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Biosensors and biomarkers: promising tools for cancer diagnosis

Abstract

Due to its high death rate, cancer has been one of the most researched diseases all over the globe. A biosensor is an analytical device, used for the detection of an analyte that combines a biological component with a physicochemical detector. Nowadays, there is an increasing interest in developing cancer biosensors as they show superior analytical performance and real-time measurement. Further with recent advances in molecular biology and bioengineering, biosensors diagnosis of cancer has taken a new direction. Due to high specificity and promise of early diagnosis, biosensors are prime candidates for current and future cancer diagnosis. With ever increasing list of biomarkers associated with various types of cancer and innovation in bioengineering, the future for diagnosis of cancer seems promising. In present article we have discussed various biosensors and biomarkers as a promising tool for cancer diagnosis.

Keywords: bioengineering, biosensor, biomarker, cancer, carcinoma, diagnosis, disease, detector, potentiometric, impedimetric

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Introduction

Cancer is one of the leading life-threatening diseases all over the world with over 200 types identified and higher than 1500 deaths occurring every day. Despite of recent technological advancements, late diagnosis and poor prognosis are leading reasons for poor survival rate of cancer patients. The conventional methods, including magnetic resonance imaging, biopsy and ultrasound are not efficient for early stage cancer detection, due to their dependence on the phenotypic properties of the tumor.[1] Cancer is a multistage disease, and a complex range of genetic and epigenetic alterations which disturb the cellular signaling are associated with its onset and progression and result in tumorigenic malignancy and transformation.[2] The biomarkers are molecules which undergo important alterations during cancer and carry high clinical significance. Biomarkers may be proteins, isoenzymes, nucleic acids, metabolites or hormones and are classified as prognostic, predictive and diagnostic.[3] Diagnostic biomarkers are used for the detection of the disease, whereas the information about course of recurrence of the disease is given by prognostic biomarkers. On the other hand, the response to treatment is estimated by predictive biomarkers.[4,5] The change in the level or presence or absence of specific biomarkers in a cell often is an indication of cancer development. Cancer-specific detection and identification of these biomarkers could help in early monitoring and diagnosis of disease progression.[6] The traditional enzyme-linked immunosorbent assay (ELISA) or Polymerase chain reaction (PCR) based methods for biomarkers detection; suffer technological limitations such as consumption of expensive reagents in every assay and slow detection.[7] Also, being manual techniques, these methods are not proficient in the continuous monitoring of the patient during treatment. Besides, within the cell multiple events are associated with all cancers involving more then one molecule. Thus simultaneous detection of multiple biomarkers for correct diagnosis and prognosis is required.[8,9]

Why biosensors for cancer diagnosis?

Clinical cancer diagnosis is now focusing on developing analytical techniques, which are clearly capable of sensitive and parallel detection of biomarkers rendering useful point-of-care testing. For detecting cancer monoclonal antibodies, aptamers and antigens are used to bind micro Ribonucleic acids (miRNAs) corresponding single stranded Deoxyribonucleic acid (ssDNA). The recognition signal is converted to electrical signal by a device called transducer. The transducer may be optical (luminescence, fluorescence, interferometry and colorimetric), calorimetric (thermistors), electrochemical (by, Amperometry, potentiometry and conductometry/impedimetry), or based upon mass changes (acoustic waves/ piezoelectric), and are needed because they give high noise signals and radios, high performance, have great resolution, cheap instrumentation and give consistent results.[10] Electrochemical biosensors are the widely used and calorimetric are the least explored.[11] Low levels of biomarkers can be measured by them in physiological samples which can assist in the diagnosis of cancer at an early stage because of their lower minimum detection limits. Besides, the reuse of biorecognition molecules and avoidance of a time lapse between the sample preparation and analysis is also facilitated by them. Moreover, high potentiality for simultaneous detection of multiple biomarkers is shown by biosensors.[3] Detection of several biomarkers has been successfully done by different types of biosensors (Figure 1).

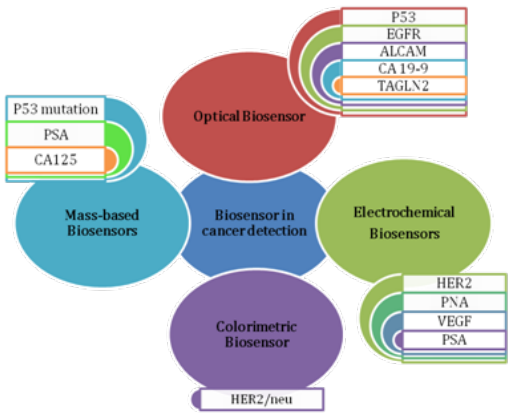

Figure 1 Common biomarkers utilized for cancer detection.

Biosensors types and uses in the diagnosis of cancer

Electrochemical biosensors

Due to low cost, portability, small size and ease of use, electrochemical biosensors are the most commonly preferred. They can be operated in a doctor's office or from. Glucose biosensor is the most widely used example of an electrochemical biosensor which is based on a screen-printed amperometric disposable electrode. Bringing diagnosis to on site analysis, this type of biosensor has been widely used all over the world for glucose testing at home. Hand held i. STAT clinical analyzer is another development which combines many electrochemical biosensors on a single chip and is used for multiple metabolites and electrolytes in clinical samples. Early cancer diagnosis is provided by electrochemical affinity sensors based on antibodies with great see and sensitivity. A range of electrochemical transducers are used and these include potentiometric, impedimetric/ conductivity and amperometric devices. Amperometric and Potentiometers biosensors are the two most common electrochemical biosensors.[12] Ion selective electrodes which detect electrical response whenever a specific element's molecular recognition occurs is used by potentiometric sensor. These biosensors have high potential in the diagnosis of cancer. They have been reported to highly selectivity detect breast tumor cell's MDA / MB231 marker hPRL-3.[13] Potential placed between electrodes produces current which is measured by amperometric transducers. The current produced by oxidation-reduction reactions is measurable. Use of amperometric biosensors have be reported for cancer detection by utilizing DNA sequences. Presence of tumor conjoined which posses genetic mutations can be detected by these sensors; the recognition occurs through hybridization of tumor-specific DNA sequences which occur within the genome of tumor cells. Mutations like BRCA1 and BRCA2 which are linked with hereditary breast sarcoma are screened by this type of biosensors.[14] Electrochemical biosensors help in detection of damaged DNA along with carcinogens that cause the damage. Protein scans and immunoassays and also uses electrochemical transducers. Antibodies are attached to an electrochemical transducer in immuno sensors, which are also used to detect of cancer.[14] The best method of detection and prevention of cancer are the biosensors that are able to detect multiple varieties of tumors. Such biosensors with several transducers are functionalized individually to detect specific antigens or proteins. Such biosensors can be inexpensive and reliable designed with semiconductor materials.[15]

Optical biosensors

Optical biosensors measure the variations in wavelengths of light. These, transducers can be colorimetric, fluorescent, interferometric or luminescent. Changes of the wavelengths in response to their cognition of the analyte are converted by optical transducers and electrical readings/ provide digital.[12] A new type of sensors with the use of an optical transducer is a biosensor which has photonic crystals. Such sensors are designed for capturing the very tiny volumes or light areas, which allows measurements at a high susceptibility, and to display results the light is transmitted to a higher electromagnetic field. This technique detects where and when the molecules or cells dissociate or bind to the surface made of crystal through the measurement of the light reflected in the crystal. Implementation of these biosensors has been done to monitor changes in apoptosis and proliferation of breast tumor cells with exposure to doxorubicin. The values were used for measuring the rate of cytotoxicity. Thus have an important role in monitoring the progression of disease.[14] Laser-induced fluorescence is another optical biosensor for the monitoring and diagnosis of throat cancer. The patient swallows the biosensor, laser beam is directed by the device and on the surface of the esophagus a specific wavelength of light is emitted. The walls of the esophagus reflect light of very specific wavelengths, and the variation in the visualization of various wavelengths is influenced by the presence or absence of cancer cells or normal cells. Over 200 patients have been tested by this sensor and have been found to be highly useful as compared to conventional methods. Surgical biopsies and the pain associated recovery are prevented by this biosensors.[14]

Mass sensitive biosensors

Acoustic and piezoelectric biosensors are two types of biosensors that rely on mass changes. Piezoelectric sensors are based on changes in the mass of a quartz crystal when the potential energy is applied to them. The frequencies generated by mass changes can be converted to signals. Micro cantilever and immunosensors biosensors which are based upon piezoelectric technologies are useful for detecting of tumor biomarkers. Over expression of human p53 gene's point mutations in several types of tumors has been reported with piezoelectric biosensors coupled with PCR amplification.[12]

Calorimetric biosensors

Calorimetric biosensors measures exothermic reactions and are not used widely in the detection of cancer. Temperature changes due to heat produced during many enzymatic reactions are used in measurement of the desired molecules. By measuring enthalpy the reactions are monitored, which indirectly gives the information required to measure the amount of the molecules. They are less widely used in the detection of cancer, even though there have been few useful characteristics of these biosensors for diagnosis of cancer. Successful detection of sarcoma by using calorimetric biosensors with gold nanoparticles based aptamers has been done by a research group. Detection of two different types of cells: Cells of Burkitt's and acute leukemia cells were done. Medley et al claim that this strategy may differentiate between cancer and normal cells.[16]

Cancer biomarkers

Biomarker is molecule of biological origin found in tissues, blood or other body fluids that is indicative of a abnormal or normal process or of any disease or condition. Body's response to treatment can also be monitored by biomarkers.[17] Biomarkers can have many molecular origins, which includes RNA, protein (antibody, tumor suppressor, oncogene or hormone) DNA (translocation, specific mutation, loss of heterozygosis, amplification) or protein. These biomarkers are unarguably the very important for early tumor diagnosis, determining Cancer's response to the treatment, monitoring disease progression and accurate pretreatment staging.[18,19] Biomarkers are usually detected in fluids such as urine, serum, cerebral spinal fluid or blood, but they also can be present on or in tumor cells.[12]

Prostate specific antigen

Prostate specific antigen (PSA) was the first identified tumor biomarker and used in clinical routine for detecting and screening prostate cancer. It has been reported that prostate cancer is directly correlated to increased PSA levels. 4.0 nanogram per milliliter is normal value of PSA. Approximately 30% of individuals with PSA level in the range of 4.1 - 9.9 nanograms per milliliter have prostate cancer.[20] Increase in PSA levels can also indicate small tumors which

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are not fatal, benign prostatic hyperplasia or prostatitis (inflammation of the prostate). Thus, levels of PSA are not always indicating malignant tumor, a fact which has prompted many controversies for the use of routine PSA test for prostate tumors. Death due to small tumors is impossible in an individual's life span due their slow growth that is detected by PSA screening due to their slow growth.[21] False positives are common which is another problem with PSA test and many individuals with above normal PSA levels have no signs of prostate tumor at all.[22,23] This drawback of PSA screening can be taken care by biosensors by removing few uncertainties surrounding the usual screening methods in use right now.[17]

Cancer antigen 125

Increase in cancer antigen (CA) 125 correlates to ovarian tumor and also is connected with cancers of cervix, uterus, pancreas, colon, liver, breast, digestive tract and lungs. Pregnancy and menstruation which are non pathological conditions can also lead to an increase in CA 125 levels.[24] 90% women who have advanced cancer of ovaries and 40% patients who have intra-abdominal tumors show elevated CA 125 levels. However, CA 25 levels are normal in 50% patients with 1st stage ovarian cancer.[24,25] Lactate dehydrogenase (LDH), alpha-fetoprotein (AFP) and human chorionic gonadotrophin (HCG) are other biomarkers for ovarian cancer which origin from germ cells.[26] Further, progression of benignancy to malignancy is identified by increase in CA 125.[27,28] Thus CA 125 is useful biomarkers for its progression monitoring along with its usefulness in diagnosis.

Cancer antigen 15-3

One of the most important biomarker for diagnosis and monitoring of breast cancer is CA 15-3. BRCA1, BRCA2, CA 27 and carcinoembryonic antigen (CEA) are additional biomarkers that correlates with breast cancer.[12,29] CA 15-3 is often mostly used in monitoring therapy in advance breast cancer cases. CA 15-3 values rises by 10%, 20%, 40% and 75% in 1st, 2nd, 3rd and 4th stages of breast cancer respectively.[29] Increase in CA 15-3 levels post treatment is an indication of disease recurrence.[30] Negative risk factors (PR/ER status and ilHer-2), tumor size and cancer stage are considered along with CA 15-3 level to determine treatment protocols. Endometriosis, hepatitis, pregnancy, lactation and pelvic inflammatory disease are conditions other then cancer that can increase CA 15-3.

Cancer antigen 19-9

Cancer antigen 19-9 (CA19-9) is an isolated Lewis antigen of the MUC1 glycoprotein with an average molecular weight of 1000kDa. It was first discovered in serum of patients with colon cancer and pancreatic cancer in 1981.[31] The normal range of serum CA 19-9 is less than 37U/ml. In recent years, this tumor marker has become the gold standard for pancreatic cancer diagnosis in clinical use.[32] The concentration of CA19-9 in human serum also plays a significant role in clinical detection of gastric and urothelial carcinomas. Therefore, there is a real need to develop operationally highly sensitive methods to detect levels of CA 19-9 in cancer patients.

Alpha-fetoprotein

Alpha-fetoprotein (AFP) represents the most prominent biomarker with a molecular weight of about 70,000Da. The yolk sac and liver of the developing baby in early fetal life produces the protein during pregnancy. AFP may also be found at high levels in the serum of adults having certain malignancies. It was first introduced as an antigen specific for human hepatocellular carcinoma by Yuri Semenovich Tatarinov in 1963.[23] Studies have shown that AFPs are clarified into three subtypes, including LCA nonreactive AFP (AFP-L1), LCA weakly reactive AFP (AFP-L2) and LCA-reactive AFP (AFP-L3), based on different affinities to lens culinaris agglutinin (LCA).[24] The normal level of AFP is below 20ng 8mL-1 in healthy human serum.[25] It is widely used for the diagnosis of hepatocellular carcinoma. In addition, elevated AFP concentration may be present in ataxia-telangiectasia syndrome, hereditary tyrosinemia, cirrhosis, alcoholic hepatitis, viral hepatitis or in several malignant diseases including liver metastasis from gastric cancer, testicular cancer and nasopharyngeal cancer. Thus, the detection of AFP is absolutely necessary in clinical assay. Because of the specific and strong binding of affinity probes to their targets, electrochemical affinity bioassays have recently gained increasing attention in the quantitative detection of AFP. A key area of electrochemical biosensors research is the use of various nanomaterials because they improve biosensor signal.

Receptor binding cancer antigen (RCAS1)

RCAS1 over expression has been reported in most of gastric malignancy and it linked with gastric cancer progression.[33] RCAS1 has further been used as a biomarker for prognosis in cancers of breast, gallbladder, endometrial and esophageal and with tumor relapse in pharyngeal and laryngeal cancer.[34] Therefore it is an important biomarker for cancer diagnosis and prognosis.

Conclusion

Biosensors are the most reliable and cost effective tool available at present. Accurate and early diagnosis of cancer will help in reducing the death rates. Further biomarkers can also be used to monitor treatment progression and thus biosensors can provide information about the effectiveness of the treatment. There is no doubt that this decade will extensively involve biosensors due to their above mentioned uniqueness.

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Conflict of interest

The author declares no conflict of interest.

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