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Application of Different Biosensors for Cancer Detection

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Abstract. Cancer is one of the main causes of death for humans while early detection can greatly lower cancer mortality and save lives. Therefore, reliable, cost-effective, and powerful technologies to detect the disease are needed. Cancer biomarkers are substances such as nucleic acids, enzymes, and metabolites, present in cancer clusters, tumours, or serum. While biosensors provide a quick, accurate, sensitive, uncomplicated, and economical method of diagnosing a particular cancer biomarker and is important to cancer detection and treatment, especially early diagnosis. Biosensors could be classified into three types: mass-based, electrochemical, or optical biosensors. With the development of science and technology and continuous research, more biosensors are designed for advanced technology, such as nanotechnology. The new and novel biosensors provide a powerful way for cancer detection. The objective of this research is to discuss the novel biosensors designed in recent years. In the future, more powerful biosensors will be designed and applied to cancer diagnosis and treatment.

Keywords: Cancer; Biomarkers; Biosensors; Detection.

1. Introduction

Cancer is a type of genetic-related disease that some cells become unnormal and form cancer clusters or tumours and it is one of the main causes of death for humans. While qualified treatment and adequate survivorship care in the early stages of cancer can improve survival rates and reduce side effects, most of the early cancer symptoms or signs are not obvious and specific enough to be observed and recognize [1]. Cancer imposes a huge financial burden on patients and their families. Especially for those diagnosed at a late stage, they often spend large amounts of money on treatment and health care, but the results are undesirable. Therefore, a reliable, cost-effective, powerful cancer detection method is in significant demand for diagnosis and treatment.

A biomarker is a medical sign that indicates a reaction between possible hazards and an organism, and it involves chemical, biological, or biological substances, structures, and processes [2]. For cancer biomarkers, it is the substances like DNA, mRNA, enzymes, metabolites, transcription factors, and cell surface receptors that present in cancer clusters, tumours, or serum. Specific types of cancer biomarkers allow for the early identification of cancers such as oral regions, pancreatic and pancreatic. For example, Alpha-fetoprotein (AFP) is a biomarker of hepatocellular carcinoma, and breast cancer cells can be used as biomarkers for the identification of breast cancer directly.

Detection of these cancer biomarkers provides a solution for the requirement to prognosis and diagnose a specific cancer and monitor the recurrence. In the field of biomarker detection, technology has advanced greatly, and various biomarker detection techniques utilizing highly specific biomarkers for recognition have been developed. Biosensor provides a quick, accurate, sensitive, uncomplicated, and economical method of diagnosing a particular cancer biomarker. A biosensor is an analytical device with a transducer that reads out the data, and a biomarker identification component that uses certain biomolecules as biorecognition components, and a converter. Biosensors can be classified by the biorecognition elements or the transducers. Based on the types of biocomponents used, biosensors can be sorted into DNA and enzyme antibodies. According to the types of transducers, there are three types of biosensors: mass-based, electrochemical, and optical biosensors. The types are shown in Fig. 1.

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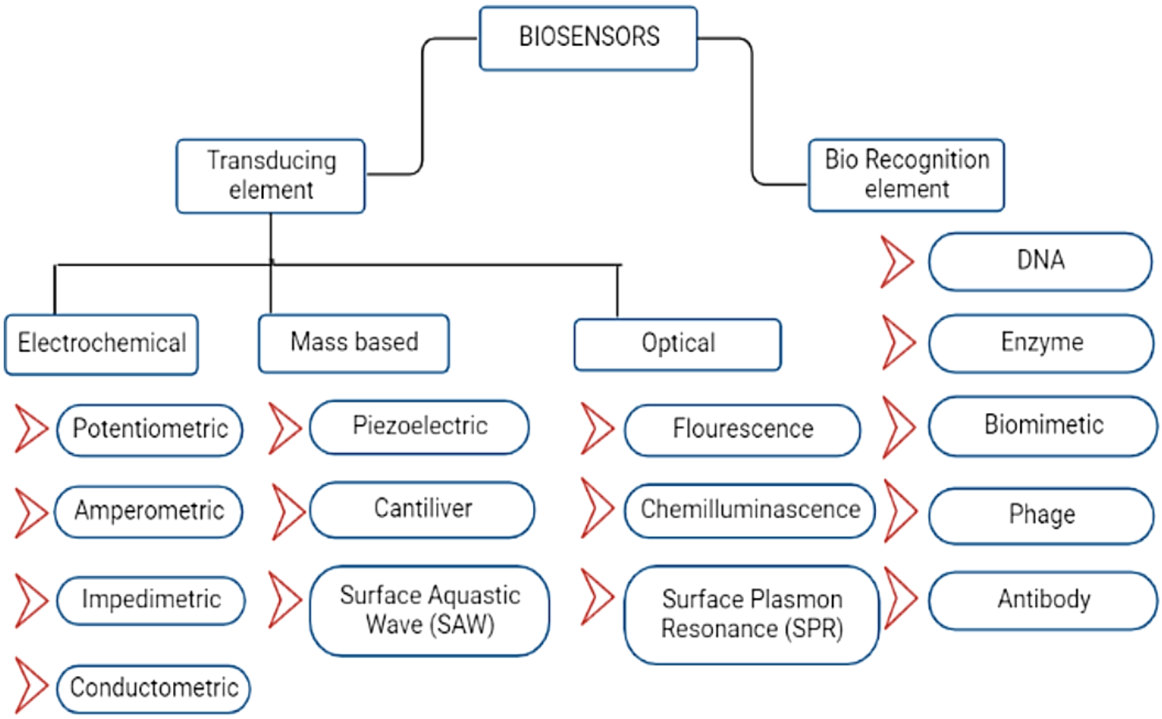

Fig. 1 Types of biosensors [3].

Different biosensors are used to detect various biomarkers. For example, an AFP tumor marker could be detected by an electrochemical biosensor, a protein biomarker carcinoembryonic antigen could be detected by an electrochemical biosensor or an optical biosensor, and ferritin biomarker can be detected by a mass-based biosensor or an optical biosensor. Numerous kinds of biosensors have been reported in the past ten years due to their exceptional qualities, which include ease of installation, increased sensitivity and specificity, a low detection limit, and the potential to multiplex in conjunction with the advancement of biomarker detection technologies. In this research, the applications of some biological detectors in recent years are introduced. The detection principles and application performance of these sensors will be discussed.

2. Detection of cancer by using different types of biosensors

2.1. Enzyme-linked Immunosorbent assay (ELISA)

The ELISA is an analysis method that quantifies the target proteins in biological samples, such as antibodies, antigens, or glycoproteins. The technique provides a rapid, easy-preformed, and cost-efficient method to detect a specific cancer biomarker.

2.1.1. Oral squamous cell carcinoma (OSCC)

OSCC accounts for about 90% of all mouth malignancies. OSCC has a nearly 50% 5-year mortality rate as around 70% of oral cancers are discovered at an advanced stage due to the ineffectiveness of traditional screening methods. However, early diagnosis can result in survival rates of more than 80% [4]. It is more desirable to detect oral cancer as soon as possible to maximize treatment efficacy and lower death and morbidity rates. EGFR, p53, and Ki67 are currently accessible and integrated in their ability to diagnose OSCC. The targets of immune checkpoint blockade therapy are PD-L1, B7-H6, and HLA-E. These six substances could be used as the biomarkers of the OSCC in the early stage. An innovative ELISA is applied to detect the six biomarkers in the cytobrush biopsies samples of patients. The Femtohunter® which is an automated ELISA developer equipment, and the Stark Oral Screening® IVD test are used to collect and analyze samples. It produces a patient report and provides the biomarkers' analytical information in less than 60 minutes. The result shows that the values of biomarkers in the tumor center are significantly higher than those in the healthy tissue [5].

2.1.2. Cervical cancer

Cervical cancer ranks fourth as common cancer among women. In 2022, there will be roughly 660,000 new cases and 350,000 fatal cases [6]. The majority of nations with lower human development indexes have been associated with higher incidence and mortality rates of cervical cancer. Especially in many underdeveloped countries, 88% of cases take place [7]. Traditional cervical cancer-detected techniques, for example, pelvic examination, have lower sensitivity. A sandwich ELISA is designed to screen cervical dysplasia and cancer in an affordable way with higher sensitivity. P16 could be a biomarker for HPV in cervical cancer detection because one downstream effect of high-risk HPV infection is p16 overexpression [8]. The sandwich ELISA is designed that 133A6G5 and 151A7B9 are capture antibodies, and biotinylated 155E11G3 and 155D11G10 are detect antibodies. ELISA plate reader records the absorbance at 492 nm. The results show this ELISA has higher detection limits and can detect p16 mouse monoclonal antibodies with a sensitivity of up to 2 pg [7].

2.2. Surface plasmon resonance (SPR) biosensors

SPR is an optical sensor technology that evaluates molecules, for example, antibodies, viruses, and nucleic acids, which bind to a metal surface by detecting changes in the localized refractive index. Compared to traditional cancer detection techniques, SPR biosensors have a number of benefits, like the capacity to immediately identify cancer in situ, with greater sensitivity, and without the need for labels. The used specimens could be clear or colorful like blood, urine, saliva, or plasma since the turbidity of the material does not affect its sensing potential.

2.2.1. Breast cancer cell

Optical biosensors have the capacity to detect cancer quickly and accurately, monitor the ontogenesis of cancer cells, image cancer cells with high accuracy, and assess the efficacy of anti-cancer chemotherapy drugs. Conventional prism-based SPR sensing has constraints including huge design and limited analysis throughput for detecting the cancerous cells. However, the Photonic Crystal Fiber (PCF)-based SPR biosensors could overcome the limits. A PCF-based SPR biosensor is designed based on a PCF structured as a spiral with a hexagonal lattice and specific dimensions. The refractive index is determined using the Sellmeier Equation, and the dielectric constant of gold is calculated using the Drude Lorentz Model. The effective range of the sensor is 1.36 to 1.401 for refractive index. With a resolution of 2.33×10^{-4}, for breast cancer cell diagnostic, the PCF-based biosensor demonstrated a high sensitivity for the refractive index [9].

2.2.2. Cancerous cells

SPR can evaluate refractive index differences of cancerous cells. Thus, for the goal of early cancer diagnosis, SPR biosensors are able to distinguish malignant cells from healthy cells. The 2D graphene layer broadens the range of biosensing uses and enhances the biosensor's capacity for biological detection by absorbing a biomolecule and interacting with the carbon-based rings. A highly sensitive SPR biosensor was designed by incorporating a graphene-layered structure using FEM-based numerical analysis and the attenuated total reflection (ATR) method, and it demonstrated improved sensitivity for detecting various types of cancer cells. The sensor exhibited high sensitivity in detecting skin (basal) cancer cells (210 deg/RIU), cervical (HeLa) cancer cells (245.83 deg/RIU), adrenal gland (PC12) cancer cells (264.285 deg/RIU), blood (Jurkat) cancer cells (285.71 deg/RIU), and breast (MCF-7) cancer cells (292.86 deg/RIU) and breast (MDA-MB-231) cancer cells (278.57 deg/RIU). Moreover, the measured signal-to-noise ratio is 3.84, the figure of merits is 48.02 RIU^{-1}, and detection accuracy is 0.263 deg^{-1} [10].

2.3. Surface-enhanced Raman spectroscopy (SERS)

SERS is a surface-sensitive method that increases molecular Raman scattering by specific nanostructured materials. Sensitive and multimodal SERS-based sensors are very helpful in analyzing biomolecular targets with minimal chemical complexity and abundance. The targets include exosomes, circulating tumor cells (CTCs), tumor-derived materials, circulating nucleic acids, and proteins.

2.3.1. Breast cancer

Breast cancer is a mean cause of mortality, and diagnostic instruments that are more affordable, precise, and practical are required in place of mammograms. Mammography, the current standard for breast cancer screening, is unpleasant for patients and its accuracy is affected by the high density of breast tissue. To address the limitations of mammography, SERS is investigated as a screening strategy for breast cancer, using urine samples for analysis 53 female patients with breast cancer and 22 healthy controls were involved in the study and the urine samples were collected without any processing to eliminate any potential pollutants or protein traces. The SERS spectra were acquired by adding urine to the silver nanoparticles and activating the colloid with $Ca(NO_3)_2$. With PCA-LDA, discrimination of the breast cancer patients from the control group using 81% sensitivity, 95% specificity, and 88% accuracy [11].

2.3.2. Cancer-related biomarkers in blood

Blood serves as an essential reservoir for a variety of metabolites and cellular components related to disease and cancer. SERS is a powerful molecular detection method that has been effectively utilized to distinguish blood samples of cancer patients from those from healthy persons because of its exceptional sensitivity and multiplexing abilities. A label-free SERS biosensor using silver nanoparticles (AgNPs) as substrates is designed for cancer detection. Tests were performed on blood samples obtained from 30 healthy people, 30 patients with various cancers, and 15 patients with various chronic illnesses. The serum samples from the cancer patients had a larger standard deviation. Two methods were applied to analyze the data. The 95% accuracy rate, 90% sensitivity, and 93% specificity were obtained in the PCA-DA-assisted separation of the cancer group from the healthy group. PLS-DA showed a 95% accuracy rate, 90% sensitivity, and 100% specificity [12].

2.4. Colorimetric biosensors

Colorimetric assay is a method of detecting the spectral absorbance of a chemical substance at a certain wavelength using a colorimeter (spectrophotometer) to quantify the quantity of the compound in a solution. Selectivity and sensitivity in colorimetric cancer biomarker detection have been increased through the introduction of nanomaterials with unique physical and chemical characteristics. The affordability, ease of use, and practicality of colorimetric techniques for real-time detection of the naked eye have sparked an increasing interest.

2.4.1. Ovarian cancer

Ovarian cancer is the seventh most common prevalent in the world to be diagnosed in females and is one of the more dangerous forms of cancer that affect women. The majority of affected women are in the 55 to 64 age range; of these, 45% of females may survive for five years or longer following diagnosis [13]. Early detection and efficient treatment are the only ways to manage this illness. A colorimetric biosensor using citrate-modified gold nanoparticles was developed for the naked eye detection of the ovarian cancer biomarker PDGF. PDGF, representing platelet-derived growth factor, could be generated and kept in platelet granules throughout the clotting process. To identify PDGF, gold nanoparticles were combined with a PDGF-specific aptamer, and alterations in color and absorbance resulting from aggregation were observed. The PDGF detection signal ranged linear from 0.01 to 10 μg/ml with a detection limit of 0.01 μg/ml under optimal conditions [14].

2.4.2. Malignant tumors

Cancer biomarkers are crucial to early cancer detection, with pH-based colorimetric strategies offering a convenient detection method. However, limitations such as poor target abundance and interference with complex compositions have hindered practical applications. To address these issues, a colorimetric method for identifying cancer biomarkers that combines pH sensing with enzyme enrichment has been developed. Tests are conducted on human PDGF-BB, a protein that is frequently overexpressed in malignant tumors. The target was captured by immunomagnetic beads, and signal amplification through multi-branched rolling circle amplification, and signal conversion using glucose oxidase. The change in pH caused by the oxidation of glucose is detected using the pH indicator bromocresol purple. The concentration of human PDGF-BB and pH variations had a positive log-linear relationship, according to the pH-based colorimetric approach. With a 0.94 pM detection limit, the detection range was linear and ranged from 1 pM to 25 pM [15].

2.5. Electrochemical biosensors

The electrochemical biosensor is a diagnostic instrument that works by converting biological processes such as the interaction between an enzyme and a substrate or an antigen and an antibody to electrical signals like the voltage, current, and impedance. For cancer diagnosis, the advantages of the electrochemical biosensor include low cost, simple instrumentation, easy miniaturization, multiplexing, automation, high sensitivity, quick reaction times, and small reaction volumes.

2.5.1. Trypsin for pancreatic cancer

Proteases, particularly trypsin, are implicated in cancer progression and are considered specific cancer biomarkers. The quantification of trypsin levels is crucial for the detection and tracking of pathological conditions, including pancreatic cancer. As existing methods for trypsin determination have limitations, a sensitive, selective, and noninvasive approach for economical trypsin detection methods is needed. An electrochemical peptide sensor was proposed with an original electroanalytical technique for the assessment of trypsin. A labeled short synthetic peptide sequence was immobilized onto magnetic beads and then digested with trypsin. The modified magnetic beads are incubated with a labeled fluorescein Fab fragment antibody. The MBs are magnetically trapped on the surface of a screen-printed carbon electrode. Amperometric detection is then carried out utilizing the hydroquinone (HQ)/HRP/H_2O_2 combination. The results showed the limit of quantification is 23 nM and the limit of detection is 7 nM [16].

2.5.2. Carcinoembryonic antigen (CEA)

Cervical, gastric, pancreatic, and colorectal carcinomas can all be clinically identified and treated with the tumor marker CEA. Electrochemical immunosensors could detect a single protein. However, the primary challenge in the design of electrochemical immunosensors is creating a sensing platform with outstanding conductivity, high operational stability, exceptional biocompatibility, and a large active surface area. Currently, the nanocomposites' great conductivity, substantial surface area, and low toxicity make them suitable materials for the development of electrochemical immunosensors. A new electrochemical immunosensor was developed using CNTs-COOH/rGO/Ag@BSA nanocomposites to detect CEA. The results show a linear relationship between biomarker concentrations and electrochemical responses with a low detection limit. The detection limit of CEA is 1×10^{-4} ng·mL^{-1} and it has been assessed with concentrations ranging from 0.0001 to 50 ng·mL^{-1} [17].

2.6. Fluorescence biosensors

Fluorescent biosensors are optical devices based on the fluorescence phenomenon to detect noninvasively the biomolecules present in biological samples, for example, proteins, glucose, or nucleic acids. The fluorescence phenomenon is triggered by the absorption of electromagnetic radiation by fluorophores or fluorescently labeled molecules. There are numerous benefits to using fluorescence biosensors to detect cancer biomarkers, including quick reaction times and visual identification.

2.6.1. Hepatocellular carcinoma (HCC)

HCC is a highly fatal and morbid disease that is prevalent worldwide, and early detection is crucial for patient diagnosis and outcome improvement. Nevertheless, current methods, such as histology and imaging, can only be helpful when HCC is advanced [18]. Finding serological tumor biomarkers was an efficient therapeutic strategy that made it possible to accurately diagnose malignancies and provide post-operative care. Serological protein alpha-fetoprotein (AFP) is the tumor biomarker of HCC while current techniques for AFP analysis have limitations like low sensitivity. A fluorescent aptasensor is designed for sensitive detection of the AFP using sandwich-structured QDs-AFP-AuNPs and the Förster resonance energy transfer (FRET) method. With a detection limit of 0.4 $ng \cdot mL^{-1}$, the FRET-based biosensor designed for AFP detection demonstrated a linear detection range of 0.5 to 45 $ng \cdot mL^{-1}$ [19].

2.6.2. CEA for cancer recurrence

A notable cancer biomarker, CEA has been linked to numerous cancers of humans, such as colorectal, pancreatic, and stomach carcinomas. Moreover, CEA has been applied to assess the effectiveness of cancer treatments, track the progress and outlook of medical conditions, and so on since it is sensitive to cancer recurrence. Existing methods for biomarker analysis often require expensive equipment and trained personnel, highlighting the need for novel, cost-effective detection technologies. The paper-based analytical device (PAD) provides a low-cost and ease-of-use tool to detect various substances, including cancer biomarkers. Fluorescent detection, particularly using lanthanide-doped upconversion nanoparticles, offers improved sensitivity and reduced background interference compared to conventional fluorescent materials. The use of FRET in conjunction with upconversion nanoparticles presents a powerful approach for detecting cancer biomarkers with enhanced accuracy and efficiency. Therefore, a paper-based FRET biosensor is fabricated for the detection of multiple cancer biomarkers with high sensitivity. The paper-based biosensor demonstrated good stability, repeatability, and anti-interference properties. With a low detection limit of 0.89 ng/mL for CEA, the device demonstrated a linear connection between the FITC520/Tm480 signal and the concentration of the CEA in the range of 0-100 ng/mL [20].

3. Conclusion

Biosensors have developed significantly in recent years. Various technology developments, like nanotechnology, enhance the advance of biosensors. The nanotechnology has been used to design biosensors with higher selectivity and sensitivity. For example, a surface-enhanced Raman spectroscopy biosensor using silver nanoparticles and a colorimetric biosensor using gold nanoparticles. Varieties of novel and advanced biosensors have been designed to detect specific cancer biomarkers. Various biosensors are able to identify the same cancer. For breast cancer, the crystal fiber-based SPR biosensors could detect breast cancer cells with a high sensitivity of -289 RIU^{-1} for the refractive index, and the SERS biosensors could also diagnose breast cancer with 81% sensitivity. Moreover, a biosensor can also detect multiple cancers at the same time. A FEM-based surface plasmon resonance can detect various cancers using blood with a high accuracy rate, sensitivity, and specificity. A paper-based FRET biosensor can detect multiple cancer biomarkers with good sensitivity and high anti-interference, stability, and reproducibility. In the future, as science and technology continue to advance, an increasing number of easy-to-operate, highly sensitive, highly selective, miniaturized, multi-purpose, high-throughput, and efficient biosensors will be studied to diagnose cancer biomarkers and applied to cancer diagnosis and treatment, especially early diagnosis.

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