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AUTOANTIBODIES AS DIAGNOSTIC BIOMARKERS FOR LUNG CANCER

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Abstract

Lung cancer is one of the leading causes of death worldwide, with two main types of the disease - non-small cell lung malignancies and small cell lung cancer - accounting for approximately 85% and 15% of mortalities respectively. Like other diseases and infections, lung cancer can also be diagnosed by tumor markers that are produced by Lung cancer patients. Antibodies from five classes of antibodies are IgG, IgM, IgA, IgD, and IgE are produced against their own antigens known as autoantibodies, have their role in stopping or minimizing cancer, and play a vital role in diagnostic analysis of lung cancer. To diagnose lung cancer, a panel of six antibodies p53, CAGE, GBU4–5, NY-ESO-1, Annexin 1, and SOX2 has been studied to monitor lung cancer with a sensitivity of 38% and a specificity of 88 percent. Patients with lung cancer can produce p53 antibodies, an altered form of tumor suppressor known as Tp53. Other antibodies like NY-ESO 1, Annexin A1 and SOX2 can also be used as diagnostic biomarkers for the detection of lung cancer. In this review, we study all possible antitumor or Autoantibodies of lung cancer and their use in earlier detection of a lung cancer diagnosis.

Keywords: *Antibodies, Autoantibodies, Diagnostic biomarkers, Lung cancer, P53*

INTRODUCTION

Lung cancer (LC) is the biggest reason of cancer-related mortality globally. Tobacco usage is thought to be responsible for up to 90% of cases, with additional known risk factors including passive smoking, radon exposure, and occupational exposure, mainly to asbestos (1). The latency period for lung cancers caused by smoking is expected to be at least 20 years (2).

Non-small cell lung malignancies (NSCLCs) account for 85 percent of lung tumors, with 2 main histological subtypes: squamous cell carcinoma (SCC) and adenocarcinoma (AC) (3). Small cells lung cancer is a type of lung malignant whose percentage is 10% to 15% of all lung malignancies and is also known as oat cell cancer. More than NSCLC, SCLC grows and spreads quickly. At the time of diagnosis, almost 70% of those with SCLC will have cancer that has already spread (4). Lung cancer was once thought to be uncommon at the starting of the twentieth century. However, in present days it has spread to extensive proportions. In 2008, it was the most frequently diagnosed tumor and the prominent reason for tumor mortality in men worldwide. It was the fourth most commonly diagnosed malignancy in women and the second most prevalent reason for cancer mortality. In the same year, LC accounted for 14% (1.7million) of all cases and 19% (1.5million) of all fatalities, and it is expected to reach three million cases per year by 2010 and more.The rate of Lung cancer is increasing by 0.5 percent each year worldwide. Including Smoker or non-smokers, the lifetime risk of lung cancer in men is about 1 in 15, while a women's lifetime risk is about 1 in 17 according to the American Cancer Society. World Health Organization reported that every minute people die from lung cancer around the world, making it "one of the epidemics" of the twentieth century.

The prevalence of LC varies greatly across geographical areas. Developed countries account for over 80% of all new reports of lung cancer globally. It continues to be the most frequent cancer in males around the world (16.5 percent of the total 1.1M cases). The highest incidence (>50 per 105 population) is found in Northern America, Central-Eastern, and Southern Europe. (35-50 per 105 population), of moderate incidence is found in China, Japan, Korea, Turkey, Western Europe, and Australia while the majority of Asian countries, Latin America, Scandinavia, and Middle and Western Africa have a low incidence respectively. Northern America has the greatest incidence rate where lung cancer is currently the second most common cancer in women, whereas Middle Africa has the lowest. In developed countries, the frequency and death rate of lung cancer in women is increasing while it is decreasing in men. The mortality to incidence ratio is 0.86 (5).

Early identification and treatment can dramatically reduce the mortality rate of lung cancer. On the other hand, Detection and diagnosis of an initial stage of lung cancer are still difficult in two ways. First, the primary stages of the disease are either asymptomatic or have symptoms that can be linked to other factors such as infection or long-term effects of smoking. Second, good screening tools are scarce. In current years, investigations have found that cancer patients produce tumor markers during the cancer transfer process, making it a vital supplementary diagnosis of LC. In many cancers, the immune system recognizes tumor-associated antigen over expressed and specific antigens and secrete autoantibodies against these (6).

ANTIBODIES

An antibody is also known as "an immunoglobulin (abbreviated as Ab or Ig) produce in a vulnerable individual by binding with the antigen. When the body is attacked by unknown molecules, antibodies are produced in response to it. Human antibodies are functionally and structurally similar glycoproteins which consist of carbohydrates and protein that examine humoral immunity (7). Antibodies are proteins that specifically bind with an antigen on the B cell membrane, secreted by plasma cells (8).

STRUCTURE

Each antibody molecule contains two undistinguishable heavy chains (HCs) and two undistinguishable light chains (LCs) which forms a Y-shaped unit, consisting of four polypeptide chain (7). This Y-shaped unit is made up of 3 functional domains, 2 antigen-specific Fragment (Fab) arms that are designed to bind with the antigen, and the constant Fc "tail", attaches to immune receptors to stimulate effector functions. The half N-terminal of the Fab arms consists of variable sequences which give the antibodies different specificities. At the antigen-binding interface, three (CDR) loops carrying hypervariable sequences are located. One intra-chain disulfide bond is present within each immunoglobulin dominion of the antibody. The linkage between 2 heavy chains within the bendable hinge region and the linkage between heavy chains with its light chain is attached by an inter-chain disulfide bond (9). The sugar chains of the antibody are added to amino-acid remnants by N-linked glycosylation and sometimes by O-linked glycosylation (8).

FUNCTIONS

Particularly Abs has two functions: first, to bind specially to their target antigens, and second, to stimulate an immune response by recruiting other cells and molecules against the bound Ag. The relationship between an Ab and an Ag involves numerous non-covalent connections between the binding site on the Ab (paratopes) and the binding site on the Ag (epitope). The capability of Abs to bind almost on any non-self surface with high affinity and deep specificity is not only the key to immunity but has also made antibodies an immensely valuable tool in biomedical research, experimental biology diagnostics, and therapy. The variety in their binding abilities is mainly given the high structural similarity amongst all Abs (10).

Furthermore, antibodies consist of crosslinking which makes precipitation of agglutination of cells or soluble antigens. The outcome comes from the bivalent and multivalent nature of Abs and several Ags respectively. As a result, effective opsonins are formed by immune complexes that are proficiently phagocytosed. (9). In addition, Abs fight against pathogenic substances, viruses, and infections. When a pathogenic element attacks an immune proficient animal, the immune system has the inherent ability to produce Abs that can get any specific Ags. An antigenic specificity on B cells is conferred by the membrane-bound antibody. The interaction between membrane antibody and antigen generates antigen-specific production of B cell clones. Thus, the amalgamation of specificity and diversity makes antibodies a vital component of the defense mechanism in contradiction of harmful pathogenic substances (8).

ANTIBODY CLASSIFICATION

Antibodies are divided into 5 structurally and functionally distinct classes: IgG, IgM, IgA, IgD, and IgE, based on the type of heavy chain. IgG, IgM, IgA, IgD, and IgE, of the heavy chain, are well-known as γ, μ, α, δ, and ε, respectively (9). The light chains of an Abs type are either lambda (λ) or kappa (κ). Though, the heavy chain defines the subclass of each antibody. The subclasses of Abs can be differentiated by the length of the hinge region and the number of their disulfide bonds.

IgG: In the blood, this class of antibody is found about 75-80% of the whole serum antibodies. IgG is further divided into four subclasses known as IgG1, IgG2, IgG3, and IgG4. IgGs can leave the circulatory system and enter the tissues. IgGs are very effective for the activation of the complement system and opsonization. The half-life of IgG is extending from 7 to 23 days

IgM: In response to infection, IgM is produced for the first time. Each monomer comprises two heavy chains and two light chains, κ or λ type and two heavy chains Secreted IgM which has pentameric nature that is very suitable for agglutination and activation of complement. The half-life of IgM is about 5 days

IgA: IgA is present in blood at low levels while in saliva, tears, and breast milk high level of IgA is reported. In humans two IgA subclasses IgA1 and IgA2 exist. However, only one type of IgA is observed in mice. Up to 85% of the total IgA is said to be the IgA1 in serum. IgA deficiency is considered one of the most mutual immunodeficiency diseases that raise vulnerability to infections. The half-life of IgA is about 5 days**.**

IgD: This type of antibody is recognized on the surface of utmost B lymphocytes. The specific function of IgD is uncertain yet but for the activation of B cell, it acts as an antigen receptor. It also plays a key role to eliminate B-lymphocytes which generate self-reactive autoantibodies. The secreted form of IgD is found in the serum in minimum quantities and has two light chains and two heavy chains of the δ type. It has a half-life of 3 days.

IgE: It is very effective in blood, mucosal surfaces, and tissues. IgE consists of two light chains and two heavy chains of ε class. Out of total serum concentration, it has a low concentration of 0.002% in serum. Production of this antibody is controlled by cytokines and it plays a critical role in hypersensitivity reactions. The half-life of IgE is about 2 days (7).

POLYCLONAL AND MONOCLONAL ANTIBODIES

Polyclonal antibodies are derived from numerous B cell clones while monoclonal antibodies from a single B cell to treat patients with autoimmune disorders and other human diseases (8). Additionally, polyclonal antibodies spot several antigen sites on the same target. but, monoclonal antibodies identify only one site of antigen (epitope) which delivers an important level of specificity (11). Human polyclonal IGs are derived from an immunized or healthy individual for the treatment of rabies, tetanus, or snake bites. Usage of polyclonal animal antibodies is restricted in three methods: (a) restriction of reproducibility, when an antigen is used for immunization of ineffectively immunogenic, (b) the nature of the antibodies is restricted by the virtue of the antigen utilized in inoculation, since antibodies responding against defiling proteins are likewise formed, and (c) the therapeutic utilization of polyclonal antibodies from individuals is usually restricted to only one treatment since the treated animal normally produce a compact response to serum proteins of different species in which Ab was raised. Polyclonal human antibodies have been protected and most usually utilized in the treatment of individuals with hereditary B-cell insufficiencies that outcome in an inability to make antibodies. In this way, remedial IGs delivered from pooled plasma of numerous human blood contributors give the major type of substitution treatment.

Monoclonal Abs can be prepared by the fusion of preserved cell line of mouse plasmacytoma with splenic or lymph-node cells of an immunized individual. The fusion cell generating monoclonal antibodies are eternalized plasma cells of programmed antibodies. Monoclonal antibodies were initially prepared from rodent species. This narrowed their therapeutic usage to conditions in which a mono treatment was enough as utmost individuals make a strong immune reaction to determining factors in the persistent domains of the rodent antibodies, or to determining factors in the variable dominions (12).

AUTOANTIBODIES

Antibodies that are produced against their own antigen are known as autoantibodies. These antigens possibly are detected in all cell kinds. For instance, chromatin, centromeres, or might be extremely explicit for a particular cell kind in one organ of the body. For example, thyroglobulin in cells of the thyroid gland. They might contain nucleic acids, proteins, lipids carbohydrates, or several amalgamations of these. AAbs are produced in response to a variety of antigens in autoimmune diseases. The involvements of numerous organs, as well as the generation of non-organ specific autoantibodies, are clinical signs of systemic autoimmune diseases. Auto-antibodies can tell us about rudimentary mechanisms of infection and inflammation in patients with autoimmune sicknesses.

The majority of AAbs have diagnostic and prognostic value about their linked disease, however, they are not all involved in disease pathogenicity. Antibodies that attach to a variation of exogenous antigens, like those on microbes and fungi, and also on self-antigens represent an important quantity of Igs in healthy individuals.

Since they emerge autonomously of known or considered immunization, they have been recognized as natural antibodies (NAAs) (13, 14). The NAA detected in a healthy and diseased condition, can be of different isotype including IgA, IgG, and IgM. A huge number of natural antibodies respond with one or more self-antigens and are termed natural autoantibodies (15). T15 IgM is one type of natural antibodies, which neutralizes bacteria or viruses directly (16).

FUNCTIONS

Autoantibodies attach to foreign or self-antigen to block or neutralize its activity. These auto-antibodies stimulate the digestion of the foreign or self-antigens by the process of opsonization. Moreover, the Fc receptor known as FcγRIII is produced by natural killer cells that attach to IgG antibodies. The activated natural killer cells release their granules, consisting of proteins that destroy the opsonized targets. Natural autoantibodies are also beneficial in the elimination of cell debris during inflammation, and autoantibodies to inflammatory cytokines might defend against untoward inflammation (17).

Another function of Auto-antibodies is said to be the diagnostic analysis because they are characteristically connected with autoimmune diseases. Though, the current proof is accruing on the existence of auto-antibodies in contradiction of one or more auto-antigens in various kinds of cancer. These auto-antibodies can be utilized for early recognition and cancer staging, and also observe cancer regression throughout the treatment. Strangely, some kinds of auto-antibodies were reported to stimulate cancer progression and metastasis, whereas others defend the body against it. Furthermore, numerous auto-antibodies respond to only one tumor antigen due to their polyclonal nature (18).

TYPES OF AUTO-ANTIBODIES

ANTI-CYTOKINES AUTOANTIBODIES

AAbs against many kinds of cytokines has been found in patients with various infections and immuno-inflammatory diseases, as well as in healthy people. These consist of interferon (α, β, and γ), interleukin (α, 2, 4, 6, 8, and 10) chemokine (α and β), nerve growth factor, leukemia inhibitory factor, tumor necrosis factor, and granulocyte-macrophage colony-stimulating factor, and receptor, which are found in both healthy people and people with numerous disorders (19).

These autoantibodies can act as prognostic indicators in autoimmune disease. AAbs to IL-6 in systemic sclerosis and AAbs against IL-18 and IL-1 in RA represent positive and negative results respectively. The autoantibodies are said to be pathogens that are found against cytokines, making patients of autoimmune more vulnerable to other kinds of diseases (13).

ANTI-NUCLEAR AUTOANTIBODIES

Anti-nuclear auto-antibodies are those autoantibodies that are produced against several nuclear components that include single or double-stranded DNA, transfer RNA, histone, and another kind of nuclear components. These autoantibodies may develop as a result of mistaken identification of normal nuclear components as unknown and harmful. By starting a chain of reactions, these autoantibodies cause inflammation and attack themselves, as well as begin to target normal proteins in the cell's nucleus. Though we all contain AAbs, which exist only in trace amounts and remain dormant in our bodies till certain elements trigger them to become active against normal nuclear components (13).

AUTO-ANTIBODIES AS DIAGNOSTIC BIOMARKERS FOR LUNG CANCER

Recent diagnostic methods have focused on TAAs markers like carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 125, CA19-9, and alpha fetal protein (AFP), which have low sensitivity and specificity for early-stage LC but are essential at diagnosing lung cancer at advanced stages. A collective number of reports define the existence of a humoral immune response to tumor-associated antigens in the form of AABs in lung and other types of tumors. Before the symptomatic disease, the presence of these autoantibodies has been described.

Detection of TAAbs, which are produced by cancer cells in response to TAAs in the blood, could be used as a cancer screening tool. The report further describes a very sensitive enzyme-linked immunosorbent test abbreviated as ELISA which detects elevated levels of autoantibodies against the tumor-associated antigen. In peripheral blood of patients with both SCLC and NSCLC, TAAbs have better sensitivity and specificity and are more stable than TAAs. Clinical experiments estimating the diagnostic value of tumor-associated auto-antibodies that could be used as detective biomarkers for lung cancer, and several candidates and multiplex TAAbs have been recognized and evaluated. Autoantibodies have been reported to be found in all histological types and stages can be a useful method for primary detection. An early CDT-Lung which is a well-validated auto-antibody such as (p53, CAGE, NY-ESO-1, Annexin 1, SOX2, and GBU4-5), has been studied in diverse screening cohorts as a metha od of monitoring high-risk patients.

Furthermore, p53 is a tumor suppressor gene, to which autoantibodies were found for the first time and it is frequently mutated in cancer. Expression of malignant testis antigens (NY-ESO-1 and CAGE) has been explained in some of the solid tumors and a DEAD-box domain is encoded by a GBU4-5 protein whose main role is unidentified yet, have been linked to the development of autoantibodies in lung cancer (1,18,20,21). This DEAD-box consists of proteins that play a role in spermatogenesis, embryogenesis, RNA processing, ribosome assembly, and cell growth and division, and in carcinogenesis, these proteins may play a vital role. They appear to be immunogenic and cancer-specific, and they could be used to identify cancer targets for diagnostic and immunotherapeutic purposes (22).

BENEFITS OF TUMOR-ASSOCIATED AUTO-ANTIBODIES

As biomarkers, TAAbs have various advantages. First, TAAbs have been found not only at the time of the early diagnosis of LC but also up to 5 years before the cancer is diagnosed in some cases (20). Second, TAAbs response to TAs is frequently enhanced in immune responses, making them more clearly detectable through TAs is normally undetectable in body fluids. Third, the corresponding TAAbs are long-lasting, more stable, and detectable as compared to TAs, which are repeatedly transiently raised in body fluids. Fourth, with well-established secondary reagents, TAAbs are highly selective and easily detectable in tiny volumes of the specimen.

The possibility of determining TAAbs in serum or plasma for lung cancer diagnosis has been proven. For example, early CDT lung assay (serum-based) with six tumor-associated auto-antibodies against p53, CAGE, GBU4–5, NY-ESO-1, Annexin 1, and SOX2 might detect lung cancer with a sensitivity of 38% and a specificity of 88 percent. However, in clinical settings, the sensitivity of serum TAAb indicators was insufficient for early lung cancer diagnosis (3).

ROLE OF P53 ANTIBODY IN LUNG CANCER

P53 is a tumor suppressor which regulates growth and plays a critical role in the progression of cell cycle DNA repair and apoptosis. The mutated p53 gene regulates the production of P53 proteins that might permit the. The survival of inherently unstable cells which might convert into cancerous cells is permitted by P53 proteins that are produced by a mutated P53 gene (23). The half-life of Mutated p53 protein is higher as compared to the half-life of wild-type p53, therefore malignant cell is accumulated. Patients with many forms of cancer, including lung cancer, can develop circulating p53 antibodies (p53 Abs) because the altered shape of p53 is produced by a mutation that might provoke an autoimmune reaction after the protein is released from the tumor cells (24). Since p53 over expression and serum p53Abs have a strong association in tumor tissues, p53Abs can be used as indicators for the existence of TP53 mutations (25).

TP53 mutations appear early in lung cancer, whereas p53 over expression has been found in pre-cancerous lesions. Serum p53Abs were also reported in heavy smokers many months before lung cancer was diagnosed (26). According to a systematic analysis, the level of serum p53Abs is higher in most tumor patients as compared to healthy and benign individuals. Thus, serum p53Ab detection can diagnose several cancers types, including lung cancer (27). The sensitivity and specificity of lung cancer detection arise by a combination of serum p53Ab with other traditional markers (28).

The Chemosensitivity in lung cancer patients can be predicted by a serum p53Abs. Essentially following neo-adjuvant chemotherapy, the level of serum p53Ab declines dramatically, and low serum p53Ab levels before neoadjuvant chemotherapy are associated with a high objective chemo response rate (29). However, the prognostic significance of p53Abs in lung cancer is debatable. It is stated that P53Abs is associated with short survival in non-small cell lung cancer but in some cases, no association is reported. Additionally, high levels of p53Abs show better survival in small cell lung cancer patients or with limited diseases, indicating a shorter survival in p53Ab positive patients (30).

NEW YORK ESOPHAGEAL SQUAMOUS CELL CARCINOMA 1 (NY-ESO-1)

New York esophageal squamous cell carcinoma 1 or NY-ESO- is one of the cancer-testis antigens (CTAs) with re-expression in non-small cell lung cancer and other cancer types. Across the tumor types, NY-ESO-1 expression has been related to progressive disease characteristics such as greater differentiation grade, clinical phase, and lymph node metastases. The importance of NY-ESO-1 expression as a prognostic biomarker is still debatable. Whereas its expression has been associated with a poor clinical result in some malignancies, For example, higher risk of recurrence, poor treatment response, and shorter survival in non-small cell lung cancer is related to NY-ESO-1 cancer expression (31).

ANNEXIN A1

Annexin A1 is an intracellular protein that may bind calcium and phospholipids and has several critical roles in cell proliferation, including apoptosis regulation, phagocytosis of apoptotic cells, and carcinogenesis (32). To investigate the clinical efficacy of annexin A1 as a serum diagnostic method and its potential capability as a clinical marker for lung cancer, researchers measured the level of annexin A1 in the serum of lung malignancy patients, benign group, and normal individuals. The results demonstrate that lung cancer tissues had higher annexin A1 frequency than normal tissues, and lung cancer patients' serum annexin A1 levels were likewise higher than control groups. The annexin A1 sensitivities for discriminating lung cancer from normal and benign groups were 98.6% and 97.1%, and the specificities were 87.3 percent and 65.4 percent, respectively.

Up-regulation of serum annexin A1 was linked to lung cancer patients' pathological grade and clinical stage, according to the final report. Moreover, serum annexin A1 concentration is a unique lung cancer biomarker that could be used as a diagnostic, prognostic, or predictive tool. However, bigger numbers of lung cancer individuals are needed for prospective research, and more studies are needed to study the likely cause of lung cancer growth (33).

SOX2

SOX2 is also known as Sex-determining region Y-box 2 and it is a subunit of reprogramming factor and transcription which has an important role in the progress and growth of lung cancer and other cancer types by a gene progression amplification (34). Some scientists measured the levels of serum SOX2 DNA in their study by extracting serum DNA from healthy individuals, benign lung diseases, and lung cancer patients and examined its diagnostic value, and matched it with clinical parameters which already exist in lung malignancy to offer a tumor marker for LC.

A study showed that in lung cancer patients, the level of serum SOX2 DNA was greater than the levels in healthy and benign lung diseases individuals. It is also reported that age, gender, smoking habit, tumor differentiation, or lymph node metastasis, has no association with the level of serum SOX2 DNA in lung malignancy patients. In addition, serum SOX2 DNA showed a specificity of 82.6 percent and sensitivity of 78.8 percent for the detection of lung cancer. The association of existing cancer markers such as cytokeratin fragment 21-1, squamous cell carcinoma antigen, and neuron-specific Enolase with serum SOX2 level increases the sensitivity of SOX2 which can serve as an important diagnostic method for the detection of lung cancer (35).

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