N-acetylneuraminic acid, and xylose are the build blocks of all human serum/plasma glycans [40]. Over 7000 different glycan structures have been identified by glycomics technologies so far [132]. However, identification of the glycan structure involves multiple steps of sample preparations and mass spectrometry-based analyses. Such procedures lack the simplicity and repeatability required for clinical applications. To overcome the technical difficulty, a Chinese patent describing a novel cancer diagnostic assay based on monosaccharide composition analysis has been published recently. This assay only uses 10  $\mu$ l of serum/plasma from either cancer patients or normal controls to hydrolyze all the serum/plasma glycans into monosaccharides. The monosaccharide compositions are then obtained by HPLC-based analysis. Interestingly, the quantity of each monosaccharide has cancer type-specific changes. Overall changes in monosaccharide compositions not only distinguish cancer patients from normal controls but also distinguish lung cancer patients from other cancer patients [133].

## Conclusion

The 12 different types of biomarkers for lung cancer diagnosis discussed above reflect the abnormal coagulation, inflammation, glycosylation, transcription, and metabolism associated with lung cancer patients. Some of these potential serum/plasma biomarkers released by “the cancer soil” into the blood circulation corroborates with lung tumor. They might be present in serum/plasma long before the tumor is visible by the physical detection methods and are hopeful to be developed into early diagnosis biomarkers for lung cancer. Most importantly, the next generation of serum/plasma biomarkers can be proteins/peptides, DNA, RNA, glycans, lipids, metabolites, or any combinations of them. Thus, the broadened concept of “lung cancer soil” and the new definition of lung cancer diagnostic biomarkers proposed in current review article based on the data obtained by current OMICS technologies might be insightful for the continued effort in developing novel biomarkers for early diagnosis of lung cancer.

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