Advances in the study of serum tumor markers of lung cancer

ABSTRACT

Lung cancer is among the most prevalently occurring carcinomas worldwide, and reducing lung cancer mortality depends on early detection, diagnosis, and treatment. Given the rapid development of molecular biology and modern techniques for diagnosis and treatment, the study of serum tumor markers has gained extensive application in early diagnosis, treatment effect monitoring, and prognosis evaluation. Serum tumor markers possess the advantages of easy detection, noninvasive operation, and cost-effectiveness. This article reviews the progress in the study of serum tumor markers of lung cancer.

KEY WORDS: Diagnosis, lung cancer, prognosis, serum tumor marker, treatment

INTRODUCTION

Lung cancer is a common malignancy that severely threatens human health. The number of patients newly diagnosed with lung cancer is increasing, accounting for 17% of the total new cancer cases and 23% of the total cancer deaths; lung cancer has become the carcinoma with the highest incidence among men. Patients with early stage lung cancer are asymptomatic in most cases without distinct imaging manifestations. Thus, distinguishing lung cancer from a benign lesion remains a problem. As a result, most patients are diagnosed when already at the middle or advanced stage. This scenario emphasizes the importance of early diagnosis and treatment. The current mainstream diagnostic method to evaluate lung cancer is imaging examination. The most prevalent approach is computed tomography, which is sometimes combined with positron emission tomography (PET). Current evidence has validated that the gradual standardized uptake value decrease of PET suggests effective treatment for lung cancer.

Serum tumor markers are considered as biological indicators detected from the serum or plasma of suspected tumor patients. The increase of such indicators indicates tumor existence, facilitating pathological analysis and evaluation of tumor development. These tumor markers also provide valuable information for treatment. The biomarkers in circulating blood are often associated with biomarkers of cell morphology; the latter includes immunohistochemical markers (particularly correlated with lowly differentiated tumors), cell surface markers of hematologic tumor, and biomarkers generated by genetic abnormality, such as proto-oncogene, anti-oncogene, and gene products. The level of tumor markers is restored to the normal range when the body completely recovers, but still remains at a higher degree compared with the normal stage if the disease is just partly alleviated or progresses. In clinical practice, serum tumor markers are often combined with imaging examination to monitor the effect of chemotherapy and determine tumor recurrence.

Hematology and immunology studies are mainly based on the immunochemistry phenotype of the macromolecular antigens on the corresponding tumor surface. These antigens include medium-sized members, such as keratin (covering more than 20 types of cell keratin), vimentin, desmin, neurofilament protein, neuroglial fiber protein, cell membrane antigen of squamous carcinoma, carcinoembryonic antigen (CEA) of oncofetal protein, onconeural antigen S-100, factor VIII-related antigen of vascular tumor, lung-specific active apoprotein, and Clara cellular antigen. Morphological studies reveal that lung tumor with neuroendocrine ability can express many biomarkers, including neuron-specific enolase (NSE), protein gene product 9, protein gene product 5, chromogranin A, and synaptophysin. Moreover, autocrine growth factor (gastrin-releasing peptide [GRP]), insulin-like growth factor, ferritin, and epidermal growth factor are also detectable. This article reviews the advances in the study of serum tumor markers of lung cancer.
SEROLOGIC MONITORING INDEXES

The precondition for diagnosis with serum tumor markers is the detectability of such biomarkers in the blood or other body fluids. The concentration of tumor markers is always determined by tumor size and development as well as the properties of the markers, including the expression degree, synthesis ability, and release level. Other factors, such as degradation of tumor markers, excretion speed, and tumor blood supply, also affect the concentration. Any variation of the aforementioned factors influences the detection of tumor markers.[8] Therefore, the clinical significance of tumor markers only indicates their correlation with tumor, but not specificity. These tumor markers are specific to an organ, not to a type of tumor.[11] In the current context, many biomarkers, which are at normal level in healthy humans, have no specificity to lung cancer, but may also increase in benign lesion. Organ directionality is dependent on the incidence. Given this basis, these tumor markers are not applicable for tumor screening; thus careful considerations are necessary for elevated tumor markers. The common tumor markers for lung cancer are concluded in the following section.

Neuron-specific enolase

Neuron-specific enolase, also known as enolase-γ, is composed of two polypeptide chains (α/γ or γ/γ), which both have a molecular weight of 39 kDa. NSE is a glycolytic enzyme that is mainly located in the central and peripheral neurons and neuroendocrine tissues. It can also be found in smooth muscle, kidney, lymphocyte, and some other tissues. Hemolysis may result in increased NSE level because NSE exists in erythrocyte and blood platelet. In addition, NSE is released into the blood if the erythrocytes housing NSE are not separated 60 min after phlebotomization.[12] As early as 1980, NSE has been reported to be elevated in small cell lung cancer (SCLC). An increased NSE level (>25 ng/mL) was observed in 72% of SCLC patients, and the ratio for other types of lung tumor was only 8%. Compared with the patients with limited SCLC, patients suffering from extensive SCLC demonstrate significantly higher level of NSE.[13,14] At present, NSE serves as an important oncology indicator, particularly in the diagnosis and treatment of SCLC.[15]

For suspected lung tumor patients, high NSE level (>100 ng/mL) suggests the high probability of SCLC, which should be discriminated from neuroendocrine tumor of other sites, liver tumor, lymphoma, and seminoma.[16] Moderate NSE increase is often observed in benign lung tumor, pancreatic cancer, gastric cancer, colon cancer, and breast cancer.[17] In multiple studies of lung cancer, NSE is normally used in the differential diagnosis, particularly in SCLC identification.[18] NSE is postulated to be greatly significant in auxiliary diagnosis when combined with pro-GRP (ProGRP).[19] Follow-up observation of NSE monitoring reveals that NSE is a valuable marker in monitoring the treatment effect of SCLC and can further be used in evaluating disease recurrence.[19,20]

Pro-gastrin-releasing peptide

Pro-gastrin-releasing peptide, a precursor of GRP, is first separated from pig stomach. GRP is unstable in serum, whereas ProGRP is relatively stable; thus, ProGRP is used as a serum marker for disease evaluation. ProGRP is expressed in human neural system and serves as a neurotransmitter that adjusts body temperature and central homeostasis. Moreover, the neuroendocrine tissues in the gastrointestinal and respiratory tract are capable of releasing ProGRP, which is mainly observed in the gastrointestinal tract, lungs, and neural system. ProGRP shows excellent specificity and sensitivity, making it a reliable tumor marker for SCLC.[21] ProGRP level is increased in SCLC (73%) and is seldom elevated in non-SCLC (NSCLC) and other benign or malignant diseases; ProGRP has an extremely low concentration in serum even when expressed.[21] The high sensitivity of 88% can be achieved in SCLC examination by combining ProGRP and NSE. A serum level of more than 200 pg/mL suggests lung cancer, whereas SCLC is indicated when a serum level exceeds 300 pg/mL. In clinical practice, ProGRP is mainly involved in the differential diagnosis, particularly in discriminating SCLC from other types of lung cancer.[22,23] As a single marker, ProGRP is more reliable than NSE. ProGRP demonstrates high clinical value when combined with NSE.[19] A high-level release of ProGRP is observed even at the early stage of SCLC but shows no correlation with disease staging.[18,24,25]

Currently, only a few data have proven the availability of ProGRP in assessing SCLC prognosis. Nonetheless, some studies reported that ProGRP can be used in monitoring treatment effect and disease recurrence after effective initial therapy.[26]

CYTOKERATIN 19 FRAGMENT

Cytokeratin 19 fragment (CYFRA 21-1) is a 36 kDa fragment of cytokeratin 19 and is observed in the cytoskeleton of epithelial cells (including bronchus epithelium). Although CYFRA 21-1 is noted in various organs of the human body, pathological studies prove that it is exclusively expressed in lung tissues. CYFRA 21-1 is preferentially excreted by the kidney; thus, renal diseases should be excluded when it is used as a marker of lung cancer and shows elevated serum level.[27,28]

Cytokeratin 19 is the only origin of CYFRA 21-1, which provides higher specificity than tissue polypeptide antigen (TPA).[29,30] At present, CYFRA 21-1 is the most sensitive tumor marker for NSCLC (sensitivity of 59% and specificity of 94%), particularly to squamous carcinoma. However, CYFRA 21-1 seldom increases in SCLC.[31,32] Numerous multivariate analyses reveal the role of CYFRA 21-1 as an important marker in assessing NSCLC prognosis.[33,34] The following data have been validated by aggregate data from nine research centers: CYFRA 21-1 is an independent prognostic factor for NSCLC of both early and advanced stages and is postulated to be a valuable marker for prognosis estimation.[35-37]
Cytokeratin 19 fragment is recognized as a significant marker in evaluating treatment effect and estimating recurrence of NSCLC (particularly for squamous carcinoma). Moreover, recent studies have presented that for patients with progressive stage NSCLC under chemotherapy, changes of CYFRA 21-1 in initial chemotherapy can be used in predicting subsequent treatment effect.

In addition to lung cancer, a slight CYFRA 21-1 increase can be noted in benign diseases, such as tuberculosis, chronic obstructive pulmonary disease, acute infection, and fibrosis. Some benign tumors also demonstrate increased level of CYFRA 21-1, such as in the sera of patients with urologic, gastrointestinal, and gynecological tumors.

SQUAMOUS CELL CARCINOMA ANTIGEN

Squamous cell carcinoma antigen (SCCA) is a traditional tumor marker of 48 kDa belonging to serine protease inhibitor family. SCCA is expressed in squamous cells of respiratory tract, gastrointestinal tract, and cervix. In studies of subcellular level, SCCA is observed in the cytoplasm and is postulated to be a type of structural protein that reflects different differentiation levels of squamous cell carcinoma. Therefore, changes of serum SCCA levels are frequently detected in squamous carcinomas of the lung, breast, cervix, esophagus, and head and neck regions. As SCCA is metabolized through the kidney, renal failure leading to increased SCCA level should be taken into consideration.

The detection of SCCA level plays a role in the differential diagnosis of lung cancer. Despite the lower sensitivity of SCCA to NSCLC compared with CYFRA 21-1, SCCA shows a relatively high specificity toward NSCLC and is often used for pathological histological classification. SCCA is also frequently combined with CEA and CYFRA 21-1 to perform differential NSCLC diagnosis with elevated levels mainly observed in various squamous cell tumors. Increased SCCA level during examination can be a result of samples contaminated by skin or saliva.

Carcinoembryonic antigen

Carcinoembryonic antigen is a general name of a glycoprotein group with the same antigenic determinant and with a molecular weight of about 180 kDa. CEA is a cancerous antigen in fetus. In the 22nd week of pregnancy, CEA level reaches a peak in fetus serum. For normal adults, a small quantity of CEA is expressed in the gastrointestinal tract, pancreas, and liver. Increased CEA level in cancer patients may be correlated with the derepression of the encoding gene of CEA, and this family contains at least 17 active genes with highly homologous structures.

Carcinoembryonic antigen is among the earliest elucidated tumor markers and is highly specific to many adenocarcinomas, particularly in colon cancer (other adenocarcinomas include lung, breast, gastric, ovarian, and liver cancers). CEA has a relatively high sensitivity in lung cancer with the highest serum concentration observed in adenocarcinoma and large cell lung cancer. Approximately 40% of patients with lung adenocarcinoma show increased CEA level. However, increased CEA level can also be observed in other types of tumor, benign diseases, and even in serum of smokers, which limits CEA application in diagnosis. CEA is often combined with CYFRA 21-1 in the diagnosis of lung malignancies.

Moreover, CEA is used to evaluate the prognosis and treatment effect of NSCLC and to determine recurrence, particularly in lung adenocarcinoma. For patients with NSCLC, high CEA level suggests a poor prognosis and high risk of cerebral metastasis.

Nucleosome

Nucleosome is composed of DNA and protein, serving as a unit of chromosome in eukaryotic cells. Cell apoptosis may be a result of acute infection, autoimmune diseases, cancer, radiotherapy, and chemotherapy. After apoptosis, nucleosome can be released from the cell and become detectable in the blood sample. Nucleosome level in serum is related to the treatment effect in patients with lung cancer.

Nucleosome DNA fragment

Nucleosome DNA fragment is a basic component of chromosome, the unit of which consists of a DNA sequence wrapped around the complex of the core histones H2A, H2B, H3, and H4. After cell membrane degradation during apoptosis, some single or oligonucleotides are produced by the hydrolysis effect of several endonucleases on special linking sites of chromosome. Oligonucleotides are then released into the blood, becoming nucleosome DNA fragments.

Increased DNA levels are observed in many malignancies and benign diseases. In lung cancer studies, DNA quantification is recommended in the application of diagnosis and staging. Although a lack of tumor and organ specificity exists, the metabolic kinetics of nucleosome DNA fragment is particularly significant in monitoring the therapeutic response of NSCLC in progressive stage and is applied in the initial monitoring of chemotherapy; thus, metabolic kinetics can serve as an early predictive marker for tumor treatment. Furthermore, the recurrence of NSCLC can be evaluated by monitoring circulating DNA.

Cancer antigen 125

Cancer antigen 125 (CA 125) is a 200 kDa glycoprotein originated from the epithelium of fetal body cavity and is observed in the mesothelium of adult peritoneum and pleura. Detecting CA 125 in serous ovarian cancer, breast cancer, and lung cancer is important.

Cancer antigen 125 is mainly released in adenocarcinoma and large cell lung cancer and is significant in the differential diagnosis of lung cancer. CA 125 level can be used as a
predictive marker for evaluating the prognosis, the treatment effect, and early treatment response in NSCLC.\(^{[64,65]}\)

**Human epidermal growth factor receptor-2/neu**

Human epidermal growth factor receptor-2 (HER-2)/neu (ErbB2) is a receptor of epidermal growth factor and a member of the transmembrane oncogene family. It induces cell differentiation and proliferation by multiple signal transductions through epidermal growth factor receptor (EGFR) tyrosine kinase in cell. HER-2/neu is overexpressed in breast and ovarian cancers; great progress has been achieved with regard to the receptor targeted therapy, making HER-2/neu a significant marker for the two cancers.\(^{[66,67]}\) Given the advances of new EGFR inhibitors in lung cancer treatment, detecting soluble HER-2/neu has gained interest among investigators in the areas of tumor staging and prognosis assessment (particularly NSCLC).\(^{[68,69]}\) However, the current results are quite controversial in either differential diagnosis or treatment effect monitoring.\(^{[70]}\)

**Tissue polypeptide antigen**

Tissue polypeptide antigen is a traditional tumor marker that detects a mixture of cytokeratin 8, 18, and 19. In pathological studies, cytokeratin and other intermediate products of cell are used to determine tumor differentiation and classification. In contrast to cytokeratin, the fragments of intermediate products are soluble in serum, which can be detected under monoclonal antibody labeling after aggregation.\(^{[71]}\) Despite the lower specificity and sensitivity of TPA compared with that of CYFRA 21-1 in NSCLC diagnosis, TPA can facilitate differential diagnosis and is a prognostic marker for NSCLC.\(^{[34,72]}\)

**TISSUE POLYPEPTIDE-SPECIFIC ANTIGEN**

Tissue polypeptide-specific (TPS) is an M3 special component of TPA and can be used to test the fragment of cytokeratin 18, which is detected in all human organs (particularly in epithelial tissue). Cytokeratin is produced in the late period of cell synthesis (S phase) and G2 phase and is released in telophase. Therefore, TPS is postulated to be an index for the proliferation of various malignancies.\(^{[71]}\)

As a single marker, TPS is not as significant as CYFRA 21-1 and TPA in the differential diagnosis of lung tumor. However, TPS has a potential role as an NSCLC marker. For large cell lung cancer, TPS provides more information than CYFRA 21-1. TPS level also provides a reference for the prognosis of NSCLC and SCLC as well as can be applied to detect the systematic treatment response of NSCLC, predict treatment effect, and determine disease recurrence.\(^{[72,73]}\)

**TUMOR M2 BETAINE KINASE**

Tumor M2 betaine kinase (TUM2-PK) is an isomer of pyruvate kinase and participates in glycolysis. Some tissue-specific isomers are expressed during normal cell proliferation. The TUM2-PK dimer is overexpressed in various tumor cells and is introduced by some investigators as a marker related to lung cancer. However, the role of TUM2-PK as a tumor marker for lung cancer is not elucidated. TUM2-PK lacks tissue specificity, which results in very low sensitivity for lung cancer diagnosis. Nonetheless, serum TUM2-PK level can be used in monitoring the systemic treatment of SCLC and NSCLC and in determining disease recurrence.\(^{[75,76]}\)

**Serum ferritin**

Serum ferritin is an iron-storing protein with a molecular weight of 450 kDa. It occurs in serum and some body fluids. High concentrations of serum ferritin are found in the cytoplasm of reticuloendothelial cells, hepatic cells, spleen cells, and the precursor of marrow erythrocytes. Serum ferritins separated from different tissues show diverse isoferritin distributions. Increased ferritin level is noted in the serum or cerebrospinal fluid in malignancies, such as lymphoma, acute leukemia, multiple myeloma, breast cancer, and testicular cancer. The mechanism may be explained by the elevated serum ferritin synthesis caused by tumor-related inflammation, increased tumor cell secretion, or reduced metabolism induced by the necrosis of hepatic cells when tumor cells metastasize to the liver.\(^{[77-79]}\)

Whether serum ferritin is clinically applicable in lung cancer remains unclear. Increased serum ferritin occurs in metastatic tumors and is not correlated with histological type. Furthermore, the treatment effect can be evaluated by measuring the changes of serum ferritin. Research indicates that serum ferritin level is higher in SCLC patients than that in normal people but is independent of disease degree and clinical course; the median survival time of patients with low serum ferritin level is longer than that with high level.\(^{[80]}\) However, an analysis of 169 pretreatment patients and 31 posttreatment patients with lung cancer showed that serum ferritin level is irrelevant to histological type, clinical staging, or treatment effect, and patients with serum ferritin lower than 236 ng/mL exhibited better prognosis.\(^{[81]}\) Given these findings, serum ferritin may serve as a guide in prognosis assessment of lung cancer\(^{[82]}\) but demonstrates limited clinical significance in disease staging and monitoring.

**Soluble interleukin-2 receptor**

Interleukin-2 (IL-2) is a cytokine with multiple immunologic functions. The most important function of IL-2 is initiating the proliferation of activated T cells through a specific receptor IL-2 receptor (IL-2R), which is not expressed in resting T cells. However, IL-2R expression can be noted in T cells several hours after activation. Activated lymphocytes not only generate soluble IL-2R (SIL-2R) and release it into the blood, but also remain as the binding ability to lymphokines. SIL-2R level increases in various conditions, including virus infection, nodule disease, Grave disease, organ transplantation, lymph proliferation dysfunction, and solid tumor.\(^{[78]}\)

Marino et al. reported the increased SIL-2 level in the serum sample of untreated patients. In other human malignancies,
SIL-2R is correlated with clinical indexes, such as tumor size and treatment response.[87] SIL-2R level in lung cancer patients is higher than that in noninflammatory benign lung diseases, but its pretreatment level is not related to staging and to the types of lung cancer. By contrast, IL-2R is significantly correlated with the disease state after treatment, particularly for nonoperative patients. High SIL-2R level in pretreatment patients indicates shorter survival time.[84-86] Moreover, high SIL-2R levels are discovered in squamous carcinoma and adenocarcinoma of the lung. SIL-2R is irrelevant to disease severity in adenocarcinoma and shows a negative correlation with tumor size in squamous carcinoma. Consequently, SIL-2R may represent the changes of the immune state in lung cancer patients. Increased SIL-2R level suggests the activation of body immune response, which may be a result of enhanced immunity or the ability of tumor to adjust self-development through various growth factors.[87,88]

CONCLUSION

This article concludes and discusses the current serum tumor markers commonly used in lung cancer and the corresponding progress in the study to serve as a guide for clinical application. Numerous serum tumor markers can be used in early diagnosis, treatment monitoring, and prognosis evaluation. However, many tests based on these markers are limited by insufficient sensitivity or specificity. Combined detection with multiple tumor markers is frequently used in clinical practice. Therefore, considerable efforts are needed to further exploit tumor markers with more sensitivity and specificity, and researchers need to further evaluate the clinical value of such tumor markers.

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