Biomarkers in Pulmonary Research

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Abstract

In this article, we reviewed the basics of biomarkers for the researchers who are interested in translational pulmonary medicine. The readers will understand why there is need for biomarkers in pulmonary diseases, what are current tools to discover a biomarker, the diverse area of omics technologies and their current uses.

Keywords: Biomarkers; Pulmonary; Translational

Introduction

In the developing molecular biology world, biomarkers had become promising tools in the field of pulmonary diseases. Because the burdens of pulmonary diseases are high, immediate need of screening, diagnostic and treatment follow-up techniques require a better understanding of biomarker biology, the omics studies and the techniques used to evaluate biomarkers. The subjects will be explained with examples following the list given below.

<table>
<thead>
<tr>
<th>Table</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Definition of Biomarker</td>
</tr>
<tr>
<td>2. Significance of Biomarkers</td>
</tr>
<tr>
<td>3. Omics Technology in the Biomarker Discovery</td>
</tr>
<tr>
<td>A. Genome and Genomics</td>
</tr>
<tr>
<td>B. Proteins and Proteomics</td>
</tr>
<tr>
<td>C. Metabolomics and Glycomics</td>
</tr>
</tbody>
</table>

Definition of biomarker

What are biomarkers and why are they so important in contemporary medicine? As a basic definition taken from Wikipedia, a biomarker is a measurable indicator of the severity or presence of some disease state. More generally, a biomarker is anything that can be used as an indicator of a particular disease state or some other physiological state of an organism [1].

The term “biomarker” is the abbreviated form of “biological marker” and there are several more definitions of biomarkers in the literature, described by National Institutes of Health, World Health Organization (WHO) or International Labor Organization (ILO) which they fortunately overlap considerably [2-5]. A broader definition considers the effects of treatments, interventions and even unintended environmental exposure, such as to chemicals or nutrients. In their report on the validity of biomarkers, WHO has stated that a more precise definition of biomarkers includes “almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical or biological. The measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction” [6].

As it can be understood from all these definitions, a biomarker is a substance which gives information on normal biological processes (organ functions), pathological processes (including disease state), pharmacological response to a given treatment or response to an intervention or even to an unintended environmental exposure such as chemicals or nutrients. In a broader sense, biomarkers are used for diagnosis, monitoring, screening, prognosis, risk assessment and the evaluation of treatment success.

A biomarker may be a specific cell type, molecule or gene, gene products, enzyme, or hormone. Examples of biomarkers include anything from pulse and blood pressure through basic chemistries to more complex laboratory tests of blood and other tissues [1,2].

The development of biomarkers relies on the understanding of the pathological basis of the disease or process. This understanding could be at any level, such as molecular, biochemical and anatomical. Simple, cheap, reliable, and feasible measures of a disease have great utility both in clinical care and in clinical trials [7]. The discovery of biomarkers in clinical research is a hot topic, and the scientific improvement studies are growing tremendously. The key issue is determining the relationship between any given measurable biomarker and relevant clinical endpoints reliably [2].

Significance of biomarkers

Biomarkers are useful in several ways both in clinical care and scientific studies and they play major roles in medicine. In today’s modern medicine, we use biomarkers for several purposes such as early diagnosis, disease prevention and treatment decision. The use of biomarkers in basic and clinical research as well as in clinical practice has become so commonplace that their presence as primary endpoints in clinical trials is now accepted almost as a standard. However, understanding the relationship between biomarkers and clinical outcomes is vital to distinguish between pathological processes and normal physiology to develop efficient diagnostic tools or treatments for all diseases [2] (Figure 1).

**Figure 1:** Main tools of biomarker studies. Biomarkers in pulmonary diseases are used for diagnostic, prognostic and predictive tools. Biological samples are preferred to be easy to obtain materials such as plasma, serum, sputum, urine or bronchio-alveolar lavage fluid. Increasing number of omic technologies are used to achieve best suitable biomarkers and ethics places in the center of the diagram to remind what to prioritize first.
One of the most common use of biomarkers is using them as surrogate endpoints in clinical trials. Since, primary clinical endpoints, such as survival can occur so infrequently, their use in clinical trials can be unfeasible or even unethical. In some cases, it may be preferable to use established biomarkers as surrogate endpoints to reduce the risk of harm to subjects: the early data provided by biomarkers can provide researchers the opportunity to stop potentially harmful interventions to subjects before the related clinical data is available [2]. In other cases, biomarkers may simply allow researchers to design smaller, more efficient studies, reducing the number of subjects exposed to a given experimental treatment. By shortening the time to approval of new treatments, scientists can provide much more effective treatment choices for the patients earlier. And also, by using biomarkers, they can maintain both material and human resources for research projects [2]. Biomarkers have many other valuable applications including:

- Diagnostic tool for diseases or abnormal condition (differential diagnosis).
- Classification or staging of the diseases.
- Prognose prediction.
- Prediction, monitoring and screening of clinical response to a new intervention or treatment either in vitro or in vivo.
- Measuring toxicity and side effects [3,7].

As indicated in the brief summary above, biomarkers play very important roles in understanding the normal biological process as well as the pathophysiology of that process in the disease state, and effects of an intervention - pharmacological, device, or otherwise - on these processes. Since our knowledge on the full picture of those types of processes is still insufficient, biomarkers will also continue being important in clinical practice and research area in the future.

**Omics technology in the biomarker discovery**

Biomarkers can be found in many different forms, including particular proteins or peptides (e.g. serum C-reactive protein in pneumonia), antibodies (e.g. serum anti-citrullinated protein antibodies for rheumatoid arthritis and interstitial lung disease), cell types (e.g. white blood cell counts in pneumonia or lung cancer), metabolites (e.g. nitric oxide in induced sputum of asthma patients with eosinophilic inflammation), lipids (e.g. cholesterol and other lipid levels in metabolic syndrome and sleep apnea), hormones (e.g. thyroid stimulating hormone in Hashimoto’s disease), enzyme levels (e.g. various hepatic enzymes for liver metastasis), physiological states such as blood pressure or fever, or imaging studies of particular organs or organ systems (e.g. pulmonary nodules in sarcoidosis [6].

A biomarker can also be a substance introduced into a patient to identify body changes at the cellular level, such as positron emission tomography-computed tomography using fluorodeoxyglucose for cancer staging.

There are many different molecules as biomarkers and more recently, the term ‘biomarker’ evolved with the increasing interaction between molecular biology research using omics technology and medicine. Biomarkers became highly important in “personalized medicine” and there are various “omics” technologies used to measure these molecules. Integrating basic and clinical science with Systems biology in combination with comprehensive bioinformatics is necessary for a personalized management approach [8]. Genomics, proteomics and metabolomics are among the most frequently used tools in pulmonary medicine area. Genomics is the analysis of genetic coding system, while proteomics refers to the analysis of the complete set of proteins or proteome [9]. Metabolomics is the systematic analysis of small molecules, including carbohydrates, amino acids, organic acids, nucleotides and lipids. These technological advances depend on the tools of many disciplines, including molecular biology and biochemistry, computational biology, chemistry, protein biochemistry, and mass spectrometry [10].

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Genome and genomics

Deoxyribonucleic acid (DNA) orchestrates all the functions and behaviors of living organisms, which are in the form of double helical strings. DNA strands are consisting of nucleotide bases named adenine (A), thymine (T), guanine (G), and cytosine (C) that generate the genetic codes which in turn the As, Ts, Cs and Gs determines the meaning of the information encoded in that part of the DNA [8]. An organism's complete set of DNAs make a genome, and every single cell in the body contains the same copy of the human genome. DNA contains the information needed to generate the whole human body. A gene is the part of DNA that carries the code to make a specific protein or set of proteins [8]. Proteins involve in the basic stones of organs and tissue, as well as control chemical reactions and carry signals between cells. A mutation in the DNA of a cell may cause production of an abnormal protein, which in turn can change the usual processes of the cell and lead to a disease such as cancer [9].

Having said all these, while genome is a complete set of DNAs of a single cell, genomics evaluates the complete behavior of genes, which orchestrate the production of proteins with the assistance of other molecules. Genomics also involves the sequencing and analysis of genomes [10]. There are several subtypes that consist the field of genomics research. These are functional genomics, which describes the function and interaction of genes and RNA transcripts (transcriptome), structural genomics that describes the 3-dimensional appearance of the protein for a specific gene, epigenomics, that focus on the modifications of epigenome which controls gene expression without altering DNA.

Transcriptomics has become a new branch of genomics, which first was studied under functional genomics. Its interest on the transcription of the gene, including mRNA and splicing elements, gave birth another new era of genomic research that is called next generation RNA sequencing. This technology has yield to understand that there are other molecules translated from DNA without coding for proteins. These macromolecules called Non-coding RNAs (ncRNA) and studies revealed that amount of these ncRNAs involve in transcription, protein folding, epigenomics, splicing and even cell signaling [11].

Types of ncRNAs include previously known transfer RNA (tRNA), ribosomes (rRNA), as well as newly recognized small RNAs such as microRNAs, small nuclear RNAs (snRNAs), long ncRNAs (lncRNAs), small interfering or silencing RNAs (siRNAs), piwi-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), extracellular RNAs (exRNAs), small canal body specific RNAs (scaRNAs), X-inactive specific transcript (Xist) and Hox transcript antisense RNA (HOTAIR).

The number of non-coding RNAs within the human genome is unknown; however, recent transcriptomic and bioinformatic studies suggest that there are thousands of them. Many of the newly identified ncRNAs have not been validated for their function. It is also likely that many ncRNAs are non-functional (Junk RNA) and are the product of spurious transcription, but some of them have been proven for being involved in the functional processes (Table 1) [12]. Especially miRNAs are focused as biomarkers for their role in the regulation of diseases particularly in cancer. Studied miRNAs for diagnose of lung cancer revealed suggestion of several diagnostic panels (Table 2).

<table>
<thead>
<tr>
<th>Functions</th>
<th>Involved ncRNAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Translation</td>
<td>rRNA, tRNA, snRNAs</td>
</tr>
<tr>
<td>In RNA splicing</td>
<td>snRNPs (U1, U2, U3, U4, U5, U6), snoRNAs (HBII-52)</td>
</tr>
<tr>
<td>In DNA replication</td>
<td>Y RNAs (Ro60 ribonucleoprotein particles)</td>
</tr>
<tr>
<td>In Gene regulation</td>
<td>miRNAs</td>
</tr>
<tr>
<td>In Genome defence</td>
<td>piRNAs</td>
</tr>
<tr>
<td>In Chromosome structure</td>
<td>lncRNA, Xist</td>
</tr>
<tr>
<td>As hormone</td>
<td>miRNA (miR-206 estrogen receptor alpha regulator)</td>
</tr>
<tr>
<td>In Diseases</td>
<td>miRNAs, lncRNAs (especially in cancer)</td>
</tr>
</tbody>
</table>

Table 1: Functions of ncRNAs.
Epigenetic modifications are biochemical changes of the chromatin, that are functionally relevant, but do not affect the nucleotide sequence of the genome. These biochemical changes include histone modifications and DNA methylations. Epigenetic modifications are best known for their effects on the accessibility of certain genomic loci to transcription enzymes and thus their expression. Any disease that alters cellular adaptive changes in the phenotype will likely involve in one or more epigenetic changes. Transcription is regulated by DNA methylation at CpG islands in promoters of protein coding genes, by post-translational modifications of histone proteins as well as ncRNAs. Because DNA methylation, the histone code and microRNA-mediated gene silencing are highly conserved processes, many clinically diverse conditions should respond to drugs that modify these epigenetic regulatory systems [19]. Therefore, the use of biomarkers in the early diagnose, screening, therapy or follow-up for might be useful tools for lung diseases.

In the field toxicogenomics, global gene expression profiles have been studied in the particulate matter (pm), air pollution and traffic pollution conditions and these studies provided numerous potential biomarkers which can be used to predict the development of lung diseases (Table 3).

<table>
<thead>
<tr>
<th>miRNA panels</th>
<th>Expression</th>
<th>Sample</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-193b, miR-301, miR-141 and miR-200b</td>
<td>Upregulation</td>
<td>Serum</td>
<td>Nadal., et al. 2015 [20]</td>
</tr>
<tr>
<td>Let-7c, miR-152</td>
<td>Downregulation</td>
<td>Plasma</td>
<td>Dau., et al. 2015 [21]</td>
</tr>
<tr>
<td>miR-125a, miR-145, miR-146a</td>
<td>Upregulation</td>
<td>Serum</td>
<td>Wang., et al. 2015 [22]</td>
</tr>
<tr>
<td>miR-429, miR-205, miR-200b, miR-203, miR-125b, miR-34b</td>
<td>Upregulation</td>
<td>Serum</td>
<td>Halvorsen., et al. 2016 [23]</td>
</tr>
<tr>
<td>A panel of 24 miRNAs</td>
<td>Relative expression</td>
<td>Plasma</td>
<td>Wozniak., et al. 2015 [24]</td>
</tr>
</tbody>
</table>

**Table 2: Suggested miRNA panels for the detection of lung cancer.**

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Related disease</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A1</td>
<td>Lung Cancer</td>
<td>Bellavia., et al. 2013 [13]</td>
</tr>
<tr>
<td>OGG1</td>
<td>Lung Cancer</td>
<td>Hemmingsen, 2015 [14]</td>
</tr>
<tr>
<td>MFN2 (mitofusin 2)</td>
<td>Lung Cancer</td>
<td>Crosbie., et al. [16]</td>
</tr>
<tr>
<td>HMOX1 (heme oxygenase 1)</td>
<td>Lung Cancer</td>
<td>Wang., et al. 2012 [17]</td>
</tr>
<tr>
<td>ID1, ID2 (inhibitor DNA binding 1 and 2)</td>
<td>Lung Cancer</td>
<td>Chu., et al. 2016 [18]</td>
</tr>
<tr>
<td>STC2 (stanniocalcin 2)</td>
<td>Lung Cancer</td>
<td>Chu., et al. 2016 [18]</td>
</tr>
<tr>
<td>SRXN1 (sulfiredoxin 1)</td>
<td>COPD</td>
<td>Chu., et al. 2016 [18]</td>
</tr>
<tr>
<td>PDGFA (platelet derived growth factor subunit A)</td>
<td>Lung Cancer</td>
<td>Wang., et al. 2012 [17]</td>
</tr>
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</table>

**Table 3: Examples of Potential biomarkers of respiratory diseases induced by particulate matter.**

Citation: Dr. Yasemin Saygideger., et al. “Biomarkers in Pulmonary Research”. EC Pulmonology and Respiratory Medicine SI.03 (2020): 21-30.
Main genomic research tool is polymerase chain reaction (PCR), is now widely used all around the world and particularly real time quantitative PCR (RT-qPCR) assays have become the invaluable method for the accurate detection of nucleic acids in various biological samples such as gene expression analysis and cancer phenotyping. PCR is a common method for amplifying DNA; for RNA-based PCR the RNA sample is first reverse-transcribed to complementary DNA (cDNA) with reverse transcriptase. In order to amplify small amounts of DNA, DNA template, at least one pair of specific primers, deoxyribonucleotides, a suitable buffer solution and a thermo-stable DNA polymerase are used. The process generally consists of a series of temperature changes that are repeated 25 - 50 times. These cycles normally consist of three stages: the first, at around 95°C, allows the separation of the nucleic acids double chain; the second, at a temperature of around 50 - 60°C, allows the binding of the primers with the DNA template; the third, at between 68 - 72°C, facilitates the polymerization carried out by the DNA polymerase [26].

The other research techniques used in genomics to determine biomarkers are the all common techniques used in molecular biology such as microarrays, DNA, RNA isolation, gene transfection, cell culture and animal modeling. For the researchers who seek to study genomic biomarkers of pulmonary diseases, we strongly recommend to understand all the basics of genome and molecular biology and not to avoid the potential genetic differences between societies and regions as they might be affected even from particulate matters as we mentioned above, before generalizing others’ research findings into their clinic. This means every population should immediately study their own genetic biomarkers for better outcome.

Proteins and proteomics

Proteins are very large molecules and consist of chains of linked amino acid sequence. There are twenty amino acids and the length of proteins varies between a few amino acids to over a thousand amino acids [27]. Amino acids come together in different combinations to form ten thousand of proteins. Proteins typically contain thousands of atoms arranged into three-dimensional structure. Protein transform into their three-dimensional form by folding, and this transformation takes a few seconds [27]. This complex curved structure determines how proteins work and interact with other units [27]. Specific amino acid sequences that make up each protein is encoded via the genes contained in the DNA of living cells. Protein synthesis is a very complicated process. A protein cannot be synthesized without its own mRNA. A great amount of mRNA may be found in a cell, but these mRNA may not be turned into a protein. Ribosomes are the protein factories of the cell [27]. Ribosomal RNA bridges are not only a supportive structure, but also take a role in protein synthesis. Peptides are small proteins and play important roles in biological processes. Peptides act as a biochemical messenger or they are formed as a protein metabolite [27].

Proteomics is a term used to describe all the “different proteins” expressed by a genome and it is the systemic analysis of protein profiles of tissue. “Different proteins” term is not only the polypeptide structure encoded by the gene, but also includes post-synthesis modifications [28]. Proteomics describe structures of all proteins present in a certain place at a certain time, their location, amount, post-translational modifications, functions in tissues and cells, and interactions with other proteins and macromolecules [28]. Unlike the genome, proteome may change over time [27]. Proteomics is a dynamic term and it is defined as the quantitative analysis technology of proteins in cells, tissue or body fluids under different conditions [28]. Proteomic is correlated with associated genomic fields [28].

There has been growing interest in proteomics technology in pulmonary medicine. Proteomics do not only provide information about the identification and quantification of proteins but it also helps to understand the determination of protein localization, modifications, interactions, activities and functions [29]. mRNA expression levels may not well correlated with protein expression levels and mRNA levels do not reflect the activity of the encoded protein. For these reasons, genome and proteome provide a complementary information [28]. In addition to proteins, peptides (low molecular weight proteins) can also be biomarkers for pulmonary diseases and they can be determined by proteomics technologies [27].

Citation: Dr. Yasemin Saygideger., et al. “Biomarkers in Pulmonary Research”. EC Pulmonology and Respiratory Medicine SI.03 (2020): 21-30.
In proteomics in pulmonary medicine body fluids (blood, urine, bronchoalveolar lavage fluid, exhaled breath condensate, sputum etc.) are used as the tissue source or lung tissue is used to detect biomarkers [27]. Two-dimensional PAGE Gel Electrophoresis and liquid chromatography multistage mass spectrophotometry system is the frequently used technologies in proteomics analysis [27].

Protein separation performed by two-dimensional electrophoresis is based on a pH gradient (first dimension) within an electric field, where protein migration is dependent on the isoelectric point. The second dimension depends on protein size (molecular weight) that is responsible for migration speed through the electrophoretic field of a dodecyl sulfate polyacrylamide gel (PAGE). Proteins can be then taken from the gel, denatured to their primary, linear structure, and digested with a protease such as trypsin, which produces predictable protein fragments [10]. Protein fractionation can also be performed using chromatographic separation, based on protein affinity for chemical substances. The most used chromatographic method is reverse-phase liquid chromatography. It is based on the separation of hydrophobic proteins from hydrophobic columns at progressively higher concentrations of organic solvents [10]. After fractionation and proteolytic digestion, protein identification is mostly done by mass spectrometry, based on separation of gaseous ions depending on their different mass and charge [30]. Therefore, mass spectrometry can identify and qualify both large and small proteins.

Proteomics is a topic of intense investigation in pulmonary medicine and protein biomarkers are now being studied in many lung diseases such as acute lung injury, cystic fibrosis, asthma, COPD, lung cancer, interstitial lung disease and tuberculosis [31]. Bowler RP, et al. presented their work on biomarker discovery in acute lung injury (ALI) in 2004. It was the first report using proteomics approach in ALI. Protein profiles in plasma and pulmonary edema fluid of ALI patients, and plasma and bronchoalveolar lavage fluid of normal subjects were investigated. They identified at least 300 different proteins expressed in ALI patients. They also analyzed protein spots that indicate posttranslational modifications in ALI patients [32]. In Peterson SK, et al. study, some candidate biomarkers expressed by the Pseudomonas aeruginosa strain PA01 have been identified from sputum of subjects with cystic fibrosis by immunoproteomic approach. All subjects with cystic fibrosis were found immunoreactive against immunocaptured Pseudomonas proteins which can be helpful in prediction of Pseudomonas aeruginosa infection in cystic fibrosis [33]. In U-BIOPRED clinical adult asthma study investigators evaluated patients with moderate-to-severe asthma and performed an omics analysis of sputum, which they found significant differences in sputum proteomics and transcriptomics in different asthma variants [34]. Compared to phenotype 2 (severe airway obstruction, smoker or ex-smoker), there was greater abundance of connective tissue-activating peptide III (CTAP-III; or chemokine [C-X-C] ligand 7), granulocyte-macrophage colony stimulating factor (GM-CSF) and trypsin 2 in phenotype 1 (well-controlled asthma). Phenotype 3 (oral corticosteroid depended group) had increased levels of arylsulfatase B precursor (ARSB) and proteasome subunit a2 (PSA2) compared to phenotype 1. This study showed that different clusters based on clinico physiologic parameters are associated with different protein pathways. Plymoth., et al. demonstrated that when baseline bronchoalveolar lavage fluid proteome is profiled in healthy smokers, compared to nonsmoker controls, and then reevaluated after 6 - 7 years, it is possible to find useful protein signatures in those subjects who are risky for COPD development [35]. There are also many sets of biomarkers for other common lung-diseases such as lung cancer and tuberculosis. However, further studies are needed to validate these biomarkers and drug targets before using them in early detection, prediction or prevention and cure of lung diseases.

Metabolomics and glycomics

Metabolomics represents the set of all metabolites in human and it detect, quantify and define the metabolites like lipid, carbohydrates, vitamins, hormones and small molecular weight metabolites arising from tissues, cells and in physiological fluids. Metabolome definition excludes small molecules such as enzymes, genetic materials and structural molecules that are divided into smaller molecules, but do not play a role in metabolic reactions. Small molecules such as peptides, oligonucleotides, sugars, nucleosides, organic acids, ketones, aldehydes, amines, amino acids, lipids, steroids, alkaloids and drugs are accepted as metabolites [36].

Genomics and proteomics give information on what may happen, and metabolomics tells what happened in fact. The metabolome is much more dynamic than either the genome or proteome. So, metabolomics can detect changes in metabolites resulting from physiological and/or environmental events over shorter time scales [36]. A single base change in DNA may cause 100,000-fold increase in
metabolite levels [27]. Less than 1% of known metabolites are used in routine clinical tests and metabolomics analysis can be performed in body fluids such as serum, urine, plasma, and saliva [27].

Two technologies are used in metabolomics studies. These are: Nuclear Magnetic Resonance and different mass spectrophotometry’s. Metabolomics markers are used in lung disease such as cystic fibrosis, COPD and asthma [27]. In a recent study Checkley W, et al. found that children with asthma had approximately 40 - 50% lower relative concentrations of ascorbic acid, 2-isopropylmalic acid, shikimate-3-phosphate, and 6-phospho-d-gluconate when compared to children without asthma, and 70% lower relative concentrations of glutathione [37]. A recent review summarized 21 existing metabolomic studies of asthma in humans. Exhaled breath condensate, plasma, serum and urine samples are used in these studies and they reported significant findings and concluded that individual metabolites and metabolomic profiles including acetate, adenosine, alanine, Hippurate, succinate, threonine and trans aconitate measured in exhaled breath condensate, urine, plasma and serum could be used to identify asthmatics and asthma phenotypes [38]. Chen Q, et al. reported that serum metabolomic biomarkers including myoinositol, glycophosphoinositol, fumarate, cysteine sulfonic acid, a modified version of fibrinogen peptide B could be useful to differentiate early stage COPD from healthy smokers [39].

All glycan structures located within a cell or organism are called as glycomes, and the glycomics identifies the amount, location and interaction of carbohydrates [40]. The behaviour of glycosyl transferases, enzyme which transfers and binds sugar, vary according to the cell type and stage of cell growth [40]. Glycomics technology is used to determine biomarkers because carbohydrate chains are a part of the cell receptors and glycosylation is affecting the function of many proteins [41]. Glycan analysis can be made in body fluids such as saliva, serum, urine, and plasma. Nuclear Magnetic Resonance and oligosaccharide analysis are used in glycomics studies [41]. Glycomics biomarkers are very new area in pulmonary medicine and it is expected that glycomics will contribute to the discovery and characterization of cancer-related biomarkers containing glycans (i.e. glyco-biomarkers) and a more detailed understanding of cancer biology and inflammatory airway disease such as asthma and COPD.

Conclusion

Biomarker technology has undergone massive advances due to the cumulative knowledge related to molecular biology. Next generation sequencing, liquid biopsy, array analysis, and omics studies combining with computational studies had developed a large series of tools to analyze biomarkers for early diagnose, treatment or follow-up for the diseases. Since most of the pulmonary diseases such as interstitial lung diseases, COPD, asthma, tuberculosis, occupational diseases and lung cancer, are chronic and have a high difficulty to overcome, it is very important to have suitable biomarkers for each condition to figure how to plan patients treatment or follow-up terms etc. In this article, we reviewed basics of biomarkers and the tools to discover them, mainly for the clinicians, those who seek to involve in translational research. It is important to know that researchers in basic science and clinical science should become organized to prioritize patients well-being in the biomarker studies.

Bibliography


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