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CANCER DETECTION USING NANOSENSOR

PRACHI V. YAWALE[1], PROF. S. M. MAHALLE[2]

1. ME Student, Department of Electronics & Telecommunication, IBSS, Amravati, Maharashtra, India.
2. Assistant Professor, Department of Electronics & Telecommunication, IBSS, Amravati , Maharashtra, India.

Abstract: Early detection of cancer is one of the most hope full approaches to reduce cancer death rates. Cancer biomarkers are molecule that can indicate the biological states of the disease, which increase in concentration during the onset of the disease . Sensitive and accurate detection of cancer biomarkers in human fluid samples could offer seminal contributions to early diagnosis. Biosensor technology has the potential to provide fast and accurate detection, reliable imaging of cancer cells, and monitoring of angiogenesis and cancer metastasis, and the ability to determine the effectiveness of anticancer chemotherapy agents. A variety of sensors based on different nanostructured materials are highly sensitive and selective for the detection of cancer biomarker . A variety of nanostructured materials including carbon nanotubes, silicon nanowires, gold nanoparticals and quantum dots , in fabrication of sensors.

Keywords: Biosensor, Biomarker, Cancer detection.

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Corresponding Author: MS. PRACHI V. YAWALE

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INTRODUCTION

Cancer is the second leading cause of death. Cancer can take over 200 distinct forms, including lung, prostate, breast, ovarian, hematologic, skin, and colon cancer, and leukemia, and both environmental factors (eg. tobacco smoke, alcohol, radiation, and chemicals) and genetic factors (eg, inherited mutations and autoimmune dysfunction) are associated with an increased risk of developing cancer.

Cancer is defined as abnormal and uncontrolled cell growth. Unregulated cell growth leads to the formation of tumor mass that over time becomes independent of normal homeostatic checks and balances. As the cancer progresses, the tumor begins to spread beyond the site of origin and metastasize to other body organs and systems, at which point, the cancer is essentially incurable.

The two major tumor genesis mechanisms are activation of oncogenes and inactivation of tumor suppressor genes (TSGs). Activation of oncogenes occurs through mutation or duplication of a normal gene (a proto-oncogene) involved in the regulation of cell growth, proliferation, and/or differentiation. This typically results in constitutive activation or excess levels of a normal gene product, leading to the deregulation of cell growth, increased cell division, and tumor formation. Perhaps more so than any other type of oncogene, growth factor receptors have been investigated as potential cancer biomarkers. The human epidermal growth factor receptor Her-2, for example, is amplified in ~33% of all breast cancers, and cancers with amplified Her-2[6] tend to grow and spread more aggressively. TSGs are involved in the regulation of inappropriate cell growth and proliferation by slowing or stopping cell division. Three of the most well-studied TSGs in cancer are retinoblastoma protein (Rb), BRCA1/2, and p53.3 The Rb is a master regulator of cell division, and mutation of Rb plays a role in many cancers. Point mutations and deletions are the most common causes of inactivation of the Rb1 gene. BCRA1 gene mutations account for about 50% of heredi- tary breast cancers and 80%–90% of hereditary breast and ovarian cancers. Another major concern with the loss of p53 is that it can serve as a mechanism of chemotherapeutic drug resistance. The development of biosensors that can detect the presence of mutations in p53, Rb, and BRCA1 is of great importance in terms of being better able to determine cancer susceptibility as well as more accurate prognosis and treatment regimens.

II. CANCER BIOMARKERS

The National Cancer Institute (NCI) defines a biomarker as "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" Cancer biomarkers are potentially one of the most valuable tools for early cancer detection, accurate pretreatment staging, determining the response of cancer to chemotherapy treatment, and monitoring disease progression. Biomarkers are typically detected in human fluids such as blood, serum, urine, or cerebral spinal fluid, but they can also be present in or on tumor cells. A partial list of tumor biomarkers is presented in Table.

Table 1: Common Biomarker utilized for cancer

Type of cancer	Biomarker
Breast	BRCA1, BRCA2, CA 15-3, CA 125, CA 27.29, CEA, NY-BR-1, ING-1, HER2/NEU, ER/PR
Colon	CEA, EGF, p53
Esophageal	SCC
Liver	AFP, CEA
Lung	CEA, CA 19-9, SCC, NSE, NY-ESO-1
Melanoma	Tyrosinase, NY-ESO-1
Ovarian	CA 125, HCG, p53, CEA, CA 549, CASA, CA 19-9, CA 15-3, MCA, MOV-1, TAG72
Prostate	PSA

Prostate-specific antigen

Prostate-specific antigen (PSA) was one of the first tumor biomarkers to be identified and put into routine clinical use for screening and diagnosis of prostate cancer. Studies have shown that above-normal PSA levels correlate directly with prostate cancer. A normal level of PSA is 4.0 ng/mL.

Cancer antigen 125

Elevated cancer antigen (CA) 125 is most commonly associated with ovarian cancer and is also linked to cancers of the uterus, cervix, pancreas, liver, colon, breast, lung, and digestive tract. Several nonpathological conditions such as menstruation and pregnancy can also result in increased levels of CA 125.22 CA 125[3] is elevated in 90% of women with advanced ovarian cancer and in 40% of patients with intra-abdominal malignancy. Overall, CA 125 is a valuable biomarker not only for cancer diagnosis, but also for various other aspects of cancer treatment and progression.

CA 15-3

CA 15-3 is an important biomarker analyzed in breast cancer patients. Other biomarkers that are linked to breast cancer are carcinoembryonic antigen (CEA), BRCA1, BRCA2, and CA 15-3 is used clinically most often to monitor patient therapy in cases of advanced breast cancer.

Cancer-testis Antigens

Cancer-testis (CT) antigens are a unique class of cancer biomarker. They are highly expressed in many tumors, but not in normal cells. Thus, they have been heavily pursued as potential immunogenic targets for cancer immune therapies (ie, cancer vaccines), and auto antibodies to CT antigens have been pursued as cancer biomarkers. One of the advantages of CT auto antibodies as cancer biomarkers is that they are present in serum.

RCAS1 (eBAG-9)

Receptor-binding cancer antigen expressed on SiSo cells (RCAS1)[4] has been shown to be over expressed in nearly 100% (98.4%) of gastric carcinomas and correlates closely with gastric tumor progression. In terms of cancer biomarkers, RCAS1 expression appears to be highly indicative of cancer progression and perhaps prognosis. As with most of the cancer biomarkers discussed here, RCAS is over expressed by many different types of tumors and should be factored in with other parameters when establishing treatment regimens.

III. REPRESENTATION OF BIOSENSOR

A sensor that integrates a biological element with a physiochemical transducer to produce an electronic signal proportional to a single analyte which is then conveyed to a detector.

Information such as whether or not the analyte is present and at what level is transduced into an electrical signal that can be amplified, displayed, and analyzed. Examples of analytes include proteins (antigen, antibody, and enzyme), nucleic acid, or other biological or metabolic component (ie, glucose).In terms of cancer, the analyte being detected by the biosensor is a tumor biomarker.

Biosensors that can detect multiple analytes may prove particularly useful in cancer diagnosis and monitoring, A biosensor is made up of three components: a recognition element, a signal transducer, and a signal processor that relays and displays the results. The molecular recognition component detects a 'signal' from the environment in the form of an analyte, and

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the transducer then converts the biological signal to an electrical output. The basic structure and function of a biosensor is shown in Figure.[1]

I. Biosensor recognition element

The recognition element is a critical component of the biosensor. Examples of recognition elements are receptor proteins, antigens, antibodies, enzymes, and nucleic acids
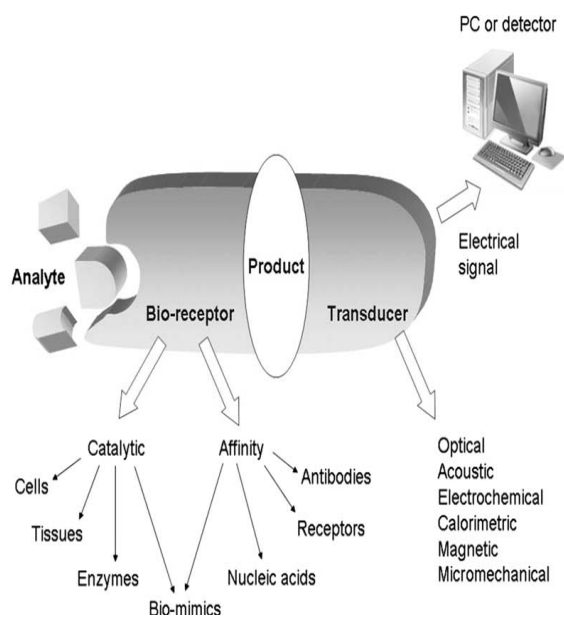

Figure [1]. Schematic representation of a biosensor. .

Receptor recognition elements

Cell surface receptors are targets for drug delivery and are useful for monitoring the effectiveness of cancer therapeutics. Activation or inactivation of receptor molecules triggers diverse signaling events within a cell. Altering the function of a receptor can result in opening or closing of ion channels and changes to membrane permeability, activation of adenyl cyclase and second messengers, and activation of small G proteins, kinases, phosphatases, and transcription factors.

Antigen/antibody recognition elements

Antigen- and antibody-based recognition elements are among the most rapid detection systems. A critical benefit of this type of element is the inherent specificity of antibody–antigen interactions and the fact that the target molecule does not need to be purified before

recognition. The recognition element for PSA biosensors, some of the most widely used biosensors in clinical use for the detection of prostate cancer, is an anti-PSA[4] antibody. Anti-PSA recognition elements have been linked to microcantilever-based transducers and to surface plasmon resonance-based sensors, in which changes in vibrational frequency upon antigen binding to antibody are used to detect PSA.

Enzymes

Allosteric enzymes show great potential as recognition elements. In most cases, the regulatory subunit takes on the role of the recognition element and the catalytic site becomes the transducer. One of the most advanced sensors of this class, and in general, is the glucose sensor, which uses glucose oxidase as the recognition element.

Nucleic acids

Aptamers are oligonucleotides that are selected from among a pool of thousands of different sequences for very high binding affinities for their targets. As a result, they are rapidly emerging as biosensor recognition elements. A combinatorial chemistry-based technology termed SELEX (systematic evolution of ligands by exponential enrichment)[2] has been developed to generate nucleic acid ligands from a library of DNA and RNA oligonucleotides. Biosensors built on this type of system have proven to be useful in the discovery of new biomarkers that are critical to early cancer diagnosis.

II Biosensor transducer

Electrochemical biosensors

Amperometric and potentiometric transducers are the most commonly used electrochemical transducers. In amperometric transducers, the potential between the two electrodes is set and the current produced by the oxidation or reduction of electroactive species is measured and correlated to the concentration of the analyte of interest. Most electrodes are made of metals like platinum, gold, silver, or carbon-based materials that are inert at the potentials at which the electrochemical reaction takes place.

Potentiometric transducers measure the potential of electrochemical cells with very low current. Field effect transistors (FET) are potentiometric devices based on the measurement of potential at an insulator electrolyte interface. The metal gate of a FET can be substituted by an ion selective membrane to make a pH transducer (pH ISFET). Enzymes have been immobilized on the surface of such pH ISFET to produce enzymesensitized field effect transistors (ENFET).

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Mass-based biosensors

Piezoelectric and acoustic wave biosensors make up the class of mass-based biosensors. In terms of cancer detection, piezoelectric biosensors are more commonly used. Piezoelectric sensors are based on changes in the mass of quartz crystals when potential energy is applied to them. This change in mass generates a frequency, which can be converted into a signal. Immunosensors and microcantilever sensors that use piezoelectric technology have proven useful in the identification of cancer biomarkers.

Calorimetric biosensors

Calorimetric biosensors are less common than other biosensors for cancer diagnostics, but the introduction of nanotechnology to the field of biosensors has increased the range of applications for these types of biosensors. Calorimetric biosensors measure exothermic reactions. Many enzymatic reactions generate heat, and changes in heat can be used to measure analyte concentration. The reaction is monitored by measuring enthalpy changes, which indirectly provide information about substrate concentration. Calorimetric biosensors are not capabilities have been demonstrated.

Carbon Nanotubes (CNTs)

CNTs, which were first discovered in 1991, are made up of graphene sheets rolled up into the shape of seamless tubular structure. CNTs can be structurally classified into two categories: single-wall CNTs[4], which consist of one layer of cylinder graphene and multi-wall CNTs, which contain multiple layers of concentric graphene cylinders. The detection of cancer biomarkers using CNT-based sensors shows high sensitivity and selectivity, as well as real-time response capabilities.
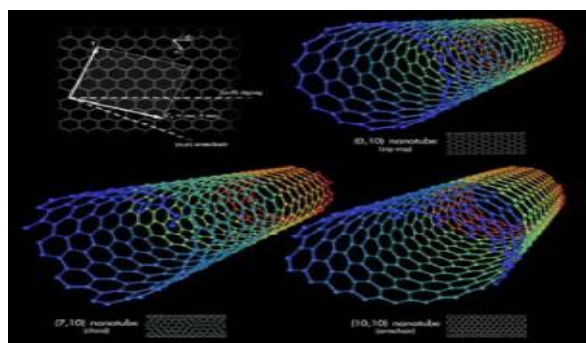
Figure[2]. Carbon nanotubes

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Back-gated chemical Field-Effect Transistor (FET)

CNTs configured with FETs are a three electrode system. The conductance between the source and drain electrodes is modulated by the gate electrode. Prostate-Specific Antigen (PSA), a 28-kDa glycoprotein produced by the prostate gland and also a serine protease enzyme, has been used as a biomarker for the diagnosis and prognosis of prostate cancer. In serum, PSA has been found either in a free form (fPSA) or as a complex with protease inhibitor alpha 1-antichymotrypsin (PSA-ACT complex). Total PSA (tPSA) refers to the sum of all detectable free and complexed PSA forms. CNT-FETs have been modified with linkers and spacers of different ratios.
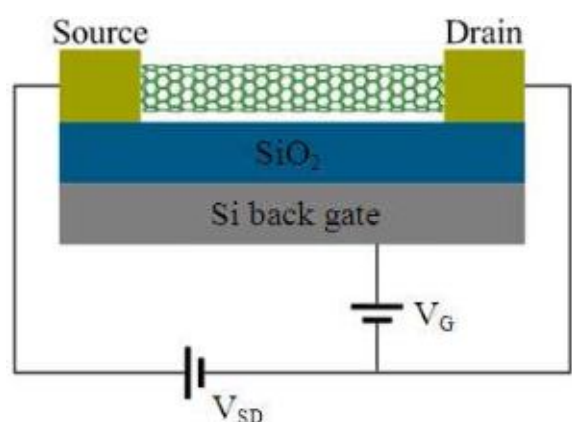
Figure[3]. Schematic diagrams of a CNT-FET

PSA-ACT complex antibodies were then immobilized on the CNT surface via the linkers. Results showed that CNT-FETs modified with only linkers could not detect. target proteins unless more than 500 ng mL⁻1 of PSAACT complex solution was injected, while those modified with linkers and spacers of a 1-to-3 ratio could detect 1.0 ng mL⁻1 of PSA-ACT complex without any pretreatment. This study implies that modifying the CNT surface with a spacer could offer a useful strategy of improving the sensitivity of the device.

IV. CONCLUSION

Cancer biomarkers are important indicators of tumor growth. They are used not only to diagnose and monitor disease, but also to provide a prognostic approach to treatment. One of the ultimate goals of biosensor technology is POC cancer diagnosis. Point-of-care-testing (POCT), or diagnostic testing that is done on site, is a field in which biosensors could have a major impact, allowing the patient and medical staff to get results rapidly and easily. Although the complexity and diversity of cancer has posed many challenges in the medical field,

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biosensor technology has the potential to provide fast, accurate results, while maintaining cost effectiveness.

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