SERUM BIOMARKERS IN EVALUATION AND VALIDATION OF DISEASES

H.D. Khanna
Department of Biophysics, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005
Email: hdkhanna@yahoo.co.in

ABSTRACT

Biomarkers are key molecular or cellular events that link a specific environmental exposure to a health outcome. Biomarkers play an important role in understanding the relationships between exposure to environmental chemicals, the development of chronic human diseases, and the identification of subgroups that are at increased risk for disease. The validation of biomarkers as early predictors of clinical disease can enhance health risk assessment and contribute to effective new disease prevention policies in environmental and occupational settings. The process of validating biomarkers involves dealing with a range of characteristics that include the intrinsic qualities of the biomarker, its determinants, and the analytic procedure. The principal goal is to discover biomarkers, with the ultimate objective of identifying differentially expressed proteins between diseased and healthy controls. Novel and fast high-throughput systems dramatically enhance the analysis of thousands of proteins and genes with very low volumes. It is becoming clear that the consideration of a single biomarker might not be potent enough to improve diagnostic specificity. Thus, it is essential to develop methods to measure several biomarkers together in a single well or on a biochip to create an accurate prognostic profile. Plasma/serum measurements are the gold standard in clinics, because they are minimally invasive and can be easily collected and processed. Plasma/serum data reflect a broad spectrum of changes. A major advantage of blood samples is that patients can be followed up and screened over several years.

Key words: Serum Biomarker, Prognostic profile, Chronic human diseases, Health risk assessment

In 2001, a consensus panel at the National Institutes of Health defined the term biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention or other health care intervention. The biomarker is either produced by the diseased organ (e.g., tumor) or by the body in response to disease. Biomarkers are potentially useful along the whole spectrum of the disease process. Before diagnosis, markers could be used for screening and risk assessment. During diagnosis, markers can determine staging, grading, and selection of initial therapy. Later, they can be used to monitor therapy, select additional therapy, or monitor recurrent diseases [1]. Thus, identifying biomarkers include all diagnostic tests, imaging technologies, and any other objective measures of a person’s health status. Biomarkers can also be used to reduce the time factor and cost of clinical trials by replacing clinical endpoints. Biomarkers span a broad sector of human health care and...
have been around since the understanding of human biology and diseases began to evolve. Genetics, genomics, proteomics, and modern imaging techniques and other high throughput technologies permit to measure more markers than before. In addition, a greater understanding of disease pathways, the targets of interventions, and the pharmacologic consequences of medicines can be achieved.

BIOMARKERS

Biomarkers are by definition molecules used to aid in the pathology diagnosis, stratify patient populations, provide information on disease progression, inform on drug safety and monitor drug efficacy and help streamline clinical trials.

Biomarkers in clinical utilities

A biomarker (also, called molecular marker and signature molecule) is a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. A biomarker is a term often used to refer to a protein measured in blood whose concentration reflects 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. A biomarker can be a substance that is introduced into an organism as a means to examine organ function or other aspects of health. It can also be a substance whose detection indicates a particular disease state, for example, the presence of an antibody may indicate an infection. More specifically, a biomarker indicates a change in expression or state of a protein that correlates with the risk or progression of a disease, or with the susceptibility of the disease to a given treatment. Biomarkers are characteristic biological properties that can be detected and measured in parts of the body like the blood or tissue. They may indicate either normal or diseased processes in the body [1]. Biomarkers can be specific cells, molecules, or genes, gene products, enzymes, or hormones. Complex organ functions or general characteristic changes in biological structures can also serve as biomarkers. Although the term biomarker is relatively new, biomarkers have been used in pre-clinical research and clinical diagnosis for a considerable time [2]. For example, body temperature is a well-known biomarker for fever. Blood pressure is used to determine the risk of stroke. It is also widely known that cholesterol values are a biomarker and risk indicator for coronary and vascular disease, and that C-reactive protein (CRP) is a marker for inflammation. A biomarker is a parameter that can be used to measure the progress of disease or the effects of treatment. The parameter can be chemical, physical or biological. In molecular terms biomarker is the subset of markers that might be discovered using genomics, proteomics technologies or imaging technologies. Biomarkers play major roles in medicinal biology. Biomarkers help in early diagnosis, disease prevention, drug target identification, drug response etc. Several biomarkers have been identified for many diseases such as serum LDL for cholesterol, blood pressure, p53 gene [3] and MMPs [4] for cancer etc. Gene based biomarker is found to be an effective and acceptable marker in the present scientific world.

Characteristics of an ideal biomarker

An ideal biomarker should be

- Safe and easy to measure.
- Economical, quick and consistent.
- Consistent across genders and ethnic groups.

Biomarker requirements

For chronic diseases, whose treatment may require patients to take medications for years, accurate diagnosis is particularly important, especially when strong side effects are expected from the treatment. In these cases, biomarkers are becoming more and more important, because they can confirm a difficult diagnosis or even make it possible in the first place [5]. A number of diseases, such as Alzheimer’s disease or rheumatoid arthritis, often begin with an early, symptom-free phase. In such symptom-free patients there may be more or less probability of actually developing symptoms. In these cases, biomarkers help to identify high-risk individuals reliably and in a timely manner so that they can either be treated before onset of the disease or as soon as possible thereafter [6, 7]. In order to use a biomarker for diagnostics, the sample material must be as easy to obtain as possible. This may be a blood sample taken by a doctor, a urine or saliva
sample, or a drop of blood like those diabetes patients extract from their own fingertips for regular blood-sugar monitoring. For rapid initiation of treatment, the speed with which a result is obtained from the biomarker test is critical. A rapid test, which delivers a result after only a few minutes, is optimal. This makes it possible for the physician to discuss with the patient how to proceed and if necessary to start treatment immediately after the test. Naturally, the detection method for a biomarker must be accurate and as easy to carry out as possible. The results from different laboratories may not differ significantly from each other, and the biomarker must naturally have proven its effectiveness for the diagnosis, prognosis, and risk assessment of the affected diseases in independent studies. A biomarker for clinical use needs good sensitivity e.g. >0.9, and good specificity e.g. >0.9 [8] although they should be chosen with the population in mind so positive predictive value and negative predictive value are more relevant.

**Biomarker classification and application**

Biomarkers can be classified based on different parameters. They can be classified based on their characteristics such as imaging biomarkers (CT, PET, and MRI) or molecular biomarkers. Molecular biomarkers can be used to refer to non-imaging biomarkers that have biophysical properties, which allow their measurements in biological samples (e.g., plasma, serum, cerebrospinal fluid, bronchoalveolar lavage, biopsy) and include nucleic acids-based biomarkers such as gene mutations or polymorphisms and quantitative gene expression analysis, peptides, proteins, lipids metabolites, and other small molecules. Biomarkers can also be classified based on their application such as diagnostic biomarkers (i.e., cardiac troponin for the diagnosis of myocardial infarction), staging of disease biomarkers (i.e., brain natriuretic peptide for congestive heart failure), disease prognosis biomarkers (cancer biomarkers), and biomarkers for monitoring the clinical response to an intervention (HbA1c for antidiabetic treatment). Another category of biomarkers includes those used in decision making in early drug development. For instance, pharmacodynamic (PD) biomarkers are markers of a certain pharmacological response, which are of special interest in dose optimization studies.

**Applications of biological markers**

To develop, validate and promote as tools:
- for monitoring environmental contamination
- for measuring intermediate events between exposure and disease

**QUANTITATION AND VALIDATION OF BIOMARKERS**

It has been known that cancer cells or other related non-tumor cells can release specific tumor markers, which are usually proteins, as tumors develop, into the circulation system in response to cancer growth. These substances are normally present in small amounts in the blood or other tissues. Cancer cells can sometimes make these substances rise above the normal indicate cancer might be present in the body. These tumor markers can be detected in blood, urine, or tissue samples, and the level of them is associated with the stage of cancer [9-12]. Alongside the development of proteomic technologies, lots of protein tumor markers have been discovered for many types of cancer [13-15]. Considering the high importance and potential application in the early diagnosis of cancer, detection of tumor markers has received more and more attention [16-20]. While some novel immunoassays have been developed, a variety of techniques have been employed for the development of these assays. Among the various detection techniques, the colorimetric method, in which the event is disclosed through a visual color change in the reaction medium, has proven the most convenient.
CONCLUSION

The use of biomarkers in medicine lies in their ability to detect disease and support diagnostic and therapeutic decisions. New research and novel understanding of the molecular basis of the disease reveals an abundance of exciting new biomarkers that present a promise for use in the everyday clinical practice. The initial evaluation of a serum biomarker concerns its expression in patients with the disease and in normal individuals in order to define sensitivity and specificity. The sensitivity of a test is defined as the proportion of patients with disease having a positive test whereas the specificity is the proportion of patients without the disease who have a negative or normal test. Prospective investigations, technical improvements and introduction of novel markers are warranted in order to elevate the association of serum biomarkers with the pathogenesis of diseases. Nonetheless, crossing the boundary from research to clinical application requires validation in multiple settings, experimental evidence supporting a pathophysiologic role, and ideally intervention trials showing that modification improves the outcome. The emergence of pioneering technologies including DNA and tissue microarrays which have already been applied with great success in the disease progression can help scientists to circumvent this problem and bridge this boundary. In the interim, these markers can be quite useful to supplement the clinical, radiological and physiological monitoring of the disease and identify high-risk patients who would benefit from aggressive management of established risk factors.

REFERENCES

19. Opoku, A.R., Maseko, N.F. and Terblanche, S.E: The in vitro antioxidative activity of some


About Author

Dr. H.D. Khanna, Professor of Biophysics at Institute of Medical Sciences, Banaras Hindu University had been the Head of the Department of Biophysics, Institute of Medical Sciences, Banaras Hindu University for three terms from 1992 to 2012. He has worked in the field of “Free Radicals and antioxidants in Health and Disease”. He has more than 90 publications in the International and National journals of repute in the area of tumor biology, low birth weight infants, eclampsia/pre-eclampsia and different disease states. He has supervised the research work of 102 candidates for PhD, MCh, MS/MD courses in Medicine along with M.Sc / M.Tech (Biotechnology) courses. He has chaired academic session in the different conferences in the country and has been awarded by different scientific bodies for his best interdisciplinary research work. He has evaluated PhD thesis of different Universities in the country.