Bio-Markers and Bio-Sensors: Unravelling the Major Mechanistic Interventions in Cancer Prognosis

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ABSTRACT

Biosensors are a tool that combines the biochemical element with a transducer that generates an indication for the identification of disease. Numbers of biosensors are used in different medical application. Biomarker and Biosensors play an important role for early stage exposure of cancer. It is a cost-effective, increased assay speed, resiliency, the ability for multi-target analysis method. Genomic and proteomic molecular tools are also used for the exposure of tumors. These methods produce a molecular mark that provides a new opening for utilizing biosensors and biomarkers. As with many disease conditions, it is not easy to find exact and responsive markers that are associated with only one marker. Different numbers of molecular signatures are used for the diagnosis of cancer, such as proteins, peptides, overexpression gene and gene mutation. This review provides a general idea of the biosensors and biomarkers technology that is currently developed and researched for cancer markers and diagnosis.

Keywords: - Molecular Signature; Cancer; Biomarkers; Biosensors; Electrochemical detection, Transducer; Point of care testing

INTRODUCTION

Cancer testing in the human body is tough. It is consists of more than two hundred dissimilar disease and distressing some humans organs[1]. nonstop cell division characterizes cancer cells. Metastasis of cancer cell to different healthy organs, self-cell division, the death of healthy cells, continuous formation of new blood vessels[2]. Cancer is the main reason of death in developed and developing countries. The largest cause of death result as of the prostate(males), pancreas, breast (females), colon, lung[3].

When emergent biosensors for cancer testing, it is important to well-known about the difficulty and some basic thing about cancer[3]. Cancer is the result of disruption of the normal cell signaling pathway, produce cancer cells[4]. The genetic disease can cause cancer. In genetic it is a modification of DNA sequence of key genes, and it changes the protein composition of tumor of cells. As DNA sequence changes, the cell's behavior becomes deregulated and produces cancer cells. Environmental factors such as lifestyle, diet, ultraviolet radiation[3].

CANCER DETECTION

Early diagnosis of cancer generates more chance for survival of the patient. For successful early diagnosis of cancer, specific methods are required [4]. Advance development in molecular biology is opening many ways for early stage cancer diagnosis. Since cancer cells development generates many signals and shows many changes. This information can be used for the diagnosis and cure of the patient[3].Innovative biosensor techniques are playing a great role for identification of early stage cancer[5]. In this review article, I will talk about the different type of biosensors for clinical testing, diagnosis.

CANCER BIOMARKERS

Cancer antigens are used as biomarkers for cancer diagnosis. This cellular molecule can be detected in cancer cells, urine, blood or other body fluid that are expressed due to cancer cell growth. There are many ranges of biomarkers that are well-known with a different type of cancers (Table.1). These biomarkers include DNA modification, RNA, proteins, hormones, a molecule of the immune system and other related molecules. Thus, multiple antigens can be identified and used as biomarkers for cancer identification and

diagnosis. Some genes are identified for specific cancer that can be used for diagnosis of cancer. Ex. The breast cancer antigens NY-BR-1 and ING-1 was tested by the use of cancer testing antigens CAGE-1 and ESO-1. In the following table, cancer type disease associated with different known biomarkers[6].

Table -1: Various cancer and their specific biomarkers

S.No	Cancer Type Disease	Biomarkers
1	Prostate	PSA, PAP
2	Leukemia	Chromosomal abnormalities
3	Testicular -	Alpha-Fetoprotein (AFP), human chorionic gonadotropin, CAGE-1, ESO-1
4	Ovarian	CA125, AFP, HCG, p53, CEA
5	Breast	CA15-3, CA125, CA27.29, CEABRCA1, BRCA2,MUC-1, CEA, NY-BR-1, ING-1
6	Colon and Pancreatic	CEA, CA19-9, CA24-2, p53
7	Lung	NY-ESO-1, CEA, CA19-9, SCC, CYFRA21-1, NSE
8	Gastric carcinoma	CA72-4, CEA, CA19-9
9	Melanoma	Tyrosinase, NY-ESO-1
10	Any solid tumor	Circulating tumor cells in biological fluids, expression of targeted growth factor receptors
11	Liver	AFP, CEA
12	Esophagus carcinoma	SCC
13	Bladder	BAT, FDP, NMP22, HA-Hase, BLCA-4, CYFRA 21-1
14	Trophoblastic	SCC, hCG

PSA (Prostate-specific antigen) Bio-marker

Prostate cancer is common cancer in men in developed and developing countries. Prostate-specific antigen (PSA) is a biomarker for the identification of prostate cancer in the male. It is the type of solid tumor, which has clinical useful protein biomarkers for diagnostics[1]. PSA has exposed sensible sensitivity for detection of early cancer[7]. Most of the men who diagnosed with prostate cancer are dying for other reasons. Most of the prostate cancer is clinically diagnosed while another prostate cancer is as such remaining over the year. All prostatic cancer patients develop a biochemical change that changes in a clinical diagnosis and finally causing death. PSA is a suitable biomarker for the detection of prostate cancer. PSA detection for prostate cancer in men is very complicated. The cutoff level of PSA in blood is four ng/ml for the detection of prostate cancer. High level (between 4 ng/ml to 10 ng/ml) of PSA in blood is not a cause of prostate cancer. While the presence of PSA < 0.5ng/ml may cause of prostate cancer. Thus, PSA for detection of prostate cancer is not reliable[8].

CEA (Carcinoembryonic antigen) and Carbohydrate Antigen 19-9 (CA 19-9) Bio-marker

CEA (Carcinoembryonic antigen) is a proteomics-based biomarker [9]. It is associated with progression of the colorectal tumor[10].CEA is a detected in the presence of gastrointestinal tract cancer. CEA is detected when the level is more than 5ng/ml in blood. CEA is elevated only in the presence of CRC (colorectal carcinoma) in most of the patient. Carbohydrate Antigen 19-9 (CA 19-9) is present in gastrointestinal tract cancer, and it is a type of glycoprotein with high molecular weight. It was detected in human blood. Carbohydrate Antigen 19-9 (CA 19-9) is utilized for the diagnosis of pancreatic, gastric, and colorectal cancer[11].

Cancer Bio-sensors

The use of biosensors for the detection and solve the problem of cancer is a sensitive, fast and cheap measurement tools. IUPAC has defined the biosensors, but the exact definition was given by the Newman et al. (2004). They define as ‘a compact analytical device incorporating a biological derived sensing element either integrated within or intimately associated with a physicochemical transducer’. The first biosensors were a catalytic system that was enzymes with the transducer. The transducer converts that biological response into an

electrical signal. In these days, next-generation biosensors are available that works in association with antibodies and receptors[12].

Biomarkers are an indicator of normal biological processes, pathogenic processes or pharmacologic response to a therapeutic intervention. Cancer biomarkers are the molecular change that can be detected in the urine, blood, cancer cells and other body fluid of cancer patient. Cancer biomarkers work on the basis of DNA modification, RNA, protein modification and in the presence of other biological molecules(Table.2)[3]. Biosensors are a point-of-care device that can be used for analyzing the clinical cancer sample at home or in doctor's surgery. For the development of specific biosensors, specific markers need to be identified to ensure specificity of the device. Biosensors can provide a multi-array sensors system for multi-marker diagnosis. It is an advanced platform for the multi-analyze testing system, for a cancer diagnosis[6]. In the following table, cancer type disease associated with different known biosensors.

Table -2: Cancer types associated with different known biosensors and their principle

S.No	Cancer Biomarkers	Biosensors	Principle
1	AFP	Electrochemical	Protein array with 36 platinum electrodes. Prussian blue with the screen-printed amperometric sensor.
2	AFP and CEA	Electrochemical	Dual-electrode with amperometric detection
3	CA15-3	Electrochemical	Functionalised Antibody sol–gel film with potentiometric detection.
4	CA125	Electrochemical	Capillary electrophoretic
5	CA19-9	Electrochemical	Titania Sol–gel on glassy carbon electrode with direct electrochemical detection of HRP.
6	CEA	Electrochemical	Faradic impedance spectroscopy using gold nanoparticle modified glassy carbon electrode Immobilized thionine as a mediator between the electrode and HRP-labelled antibody. Direct electrochemical detection of HRP in an immune sensor.
7	PSA	Electrochemical	Gold coated microporous membrane. Amperometric disposable electrode. Capacitive immunogens using lateral flow and impedance detection

BIOSENSORS IN CANCER DISEASE

Biosensors for the detection of PSA (Prostate-specific antigen) Bio-mark

On a global scale, prostate cancer has a chief health issue, and it is a third common cancer in men. PSA (Prostate-specific antigen) is biomarkers to screen prostate cancer patient, and it is an important marker for the detection of early-stage prostate cancer[6]. PSA is found in human serum, either in free form or in combined with various protease inhibitors. The level of 10 ng/ml or higher PSA is a probable indicator for prostate cancer. The intensity of PSA greater than four ng/ml in serum is an indicator for the biopsy. Testing of PSA is very expensive and time-consuming[12].

Biosensor for the Detection of CEA (carcinoembryonic antigen) Biomarker

Breast cancer is the most common cancer in women and leading cause of death in women. Due to improvement in detection and diagnosis has decreased the death rate. For early detection of breast cancer in women, a bio-mark signal is used[13]. Carcinoembryonic antigen (CEA) is a well-known biomarker that is associated with progression of colorectal tumors. An immune sensor for determination was prepared by positively charged toluidine blue (TB) coated on negatively charged poly-sulfanilic acid (PSAA) customized glassy carbon electrode (GCE). The prostate-specific antigen can be identified by the use of electrochemical detection of colloidal gold/alumina solution. In prostate-specific antigen, a potential change occurs before and after the antigen-antibody interaction[10].

Biosensor for the Detection of CA 125 (cancer antigen 125, carcinoma antigen 125, or carbohydrate antigen 125) Biomarker

CA 125 is also known as mucin 16 or MUC 16. MUC 16 is a protein that is identifying in a human being by the use of MUC 16 genes. CA 125 is a tumor marker or biomarker that is present in the blood of patients with a specific type of cancer. CA 125 is used as the marker for ovarian cancer. Enzymatic activity of the protein can be used as the biomarker for cancer activity. Ex-telomerase that activity is regulated in malignant tumors[3]. Proteomics approaches have been used to generate protein expression of the normal breast cell that compared with the cancer cell of the breast[3].

Biosensors for the detection of AFP (Alpha-Fetoprotein) Bio-mark

AFP (Alpha-Fetoprotein) is a widely used as a tumor marker for germ cell tumor and hepatocellular carcinoma. An immunosensor based AFP was prepared by the entrapping reaction of thionine (is a metachromatic dye that is used for biological staining) into Nafion (this is an engineering based polymer used in preparation of enzyme-based sensors) to form a composite of Thi/Nf membrane. This membrane is a borderline that contain amine group in assembling with gold nanoparticle layer to check the alpha-fetoprotein antibody. For detection of AFP, a new enzyme immune sensors has developed. This enzyme immune sensor was developed with layer by layer assembly of gold nanoparticle and thionine immobilized on the Nafion-modified electrode surface by electrostatic adsorption[10].

Simultaneous multi-marker detection

There is multi-cancer marker are available in the market, in this a multi-ELISA (multi-analyte enzyme-linked immunosorbent) assay kit is used on the same chip to detect several analytes at the same time by the using immunogens principle. A simple development for disposable electrochemical immune sensor for simultaneous determination of CA19-9 and CA125[4].

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TRANSDUCER

A biosensors is a bio-analytical device (ex tissue, microorganism, cell organelles, cell receptors, enzyme, antibodies, nucleic acid etc) which is very closely related with physicochemical transducer or transducing microsustem[4]. The transducer is a biological component that convert the biological response into a measurable electronic signal[12]. The transducers used in biosensors are optical, thermometric, piezoelectric and magnetic. Amperometric and potentiometric transducers are most commonly used in conjunction with electrochemical biosensors. Thus, some transducer method is possible for the development of biosensors technology[14] Electrochemical sensors measure the electrochemical changes that occur on the surface of detecting electrode when analytes interact with a sensing surface. The electrochemical test is simple, reliable and low detection limit. The electrical change can be potentiometric (a change in the measured voltage between the indicator and reference electrodes), or amperometric (a change in the measured current of applied voltage) or conductometric (a change in the transport charge). An optical transducer is used to determine the affinity reaction of antigen- antibody and DNA interaction[15].

Electrochemical transducer

Electrochemical biosensors are portable, simple, easy to use, cost-effective and disposable. It is a small pocket size device that make applicable for home use and in the doctor's surgery. The glucose biosensors are the best example of electrochemical biosensors. This is widely used throughout the world for glucose testing in the home and at the site and one important thing this is a handheld device that is combining with several electrochemical biosensors on a single chip. This is used for multiple electrolyte systems. For cancer biomarkers, analysis a bio-affinity based electrochemical biosensors are used to determine the gene mutation of biomarkers and protein biomarkers. Electrochemical-based bio-sensors for cancer detection based on DNA hybridization and for gene mutation detection. In this device, a single standard DNA is placed on the electrode surface and when DNA hybridization takes place than detection conduct in the presence of a number of methodologies [6]. Wang and Kawde used a chronopotentiometric transduction for electrochemical detection of mutation related to the breast cancer genes BRCA1 (BReast CAncer gene one) and BRCA2 (BReast CAncer gene two. Tansil et al. use the catalytic oxidation of the guanine nucleobase for the detection of cancer marker genes from breast tissue. Protein biomarkers are more widely used for cancer analysis. For detection principle, change in electrochemical properties on the sensor surface due to the antibody antigens interaction is used. Faradic impedance spectroscopy has been reported for the CEA biomarkers analysis. In this gold nanoparticle modified glassy, carbon electrode is used[5].

Optical transducer

Optical transducer based on the method of internal reflectance spectroscopy, surface Plasmon resonance and evanescent wave sensing. In this light passes through optical fibers towards sensing surface and reflected back again. The measured optical signals often include absorbance, fluorescence and surface plasmon resonance. Optical biosensors are mainly used for screening a large number of samples. Manly fluorescence labels are used for the detection. An Affymetrix gene chip is used for the cancer gene identification[6]. Other biosensors such as grating couplers, resonance mirrors, and surface plasmon are used for the cancer biomarkers diagnosis. Surface plasmon system such as BiaCore™ biosensor chip is a most widely used optical transducer for biosensor platform. These systems are also applied for other application rather than biomarkers detection. Different surface plasmon resonances have been developed for cancer marker detection. These sensors are more suitable for laboratory-based testing rather than a point of care device for onsite analysis[16].

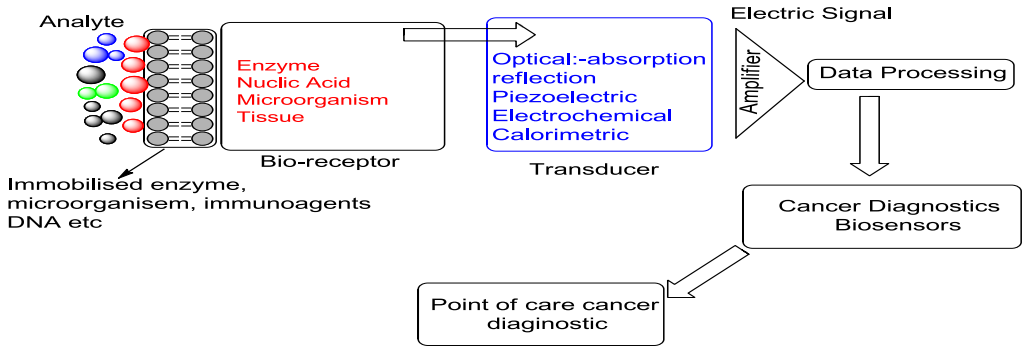
Mass-sensitive transducer

Mass-sensitive transducer technology is also a label-free technology. Piezoelectric immune sensors are widely used for the detection of cancer markers where the specific antibody is immobilized on the sensors chip. There are some devices available on the market, which is based on this technology. One best example is QCMA-1 (quartz crystal microbalance) sensors that are fully automated[17]. This technique is based on the use of gold chip with antibody immobilized on the surface of the sensors. In these days, microcantilever-based sensors are widely used for cancer detection (Figure.1). In microcantilever, affinity interaction works between the antibody on the surface of the cantilever and the biomarkers are detected through the amount of bending of the sensors due to mass change in the resonance frequency[18].

CONCLUSION

Cancer testing and diagnosis is very typical task yet new development in physical science and engineering science has opened the new way of clinical testing and diagnosis in the field of cancer. Development of molecular tools on the basis of gene expression, protein profile, and protein post-translation modification has opened the new way for utilization of biosensors for cancer testing. The use of biosensors for cancer clinical testing may increase assay speed and flexibility, multi-target analyzes and automation has reduced the cost of cancer testing and diagnosis.

Figure.1 Schematic representation of biosensor containing the biorecognition element, transducer and the physical output whose level is correlated to the concentration of the analyte of interest



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