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

Alexander Lu[1] and Lijuan Zhang[2*]

[1]St. Charles West High School, 3601 Droste Road, St. Charles, MO 63301, USA
[2]School of Medicine and Pharmacy, Ocean University of China, 5 Yushan Road, Qingdao, China

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) 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

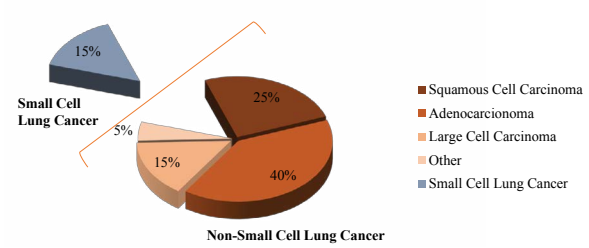

Figure1: Types of lung cancer

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

***Corresponding author:** Zhang L, School of Medicine and Pharmacy, Ocean University of China, 5 Yushan Road, Qingdao, China, Tel: +86-532-82031615; E-mail: lijuanzhang@ouc.edu.cn

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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).

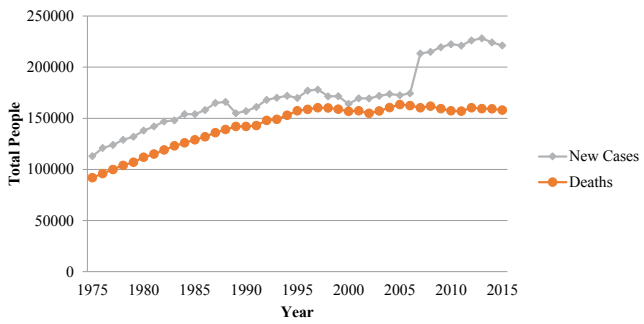

Figure 2: Lung Cancer Statistics in the United States.

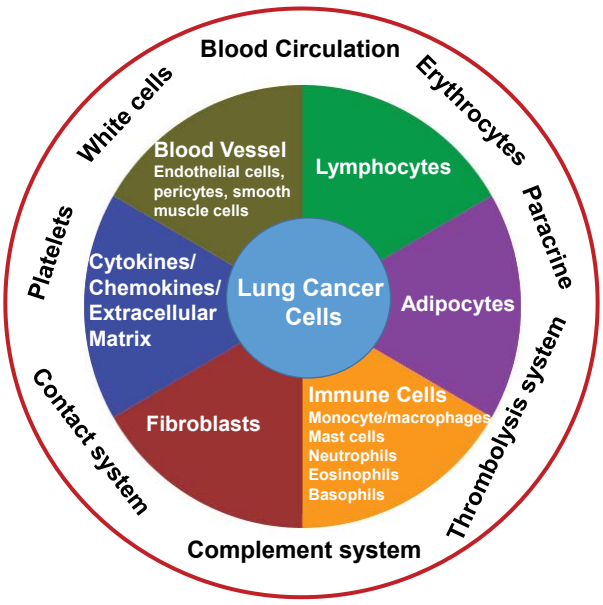

Figure 3: Possible sources of lung cancer biomarkers.

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

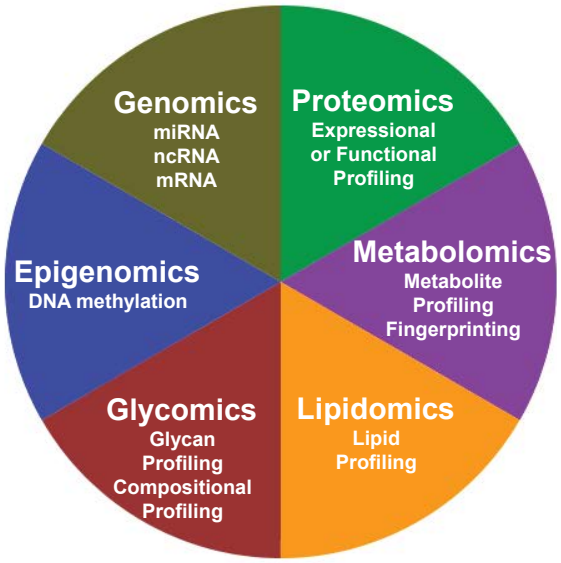

Figure 4: The molecules identified by current OMICS technologies that can be used for lung cancer biomarker discovery.

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 contract, 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 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 SLex 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 α-fetoprotein [129,130]. As a result, detecting both protein and glycan levels of α-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 μl 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.

References

1. Silverberg E, Lubera JA (1989) Cancer statistics. Cancer J Clin 39: 3-20.
2. Silverberg E, Boring CC, Squires TS (1990) Cancer statistics. Cancer J Clin 40: 9-26.
3. Boring CC, Squires TS, Tong T (1991) Cancer statistics. Cancer J Clin 41: 19-36.
4. Boring CC, Squires TS, Tong T (1992) Cancer statistics. Cancer J Clin 42: 19-38.
5. Boring CC, Squires TS, Tong T (1993) Cancer statistics. CA Cancer J Clin 43: 7-26.
6. Boring CC, Squires TS, Tong T, Montgomery S (1994) Cancer statistics. Cancer J Clin 44: 7-26.
7. Wingo PA, Tong T, Bolden S (1995) Cancer statistics. Cancer J Clin 45: 8-30.
8. Parker SL, Tong T, Bolden S, Wingo PA (1996) Cancer statistics. CA Cancer J Clin 46: 5-27.
9. Parker SL, Tong T, Bolden S, Wingo PA (1997) Cancer statistics. CA Cancer J Clin 47: 5-27.
10. Landis SH, Murray T, Bolden S, Wingo PA (1998) Cancer statistics, 1998. Cancer J Clin 48: 6-29.
11. Landis SH, Murray T, Bolden S, Wingo PA (1999) Cancer statistics, 1999. Cancer J Clin 49: 8-31.
12. Greenlee RT, Murray T, Bolden S, Wingo PA (2000) Cancer statistics. Cancer J Clin 50: 7-33.
13. Greenlee RT, Hill-Harmon MB, Murray T, Thun M (2001) Cancer statistics. Cancer J Clin 51: 15-36.
14. Jemal A, Thomas A, Murray T, Thun M (2002) Cancer statistics. Cancer J Clin 52: 23-47.
15. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, et al. (2003) Cancer statistics. Cancer J Clin 53: 5-26.
16. Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, et al. (2004) Cancer statistics. Cancer J Clin 54: 8-29.
17. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, et al. (2005) Cancer statistics. Cancer J Clin 55: 10-30.
18. Jemal A, Siegel R, Ward E, Murray T, Xu J, et al. (2006) Cancer statistics. Cancer J Clin 56: 106-130.
19. Jemal A, Siegel R, Ward E, Murray T, Xu J, et al. (2007) Cancer statistics. CA Cancer J Clin 57: 43-66.
20. Jemal A, Siegel R, Ward E, Hao Y, Xu J, et al. (2008) Cancer statistics, 2008. Cancer J Clin 58: 71-96.
21. Jemal A, Siegel R, Ward E, Hao Y, Xu J, et al. (2009) Cancer statistics, 2009. Cancer J Clin 59: 225-249.
22. Jemal A, Siegel R, Xu J, Ward E (2010) Cancer statistics. Cancer J Clin 60: 277-300.
23. Siegel R, Naishadham D, Jemal A (2012) Cancer statistics. CA Cancer J Clin 62: 10-29.
24. Siegel R, Naishadham D, Jemal A (2013) Cancer statistics. Cancer J Clin 63: 11-30.
25. Siegel R, Ma J, Zou Z, Jemal A (2014) Cancer statistics. Cancer J Clin 64: 9-29.
26. Siegel RL, Miller KD, Jemal A (2015) Cancer statistics. CA Cancer J Clin 65: 5-29.
27. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Dicker D, Pain A, Hamavid H, et al. (2015) The Global Burden of Cancer. JAMA Oncol : 505-527.
28. Kim H, Park CM, Goo JM, Wildberger JE, Kauczor HU (2015) Quantitative Computed Tomography Imaging Biomarkers in the Diagnosis and Management of Lung Cancer. See comment in PubMed Commons below Invest Radiol 50: 571-583.
29. Ahn JM, Cho JY (2013) Current serum lung cancer biomarkers. J Mol Biomark Diagn 4: 2.
30. Greenberg AK, Lee MS (2007) Biomarkers for lung cancer: clinical uses. Curr Opin Pulm Med 13: 249-255.
31. Sharma D, Newman TG1, Aronow WS2 (2015) Lung cancer screening: history, current perspectives, and future directions. Arch Med Sci 11: 1033-1043.
32. Thun MJ1, Hannan LM, Adams-Campbell LL, Boffetta P, Buring JE, et al. (2008) Lung cancer occurrence in never-smokers: an analysis of 13 cohorts and 22 cancer registry studies. PLoS Med 5: e185.
33. O'Reilly KM, Mclaughlin AM, Beckett WS, Sime PJ (2007) Asbestos-related lung disease. Am Fam Physician 75: 683-688.
34. Correia AL, Bissell MJ (2012) The tumor microenvironment is a dominant force in multidrug resistance. Drug Resist Updat 15: 39-49.
35. Bissell MJ, Hines WC (2011) Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. Nat Med 17: 320-329.

36. Deng G, Lu Y, Zlotnikov G, Thor AD, Smith HS (1996) Loss of heterozygosity in normal tissue adjacent to breast carcinomas. Science 274: 2057-2059.

37. Washington C, Dalbegue F, Abreo F, Taubenberger JK, Lichy JH (2000) Loss of heterozygosity in fibrocystic change of the breast: genetic relationship between benign proliferative lesions and associated carcinomas. Am J Pathol 157: 323-329.

38. Folkman J, Kalluri R (2004) Cancer without disease. Nature 427: 787.

39. Yotsukura S, Mamitsuka H (2015) Evaluation of serum-based cancer biomarkers: a brief review from a clinical and computational viewpoint. Crit Rev Oncol Hematol 93: 103-115.

40. Marth JD (2008) A unified vision of the building blocks of life. Nat Cell Biol 10: 1015-1016.

41. Gagneux P, Varki A (1999) Evolutionary considerations in relating oligosaccharide diversity to biological function. Glycobiology 9: 747-755.

42. Fahy E, Subramaniam S, Murphy RC, Nishijima M, Raetz CR, et al. (2009) Update of the LIPID MAPS comprehensive classification system for lipids. J Lipid Res 50 Suppl: S9-14.

43. Fahy E, Subramaniam S, Brown HA, Glass CK, Merrill AH Jr, et al. (2005) A comprehensive classification system for lipids. J Lipid Res 46: 839-861.

44. Dube DH, Bertozzi CR (2005) Glycans in cancer and inflammation--potential for therapeutics and diagnostics. Nat Rev Drug Discov 4: 477-488.

45. Ohtsubo K, Marth JD (2006) Glycosylation in cellular mechanisms of health and disease. Cell 126: 855-867.

46. Zhang L (2010) Glycosaminoglycans in development, health and disease. Preface. Prog Mol Biol Transl Sci 93: 17-18.

47. Nie K, Jia Y, Zhang X (2015) Cell-free circulating tumor DNA in plasma/serum of non-small cell lung cancer. Tumour Biol 36: 7-19.

48. Lee SM, Park JY, Kim DS (2012) Methylation of TMEFF2 gene in tissue and serum DNA from patients with non-small cell lung cancer. Mol Cells 34: 171-176.

49. Qin X, Xu H, Gong W, Deng W (2015) The Tumor Cytosol miRNAs, Fluid miRNAs, and Exosome miRNAs in Lung Cancer. Front Oncol 4: 357.

50. Stephens PJ, Tarpey PS, Davies H, Van Loo P, Greenman C, et al. (2012) The landscape of cancer genes and mutational processes in breast cancer. Nature 486: 400-404.

51. Gomperts BN, Spira A, Massion PP, Walser TC, Wistuba II, et al. (2011) Evolving concepts in lung carcinogenesis. Semin Respir Crit Care Med 32: 32-43.

52. Sturm D, Witt H, Hovestadt V, Khuong-Quang DA, Jones DT, et al. (2012) Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. ncer Cell 22: 425-437.

53. Rohlff C (2004) New approaches towards integrated proteomic databases and depositories. Expert Rev Proteomics 1: 267-274.

54. Vanderschaeghe D, Festjens N, Delanghe J, Callewaert N (2010) Glycome profiling using modern glycomics technology: technical aspects and applications. Biol Chem 391: 149-161.

55. Han X (2007) An update on lipidomics: progress and application in biomarker and drug development. Curr Opin Mol Ther 9: 586-591.

56. Wang X, Zhang A, Sun H (2013) Power of metabolomics in diagnosis and biomarker discovery of hepatocellular carcinoma. Hepatology 57: 2072-2077.

57. Bhati A, Garg H, Gupta A, Chhabra H, Kumari A, et al. (2012) Omics of cancer. Asian Pac J Cancer Prev 13: 4229-4233.

58. Aronson JK (2005) Biomarkers and surrogate endpoints. Br J Clin Pharmacol 59: 491-494.

59. Strimbu K, Tavel JA (2010) What are biomarkers? Curr Opin HIV AIDS 5: 463-466.

60. Biomarkers Definitions Working Group (2001) Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 69: 89-95.

61. Oldenhuis CN, Oosting SF, Gietema JA, de Vries EG (2008) Prognostic versus predictive value of biomarkers in oncology. Eur J Cancer 44: 946-953.

62. Hassanein M, Callison JC, Callaway-Lane C, Aldrich MC, Grogan EL, et al. (2012) The state of molecular biomarkers for the early detection of lung cancer. ncer Prev Res (Phila) 5: 992-1006.

63. Hori SS, Gambhir SS (2011) Mathematical model identifies blood biomarker-based early cancer detection strategies and limitations. Sci Transl Med 3: 109ra116.

64. Tsay JC, DeCotiis C, Greenberg AK, Rom WN (2013) Current readings: blood-based biomarkers for lung cancer. Semin Thorac Cardiovasc Surg 25: 328-334.

65. Chen Y, Ma Z, Min L, Li H, Wang B, et al. (2015) Biomarker identification and pathway analysis by serum metabolomics of lung cancer. Biomed Res Int 2015: 183624.

66. Gold P, Freedman SO (1965) Specific carcinoembryonic antigens of the human digestive system. J Exp Med 122: 467-481.

67. Gold P, Freedman So (1965) Demonstration of Tumor-Specific Antigens in Human Colonic Carcinomata by Immunological Tolerance and Absorption Techniques. J Exp Med 121: 439-462.

68. Ohwada A, Takahashi H, Nagaoka I, Iwabuchi K, Mikami O, et al. (1995) Effect of cigarette smoke on the mRNA and protein expression of carcinoembryonic antigen (CEA), a possible chemoattractant for neutrophils in human bronchioloalveolar tissues. Thorax 50: 651-657.

69. Grunnet M, Sorensen JB (2012) Carcinoembryonic antigen (CEA) as tumor marker in lung cancer. Lung Cancer 76: 138-143.

70. Okada M, Nishio W, Sakamoto T, Uchino K, Yuki T, et al. (2004) Prognostic significance of perioperative serum carcinoembryonic antigen in non-small cell lung cancer: analysis of 1,000 consecutive resections for clinical stage I disease. Ann Thorac Surg 78: 216-221.

71. Buccheri G, Ferrigno D (2001) Lung tumor markers of cytokeratin origin: an overview. Lung Cancer 34 Suppl 2: S65-69.

72. PaviÄ‡eviÄ‡ R, BubanoviÄ‡ G, FranjeviÄ‡ A, StanciÄ‡-Rokotov D, Samarzija M (2008) CYFRA 21-1 in non-small cell lung cancer--standardisation and application during diagnosis. Coll Antropol 32: 485-498.

73. Ono A, Takahashi T, Mori K, Akamatsu H, Shukuya T, et al. (2013) Prognostic impact of serum CYFRA 21-1 in patients with advanced lung adenocarcinoma: a retrospective study. BMC Cancer 13: 354.

74. Xu RH, Liao CZ, Luo Y, Xu WL, Li K, et al. (2015) Optimal cut-off values for CYFRA 21-1 expression in NSCLC patients depend on the presence of benign pulmonary diseases. Clin Chim Acta 440: 188-192.

75. Piao X, Kong TW, Chang SJ, Paek J, Chun M, et al. (2015) Pretreatment serum CYFRA 21-1 level correlates significantly with survival of cervical cancer patients: a multivariate analysis of 506 cases. Gynecol Oncol 138: 89-93.

76. Chantapet P, Riantawan P, Lebnak P, Getngern P (2000) Utility of serum cytokeratin 19 fragment (CYFRA 21-1) and carcinoembryonic antigen (CEA) as tumour markers for non-small cell lung cancer. J Med Assoc Thai 83: 383-391.

77. Kanemoto K, Satoh H, Ishikawa H, Sekizawa K (2006) Neurone-specific enolase and liver metastasis in small cell lung cancer. Clin Oncol (R Coll Radiol) 18: 505.

78. Kobayashi Y, Tokuchi Y, Hashimoto T, Hayashi M, Nishimura H, et al. (2004) Molecular markers for reinforcement of histological subclassification of neuroendocrine lung tumors. ncer Sci 95: 334-341.

79. Karnak D, Beder S, Kayacan O, IbiÅŸ E, Oflaz G (2005) Neuron-specific enolase and lung cancer. Am J Clin Oncol 28: 586-590.

80. FranjeviÄ‡ A, PaviÄ‡eviÄ‡ R, BubanoviÄ‡ G (2012) Differences in initial NSE levels in malignant and benign diseases of the thoracic wall. Clin Lab 58: 245-252.

81. Yang H, Mi R, Wang Q, Wei X, Yin Q, et al. (2014) Expression of neuron-specific enolase in multiple myeloma and implications for clinical diagnosis and treatment. PLoS One 9: e94304.

82. Zaenker P, Ziman MR (2013) Serologic autoantibodies as diagnostic cancer biomarkers--a review. ncer Epidemiol Biomarkers Prev 22: 2161-2181.

83. Abendstein B, Marth C, Müller-Holzner E, Widschwendter M, Daxenbichler G, et al. (2000) Clinical significance of serum and ascitic p53 autoantibodies in epithelial ovarian carcinoma. ncer 88: 1432-1437.

84. Lubin R, Zalcman G, Bouchet L, Trédanel J, Legros Y, et al. (1995) Serum p53

antibodies as early markers of lung cancer. Nat Med 1: 701-702.

85. Chapman CJ, Murray A, McElveen JE, Sahin U, Luxemburger U, et al. (2008) Autoantibodies in lung cancer: possibilities for early detection and subsequent cure. Thorax 63: 228-233.

86. Qiu J, Choi G, Li L, Wang H, Pitteri SJ, et al. (2008) Occurrence of autoantibodies to annexin I, 14-3-3 theta and LAMR1 in prediagnostic lung cancer sera. J Clin Oncol 26: 5060-5066.

87. Pereira-Faca SR, Kuick R, Puravs E, Zhang Q, Krasnoselsky AL, et al. (2007) Identification of 14-3-3 theta as an antigen that induces a humoral response in lung cancer. ncer Res 67: 12000-12006.

88. Lin Y, Jiang T, Zhou K, Xu L, Chen B, et al. (2009) Plasma IGFBP-2 levels predict clinical outcomes of patients with high-grade gliomas. Neuro Oncol 11: 468-476.

89. Zhang Y, Ying X, Han S, Wang J, Zhou X, et al. (2013) Autoantibodies against insulin-like growth factorâ€'binding protein-2 as a serological biomarker in the diagnosis of lung cancer. Int J Oncol 42: 93-100.

90. Liszewski MK, Farries TC, Lublin DM, Rooney IA, Atkinson JP (1996) Control of the complement system. Adv Immunol 61: 201-283.

91. Merle NS, Church SE, Fremeaux-Bacchi V, Roumenina LT (2015) Complement System Part I - Molecular Mechanisms of Activation and Regulation. Front Immunol 6: 262.

92. Merle NS, Noe R, Halbwachs-Mecarelli L, Fremeaux-Bacchi V3, Roumenina LT1 (2015) Complement System Part II: Role in Immunity. Front Immunol 6: 257.

93. Narayanasamy A, Ahn JM, Sung HJ, Kong DH, Ha KS, et al. (2011) Fucosylated glycoproteomic approach to identify a complement component 9 associated with squamous cell lung cancer (SQLC). J Proteomics 74: 2948-2958.

94. Pan J, Qian Y, Weiser P, Zhou X, Lu H, et al. (2010) Glycosaminoglycans and activated contact system in cancer patient plasmas. Prog Mol Biol Transl Sci 93: 473-495.

95. Vitale C, D'Amato M, Calabrò P, Stanziola AA, Mormile M, et al. (2015) Venous thromboembolism and lung cancer: a review. Multidiscip Respir Med 10: 28.

96. Sheng L, Luo M, Sun X, Lin N, Mao W, et al. (2013) Serum fibrinogen is an independent prognostic factor in operable nonsmall cell lung cancer. Int J Cancer 133: 2720-2725.

97. Desrochers PE, Jeffrey JJ, Weiss SJ (1991) Interstitial collagenase (matrix metalloproteinase-1) expresses serpinase activity. J Clin Invest 87: 2258-2265.

98. Brinckerhoff CE, Rutter JL, Benbow U (2000) Interstitial collagenases as markers of tumor progression. Clin Cancer Res 6: 4823-4830.

99. Li M, Xiao T, Zhang Y, Feng L, Lin D, et al. (2010) Prognostic significance of matrix metalloproteinase-1 levels in peripheral plasma and tumour tissues of lung cancer patients. Lung Cancer 69: 341-347.

100. Li Q, Park PW, Wilson CL, Parks WC (2002) Matrilysin shedding of syndecan-1 regulates chemokine mobilization and transepithelial efflux of neutrophils in acute lung injury. Cell 111: 635-646.

101. Liu D, Nakano J, Ishikawa S, Yokomise H, Ueno M, et al. (2007) Overexpression of matrix metalloproteinase-7 (MMP-7) correlates with tumor proliferation, and a poor prognosis in non-small cell lung cancer. Lung Cancer 58: 384-391.

102. Hadler-Olsen E, Winberg JO, Uhlin-Hansen L (2013) Matrix metalloproteinases in cancer: their value as diagnostic and prognostic markers and therapeutic targets. Tumour Biol 34: 2041-2051.

103. Peng WJ, Zhang JQ, Wang BX, Pan HF, Lu MM, et al. (2012) Prognostic value of matrix metalloproteinase 9 expression in patients with non-small cell lung cancer. Clin Chim Acta 413: 1121-1126.

104. Szturmowicz M, Rudzinski P, Kacprzak A, Langfort R, Bestry I, et al. (2014) Prognostic value of serum C-reactive protein (CRP) and cytokeratin 19 fragments (Cyfra 21-1) but not carcinoembryonic antigen (CEA) in surgically treated patients with non-small cell lung cancer. Pneumonol Alergol Pol 82: 422-429.

105. Jing X, Huang C, Zhou H, Li C, Fan L, et al. (2015) Association between serum C-reactive protein value and prognosis of patients with non-small cell lung cancer: a meta-analysis. Int J Clin Exp Med 8: 10633-10639.

106. Yamaguchi T, Kimura H, Yokota S, Yamamoto Y, Hashimoto T, et al. (2000) Effect of IL-6 elevation in malignant pleural effusion on hyperfibrinogenemia in lung cancer patients. Jpn J Clin Oncol 30: 53-58.

107. Lukaszewicz-ZajÄ…c M, Mroczko B, Gryko M, KÄ™dra B, Szmitkowski M (2011) Comparison between clinical significance of serum proinflammatory proteins (IL-6 and CRP) and classic tumor markers (CEA and CA 19-9) in gastric cancer. Clin Exp Med 11: 89-96.

108. Ono S, Lam S, Nagahara M, Hoon DS (2015) Circulating microRNA Biomarkers as Liquid Biopsy for Cancer Patients: Pros and Cons of Current Assays. J Clin Med 4: 1890-1907.

109. Jeong HC (2014) Clinical Aspect of MicroRNA in Lung Cancer. Tuberc Respir Dis (Seoul) 77: 60-64.

110. Wang P, Yang D, Zhang H, Wei X, Ma T, et al. (2015) Early Detection of Lung Cancer in Serum by a Panel of MicroRNA Biomarkers. Clin Lung Cancer 16: 313-319.

111. Saddoughi SA, Song P, Ogretmen B (2008) Roles of bioactive sphingolipids in cancer biology and therapeutics. Subcell Biochem 49: 413-440.

112. Wen C, Zhang M, Ma J, Hu L, Wang X, et al. (2015) Urine metabolomics in rats after administration of ketamine. Drug Des Devel Ther 9: 717-722.

113. Zeng M, Liang Y, Li H, Wang M, Wang B, et al. (2010) Plasma metabolic fingerprinting of childhood obesity by GC/MS in conjunction with multivariate statistical analysis. J Pharm Biomed Anal 52: 265-272.

114. Chen Y, Ma Z, Min L, Li H, Wang B, et al. (2015) Biomarker identification and pathway analysis by serum metabolomics of lung cancer. Biomed Res Int 2015: 183624.

115. Wells L, Hart GW; Athens Guidelines for the Publication of Glycomics Data (2013) Glycomics: building upon proteomics to advance glycosciences. Mol Cell Proteomics 12: 833-835.

116. Zhang L (2010) Glycosaminoglycans in development, health and disease. Preface. Prog Mol Biol Transl Sci 93: 17-18.

117. Schnaar RL (2015) Glycans and glycan-binding proteins in immune regulation: A concise introduction to glycobiology for the allergist. J Allergy Clin Immunol 135: 609-615.

118. Schwarz F, Aebi M (2011) Mechanisms and principles of N-linked protein glycosylation. Curr Opin Struct Biol 21: 576-582.

119. Taniguchi N, Kizuka Y (2015) Glycans and cancer: role of N-glycans in cancer biomarker, progression and metastasis, and therapeutics. Adv Cancer Res 126: 11-51.

120. ZoldoÅ¡ V, Novokmet M, BeÄ□eheli I, Lauc G (2013) Genomics and epigenomics of the human glycome. Glycoconj J 30: 41-50.

121. Freeze HH, Chong JX, Bamshad MJ, Ng BG (2014) Solving glycosylation disorders: fundamental approaches reveal complicated pathways. Am J Hum Genet 94: 161-175.

122. Swiedler SJ, Freed JH, Tarentino AL, Plummer TJ, Hart GW (1985) Oligosaccharide microheterogeneity of the murine major histocompatibility antigens. Reproducible site-specific patterns of sialylation and branching in asparagine-linked oligosaccharides. J Biol Chem 260: 4046-4054.

123. Varki A (1993) Biological roles of oligosaccharides: all of the theories are correct. Glycobiology 3: 97-130.

124. Pinho SS, Reis CA, et al. (2015) Glycosylation in cancer: mechanisms and clinical implications. Nat Rev Cancer 15: 540-555.

125. Stowell SR, Ju T, Cummings RD (2015) Protein glycosylation in cancer. Annu Rev Pathol 10: 473-510.

126. Arnold JN, Saldova R, Galligan MC, Murphy TB, Mimura-Kimura Y, et al. (2011) Novel glycan biomarkers for the detection of lung cancer. J Proteome Res 10: 1755-1764.

127. Adamczyk B, Tharmalingam T, Rudd PM (2012) Glycans as cancer biomarkers. Biochim Biophys Acta 1820: 1347-1353.

128. Silva ML (2015) Cancer serum biomarkers based on aberrant post-translational modifications of glycoproteins: Clinical value and discovery strategies. Biochim Biophys Acta 1856:165-177.

129. Miyoshi E, Moriwaki K, Nakagawa T (2008) Biological function of fucosylation in cancer biology. J Biochem 143: 725-729.

130. Okuyama N, Ide Y, Nakano M, Nakagawa T, Yamanaka K, et al. (2006) Fucosylated haptoglobin is a novel marker for pancreatic cancer: a detailed

analysis of the oligosaccharide structure and a possible mechanism for fucosylation. Int J Cancer 118: 2803-2808.

131. Hart GW, Copeland RJ (2010) Glycomics hits the big time. Cell 143: 672-676.

132. Raman R, Venkataraman M, Ramakrishnan S, Lang W, Raguram S, et al. (2006) Advancing glycomics: implementation strategies at the consortium for functional glycomics. Glycobiology 16: 82R-90R.

133. Zhang , Zeng X, Lan Y, Qiu P, Zeng Y, et al. (2015) Cancer diagnosis based on monosaccharide compositional analysis of patient serum/plasma . Chinses Patent 3.