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Disease Biomakers in Serum: Analytical Methods of Identification and Quantification

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Biomarker is a biomolecule that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacological responses to a therapeutic drug treatment [1,2]. Alternatively, it can be defined as a chemical, its metabolite, or the product of an interaction between a chemical and some target molecule (genes, gene products, enzymes or hormones, etc.) or cell that is measured in the human body. The effectiveness of a biomarker is determined by the degree to which biomarker reflect clinical outcomes. Therefore, an ideal biomarker is expected to be: (i) able to detect a fundamental feature of a specific disease, validated in and confirmed by those specific disease cases; (ii) able to detect the early stages of this specific disease and differentiate it from other similar disease cases or family members of that disease; (iii) precise, accurate, sensitive, specific, non-invasive and inexpensive [3].

Disease-related biomarkers [4] indicate the probable effect of treatment on patient (predictive biomarkers), if a disease already exists (diagnostic biomarker), or how such a disease may develop in an individual case regardless of the type of treatment (prognostic biomarker).

Biomarkers can be classified into:

1. Electrolytes and ions - sodium (Na^+), potassium (K^+), chloride (Cl^-), carbondioxide (CO_2), calcium (Ca^{2+}), phosphorus (phosphate, PO_4^{3-}), magnesium (Mg^{2+}), iron (Fe^{2+}).
2. Small molecules and metabolites (under a molecular weight of 1000) - those that reflect nutritional status (glucose, vitamin B12, folic acid, etc.), those that reflect the elimination of waste products (bilirubins, lactic acid, creatinine, uric acid, urea nitrogen, ammonia, etc.) and those that reflect metabolic control (thyroid stimulating hormone, estrogen, testosterone, beta-human chorionic gonadotropin, etc.)
3. Large molecules and metabolites (molecular weights ranging from 30,000 to over 500,000) - plasma proteins (albumin, globulins, prealbumin), transport proteins (ferritin, transferring, haptoglobin ceruloplasmin), defense proteins (immunoglobulins IgA, IgG, IgM, IgE, complements C3, C4), clotting proteins (fibrinogen, D-dimer), enzymes (alanine aminotransferase ALT, aspartate aminotransferase AST, alanine phosphatase ALP, gamma-glutamyltransferase, lactate hydrogenase LD, creatine kinase CK, amylase, lipase and pseudocholinesterase), tumor markers (prostate specific antigen PSA, carcinoembryonic antigen CEA, cancer antigen 125 CA125, cancer antigen 15-3 CA15-3, alpha-fetoprotein AFP, rheumatoid factor RF, C-reactive protein CRP, high sensitivity C-reactive protein hsCRP, beta natriuretic peptide β-NP and antistreptolysin-O ASO).
4. Lipids and lipoproteins - (total cholesterol, high density lipoprotein HDL cholesterol, low density lipoprotein LDL cholesterol, triglycerides, lipoprotein a, apopoproptein A and B).
5. Hypothesis-driven - quiescin Q6 sulfhydryl oxidase 1 (QSOX-1). It is a protein and the most promising candidate to identify patients with acute decompensated heart failure (ADHF).
6. Genetic - These biomarkers are based on the determination of genetic polymorphisms and can be either of intake or of effect (metabolism) or as disease risk. They can be determined in the DNA of any biological sample that contains cells with a nucleus.
7. Environmental - biomarkers that measure exposure in the human body (cotinine in blood or urine for second-

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hand tobacco smoke, benzene metabolites in urine for traffic-related pollution, etc.); biomarker of effect that is associated with an established or possible health impairment or disease (DNA adducts) and biomarker of susceptibility that is associated with inherent or acquired ability of an organism to respond to the challenge of exposure to a specific chemical substance (glucose-6-phosphate dehydrogenase G6PD deficiency).

These biomarkers can be found in biological samples such as blood (whole blood, plasma or serum), urine, saliva, cerebrospinal fluid, amniotic fluid, synovial fluid, pleural fluid, pericardial fluid, peritoneal fluid (ascetic fluid), faeces, hair, nails, adipose tissue and other specific tissues depending on the aims of the study.

A human serum is the clear portion of the human's body fluid that separates from blood upon clotting. The serum contains proteins (60-80 mg/ml) in addition to various small molecules such as amino acids, lipids, salts and sugars [5]. Human serum contains numerous biomarkers for a number of diseases such as cancer, cardiovascular, rheumatoid arthritis, respiratory, neurodegenerative, etc. Typical examples are prostatic acid phosphatase [6] and PSA [7] for prostate cancer; carcinoembryonic antigen CEA [8], for colorectal, lung, breast, liver, pancrease, bladder cancers and CA 125 [9] for ovarian cancer, etc. Serum biomarkers for cardiovascular disease are B-type natriuretic peptide, nesiritide [10], N-terminal proB-type natriuretic peptide [11] and C-reactive protein [12], etc. Rheumatoid arthritis has stromelysin-1 [13], interleukin-15 [14] and cytokines tumor necrosis factor-α, interleukins-12, -15, and -18 [15] as serum biomarkers. The respiratory serum biomarkers are urinary-trypsin-inhibitor [16], eosinophil cationic protein [17] while cystic fibrosis (CF) has serum CA 19-9 [18], trypsinogen [19] and prolyl hydroxylase serum [20], etc. as biomarkers.

Due to the high abundance of albumin and heterogeneity of plasma lipoproteins and glycoproteins, biomarkers are difficult to identify and quantify in human serum. Therefore, analytical method to be adopted has to be accurate, precise, selective, specific and sensitive. Biomarkers that are proteins have been separated, identified and quantified from crude biological samples by using analytical methods which exploit the physicochemical properties (isoelectric point, hydrophobicity and molecular mass and size) of proteins. Separation based on isolelectric point is done using ion exchange chromatography [21] as well as gel electrophoresis [22,23]. Separation based on hydrophobicity is carried out using reversed phase high performance liquid chromatography, RP-HPLC [24]. Separation based on molecular mass and size is done using gel electrophoresis as well as size exclusion chromatography [25]. Other methods utilized for protein analysis are immunological techniques [26], mass spectrometry techniques [27], tandem-mass spectrometry [28], liquid chromatography-mass spectrometry [29]. In addition, analytical methodologies for the determination serum biomarkers that are not proteins include atomic absorption spectrometry, inductively coupled plasma spectrometry, liquid chromatography (LC), gas chromatography (GC), mass spectrometry(MS) and hyphenated systems (GC-MS, LC-MS/MS techniques), etc.

In conclusion, biomarkers (chemical, physical or biological) play major roles in medicinal biology and help in early diagnosis, disease prevention, drug target identification and drug response. They are useful in measuring the progress of disease, evaluating the most effective therapeutic regimes for a particular disease and establish a long-term susceptibility to disease or its recurrence. Currently, techniques such as genomics, proteomics, metabolomics, lipidomics, glycomics, secretomics are also being employed to accurately measure the disease biomarker levels and establish criteria for disease diagnosis and prognosis. Finally, to enhance future serum biomarker identification and quantification, techniques should be improved and combinations of different technologies and statistical analysis are required to increase the accuracy, sensitivity, reproducibility and specificity of biomarker detection.

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