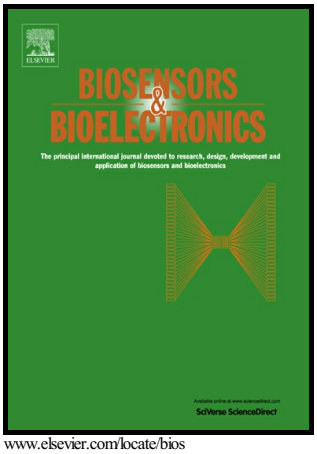

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Recent Advances in Biosensor Development for the Detection of Cancer Biomarkers

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Abstract

Cancer is the second largest disease throughout the world with an increasing mortality rate over the past few years. The patient's survival rate is uncertain due to the limitations of cancer diagnosis and therapy. Early diagnosis of cancer is decisive for its successful treatment. A biomarker-based cancer diagnosis may significantly improve the early diagnosis and subsequent treatment. Biosensors play a crucial role in the detection of biomarkers as they are easy to use, portable, and can do analysis in real time. This review describes various biosensors designed for detecting nucleic acid and protein-based cancer biomarkers for cancer diagnosis. It mainly lays emphasis on different approaches to use electrochemical, optical, and mass-based transduction systems in cancer biomarker detection. It also highlights the analytical performances of various biosensor designs concerning cancer biomarkers in detail.

Keywords: cancer, biosensor, biomarker, nanotechnology, diagnosis

1. Introduction

Cancer is a leading life-threatening disease all over the world with over 200 types of cancers identified and more than 1500 deaths occurring each day. In spite of recent technological advancement, the survival rate of cancer patients is still poor because of diagnosis at the late stage and poor prognosis of cancer. The conventional methods, including ultrasound, magnetic resonance imaging, and biopsy are inefficient for early stage cancer detection as these methods depend on the phenotypic properties of the tumor (Altintas et al., 2011). Cancer is a multistage disease, and its onset and progression are associated with a complex array of genetic or epigenetic alterations (Fig. 1) which disturb the cellular signaling and result in tumorigenic transformation and malignancy (del Sol et al., 2010). The molecules

which undergo prominent alterations during cancer are recognized as biomarkers and have high clinical significance. Biomarkers may be nucleic acids, proteins, metabolites, isoenzymes or hormones and are classified as diagnostic, prognostic and predictive (Fig. 1). Diagnostic biomarkers are related to the detection of the disease, whereas prognostic biomarkers offer information about the course of recurrence of the disease. Predictive biomarkers, on the other hand, estimate the response to treatment (Fong and Winter, 2012; Hayes et al., 1996). The presence or absence or change in the level of the specific biomarkers in a cell often indicate cancer development (Chatterjee and Zetter, 2005). Cancer-specific identification and detection of these biomarkers could help in early diagnosis and monitoring disease progression (Kumar et al., 2006; Srinivas et al., 2001; Verma and Srivastava, 2003). The traditional enzyme-linked immunosorbent assay (ELISA) or polymerase chain reaction (PCR) based methods for biomarkers detection, suffer technological limitations like slow detection and consumption of expensive reagents in every assay (Rusling et al., 2010). Also being manual, these methods are not proficient in the continuous monitoring of the patient during treatment. Besides, all cancers are multifactorial and associated with multiple events in the cell involving more than one molecule. Therefore, simultaneous detection of multiple biomarkers is essential for correct diagnosis and prognosis (Carpelan-Holmstrom et al., 2002; Hayakawa et al., 1999). The focus of clinical cancer diagnosis is to develop analytical techniques, which are explicitly capable of sensitive and parallel detection of biomarkers rendering useful point-of-care testing. In recent times, there is a growing interest in developing cancer biosensors as they show superior analytical performance and real-time measurement. Because of their lower minimum detection limits, they can measure very low levels of biomarkers in physiological samples which can assist in the diagnosis of cancer at an early stage. Besides, they also facilitate the reuse of biorecognition molecules and avoid a time lapse between the sample preparation and analysis. Moreover, biosensors show high potential for simultaneous detection of multiple biomarkers. In this review, we have discussed the established molecular alterations and related biomarkers in cancer. Latest design and fabrication approaches of biosensors to detect these cancer biomarkers are addressed. In comparison to the earlier articles, this review highlights the analytical performance of these biosensors in terms of sensitivity, stability, linear detection range and detection limit obtained with various fabrication strategies.

2. Fabrication strategies for cancer biosensors

Depending on the target, cancer biosensors utilize antibodies, complementary nucleic acid probes or other specific biorecognition molecules immobilized on a transducer surface (Fig. 2). The transducer converts the biological response generated by the interaction of biorecognition molecules with the biomarker (target) into a measurable signal (Thevenot et al., 2001). Cancer biosensors predominantly utilize electrochemical, optical, and mass-based transducers, the choice of which depends on the type of biological response. Electrochemical transducers convert the interaction of biorecognition molecules and the biomarker into a measurable electrochemical signal (current, potential, conductance, impedance) (Chikkaveeraiah et al., 2012) (Fig. 3A). Sometimes, an electrochemical probe is used to enhance the signal. Optical transducers utilize light absorption, fluorescence, luminescence, total internal reflection, surface plasmon resonance (SPR) and other optical phenomena to detect the target (Fig. 3B) (Jeronimo et al., 2007). Optical biosensors are particularly attractive as they are capable of multiplexed detection (Fan et al., 2008). In these optical biosensors, optical fibers and waveguide devices are used to improve detection sensitivity by increasing the interaction between the guided light and the sensor surface. Mass-based transducers, on the other hand, detect the mass change to identify the biomarker. They consist of a piezoelectric crystal which oscillates at a particular frequency on the application of an electric field. The mass of the crystal and the electrical frequency applied, influence the frequency of oscillation of the crystal. When the biorecognition molecule, immobilized on piezoelectric crystal binds the target, due to the change in mass, the oscillation frequency of the crystal changes which is detected to measure the concentration of the biomarker (Fig. 3C) (Ngeh-Ngwainbi et al., 1990; Suleiman and Guilbault, 1994; Zhang and Fu, 2004). Commonly used piezoelectric crystals are quartz crystals known for their high sensitivity (Bunde et al., 1998).

Even though cancer biosensors have numerous advantages, there are a few challenges linked to them. Most of the cancer biosensors show reduced stability due to the lack of biocompatibility of the immobilization matrices used to fabricate them. Also, often weak biological signals generated by the biorecognition molecules-biomarker interaction may lead to reduced sensitivity of detection. In recent years, nanomaterials are widely applied in the development of cancer biosensors (Jianrong et al., 2004; Zhang et al., 2009) intended to improve their analytical performance. Nanomaterials play diverse roles in biosensors with their extraordinary optical (Csaki et al., 2011), thermal (Rieth et al., 2000), electronic

(Ebbesen et al., 1996; Schmid, 2011) and catalytic properties (Bell, 2003). Their excellent biocompatibility and ability to capture a high amount of biomolecules deliver high stability and sensitivity to the biosensors (Holzinger et al., 2014). They also have dimensional similarity with biomolecules and therefore can be readily conjugated to them to form functional hybrid systems. (Willner et al., 2007). Among different nanomaterials, nanoparticles are extensively used in cancer biosensors as they exhibit enhanced surface area, size and shape tunable optical and electronic properties (Ding et al., 2013). The use of semiconductor quantum dots (QDs) is also progressively increasing in cancer diagnosis (Cabral Filho et al., 2015; Carbary-Ganz et al., 2015). Their unusual optical properties like broad excitation spectra and narrow emission spectra allow their use in high throughput multiplexed detection (Li and Zhu, 2013; Tian et al., 2012). Carbon nanotubes (CNTs), which are of two types, namely single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) are also widely applied in cancer biosensors (Lin et al., 2013; Salimi et al., 2013). The unique structure of CNTs offers them exceptional properties. Their high surface area, excellent conductivity, and chemical stability make them suitable for biosensing applications (Balasubramanian and Burghard, 2006). Other nanomaterials like nanocantilevers, nanowires, and composite nanomaterials have also been used for the detection of cancer biomarkers (Gdowski et al., 2014). Different strategies have been reported to utilize nanomaterials in cancer biosensors. In electrochemical biosensors, nanomaterials can be used as an interfacial film between the biorecognition element and the transducer surface to facilitate the electron transfer process and amplify the biosensor signal (Fig. 4A). In another approach of multiplexed detection of biomarkers, different QDs can be used as labels in a sandwich assay, which can be further detected by stripping techniques (Fig. 4B). Most of the reported cancer biosensors are designed to detect nucleic acids and protein biomarkers. The following sections describe in detail different strategies to fabricate these biosensors.

3. Nucleic acid biomarkers based cancer biosensors

The transformation of a normal cell into a cancerous cell involves the accumulation of multiple anomalies in its genetic events transforming the molecular signature of the cell. These genetic changes include inactivation of tumor suppressor genes, activation of

oncogenes, chromosomal changes, gene hypermethylation, etc. The significant alterations at the genetic level can act as nucleic acid-based biomarkers in diagnosis. Hypermethylation of glutathione S-transferase p1(GSTP1) gene, p53 gene mutation, microRNAs (miRNAs) are some examples of nucleic acid-based biomarkers used in cancer diagnosis and prevention (Vogelstein and Kinzler, 1992). Nucleic acid-based biomarkers are of high importance as they assist in early detection of cancer, even when no physical signs of cancer are present. Nucleic acid-based biomarkers can be monitored using fluorescent in situ hybridization, single nucleotide polymorphisms, DNA fingerprinting, microarrays, reverse transcriptase PCR or sequencing-based diagnostic techniques (Fu et al., 2015; Kao et al., 2015; Pollack et al., 2002). However, most of these techniques require careful pre-processing of samples and thus not often suitable for real-time analysis. From the past few decades, there is a tremendous growth in the development of nucleic acid-based biosensors. Nucleic acid-based biosensors make use of highly selective sequence complementarity exploiting single stranded DNA, RNA, aptamers, etc. as biorecognition elements (Fig. 2). The reported cancer biosensors for detecting nucleic acid-based biomarkers mostly exploited electrochemical and optical transduction techniques.

3.1. Electrochemical detection techniques

Various electrochemical biosensors have been reported to detect nucleic acid-based cancer biomarkers. Topkaya et al. (2012) have reported an electrochemical biosensor for detecting hypermethylation of GSTP1 gene, which is a marker for prostate cancer. Here methylation was detected by guanine oxidation and resistance changes using differential pulse voltammetry (DPV) and electrochemical impedance spectroscopy (EIS) respectively. Another DPV based electrochemical sensor is developed for multidrug resistance 1 (MDR1) gene. This biosensor exploited the synergistic properties of gold nanoparticles (AuNPs), toluidine blue and graphene oxide in the form of immobilization matrix that provided high sensitivity and reproducibility to the fabricated biosensor. The linear detection range of the biosensor is 1.0×10^{-11}–1.0×10^{-9} M with a detection limit of 2.95×10^{-12} M (Peng et al., 2015). Fayazfar et al. (2014) developed an impedance based DNA sensor for detecting p53 gene mutation. For this, they employed the electrochemical growth of AuNPs on MWCNTs and EIS for target DNA hybridization measurements. With the aid of AuNPs for signal enhancement, an extended linear range of 1.0×10^{-15}–1.0×10^{-7} M and detection limit of 1.0×10^{-17} M is obtained. Mohd Azmi et al. (2014) developed a silicon nanowire (SiNW) based sensor for 8-hydroxy deoxyguanosine (8-OHdG). 8-OHdG is an oxidative DNA lesion and a

potent marker for oxidative DNA damage linked to prostate cancer. In this biosensor, anti-8-OHdG antibodies are immobilized onto SiNW surfaces and the interaction between 8-OHdG and anti-8-OHdG antibodies is observed by monitoring conductance changes. The detection limit obtained is 1 ng mL^{-1}. Different electrochemical cancer biosensors have been developed for the detection of miRNAs (a small noncoding RNA molecule of around 19-24 nucleotides) as the latter play a fundamental role in controlling various cellular processes and also cancer progression (Hayes et al., 2014). Wang et al. (2013) reported a magnetic controllable electrochemical biosensor for detection of oral cancer-related miRNAs. The biosensor is shown to have very high sensitivity with a very low minimum detection limit of 0.22 aM and a recovery of 98–103%. Hong et al. (2013) also developed a highly sensitive biosensor for the detection of cancer-associated circulating miRNAs using DNA concatamers amplification. This biosensor was successfully exploited to analyse serum human samples for miRNA detection. Besides, other electrochemical cancer biosensors for miRNA detection are also reported (Gao et al., 2013; Ren et al., 2013; Zhang et al., 2015).

3.2. Optical detection techniques

3.2.1. SPR based detection techniques

Most of the optical biosensors for nucleic acid cancer biomarkers utilize the phenomena of SPR, a potent tool for examining real-time interactions of biomolecules (Zeng et al., 2014). In SPR based sensors, biorecognition molecules are immobilized on a metal surface (typically gold) where it interacts with the biomarker. This interaction causes a change in the mass and the refractive index of sensor surface layer and a shift in SPR signal (Fig. 5) (Guo, 2012). Sato et al. (2003) exploited SPR mechanism to develop a biosensor for detecting a specific point mutation in the K-ras gene which is useful for early detection of cancer. This biosensor has used surface immobilized peptide nucleic acid (PNA) probes as biorecognition molecules. An SPR based biosensor has also been reported to sense DNA methylation using a molecular inversion probe (with two inverted recognition ends), highly specific to methylated DNA (Carrascosa et al., 2014). A few nucleic acid-based cancer biosensors utilized the phenomenon of localized SPR (LSPR) for sensing. LSPR occurs due to the excitation of surface plasmons by light incident on the surface of metallic nanoparticles including AuNPs or metallic nanostructures because of which they create sharp spectral absorption and scattering peaks (Mayer and Hafner, 2011). This absorption and scattering spectra are significantly affected by composition, shape, and size of the nanoparticles (Haes et al., 2004;

Liu et al., 2007) and any change in the surrounding medium (Mock et al., 2003; Murray et al., 2009). This observable fact made the basis of LSPR based biosensors. Nguyen and Sim (2015) have reported an LSPR based biosensor for the parallel detection of tumor-specific mutations (E542K and E545K) and methylation of circulating tumor DNA (ctDNA) of PIK3CA (phosphotidylinositol-4,5 biophosphate 3-kinase catalytic subunit alpha) gene. They have utilized PNA probes conjugated AuNPs and immunogold colloids for detecting ctDNA mutations and methylation respectively. The use of immunogold colloids increased the sensitivity of the biosensor. An LSPR based nanoplasmonic biosensor is also developed for detecting two cancer markers, mutant DNA and telomerase and this biosensor is practically validated in HeLa cells (Ma et al., 2015).

3.2.2. Other optical detection techniques

Surface-enhanced Raman scattering (SERS) is gaining extensive interest for the development of cancer biosensors because of its comparable sensitivity to fluorescence based methods (Nolan et al. 2012). Ouyang et al. (2016) have used AuNPs modified with methylation-sensitive antibody in a SERS platform to detect methylated DNA and its oxidation derivatives in real cell samples. Use of SYBR Green I as Raman tag lend a high sensitivity and a reasonably good detection limit of 0.2 pg μL^{-1} to the biosensor. Another magnetic nanoparticles based SERS biosensor with a very low detection limit of 0.3 fM is reported for miRNA detection in total RNA extract from cancer cells (Pang et al. 2016). A paper based optical biosensor is developed for naked-eye detection of lung cancer-associated miRNA using a luminescent reporter poly(3-alkoxy-4-methylthiophene). This biosensor shows a high potential for point-of-care diagnostic applications (Yildiz et al. 2013).

4. Protein biomarkers based cancer biosensors

Functional alterations in proteins involved in cell cycle control can have deleterious effects on normal physiological processes and may lead to cancer. A gain of function of proto-oncogenes or loss of function of tumor suppressor genes guide deregulated cell growth during cancer (Bhatt et al., 2010). These functional deviations are the result of variation in the expression profile of these genes or variability in protein structure and function guided by genetic mutations, alternative splicing, gene duplications, as well as post-translational changes such as glycosylation, phosphorylation, and methylation. Proteins which show a

considerable change in their concentration or functional status during cancer can serve as potential biomarkers (Fig. 1). Hence, quantification of these protein biomarkers in physiological samples has the prognostic value to assess the cancer risk. Some of the protein biomarkers already targeted to design cancer biosensor are carcinoembryonic antigen (CEA), cancer antigens (CA125, CA15-3), alpha-fetoprotein (AFP), prostate specific antigen (PSA), human epidermal growth factor receptor (HER), and insulin-like growth factors (IGF1&2) (Polanski and Anderson, 2007). Antibody-based biosensors are most suitable for the detection of protein biomarkers (Fig. 2). Various electrochemical, optical and mass based cancer biosensors are reported for the identification of protein biomarkers.

4.1. Electrochemical detection techniques

HER, a member of the family of epidermal growth factor receptors (EGFRs), has been the target of various cancer diagnostic assays because its overexpression has a strong association with the development of breast cancer (Mitri et al., 2012; Sainsbury et al., 1987). Canbaz et al. (2014) fabricated an immuno-sensor for HER3 using the anti-HER3 antibody as biorecognition molecule covalently immobilized on AuNPs layered electrode surface. The biosensor has a linear detection range of 0.2–1.4 pg mL^{-1}. Sonuc and Sezginturk (2014) also reported an immuno-sensor for HER3 based on impedimetric technique with a linear detection range of 0.4–2.4 pg mL^{-1}. Elshafey et al. (2013) have developed an immuno-sensor for HER1 by immobilizing anti-EGFR antibodies on AuNPs modified electrode surface using a scaffold protein G. Here AuNPs are found to improve the electroactive surface of the electrode and therefore the biosensor showed a very wide linear range of 1 pg mL^{-1}–1 μg mL^{-1}. The biosensor showed a detection limit of 0.88 pg mL^{-1} in human plasma. An electrochemical immuno-sensor is developed for the detection of a lung cancer-associated biomarker namely alpha enolase (ENO1). In this biosensor, the anti-ENO1 monoclonal antibody has been immobilized on screen printed electrode modified with polyethylene glycol. The signal probes utilized are polyclonal secondary anti-ENO1 antibody tagged AuNPs congregates. The biosensor used square wave voltammetry (SWV) to detect electrochemical signals and exhibited a linear range of 10^{-8}–10^{-12} g mL^{-1} with a detection limit of 11.9 fg (equivalent to 5 μL of 2.38 pg mL^{-1} solution) (Ho et al., 2010). Vascular endothelial growth factor (VEGF) is another important cancer biomarker as it is a key mediator of angiogenesis during cancer progression (Carmeliet, 2005). Different approaches have been used for its detection. A DPV based biosensor reported by Lin et al. (2015) used Avastin as biorecognition molecule and exhibited a wide linear range of 31.25–2000 pg mL^{-1}.

This biosensor also showed a good performance in serum samples. Another electrochemical immuno-sensor for VEGF exploited disc-shaped carbon fiber microelectrodes as the sensing platform on which anti-VEGF antibodies are immobilized. The detection limit of this biosensor is found to be 38 pg mL^{-1} (Prabhulkar et al., 2009). Qureshi et al. (2015) have also developed a biosensor for VEGF using capacitive aptamer and antibody based sandwich assay. Wang et al. (2014a) fabricated a sandwich-type immuno-sensor for human tissue polypeptide antigen (hTPA) using Pd-Pt nanocrystals as labels for the secondary antibodies. The biosensor displayed a detection limit of 1.2 pg mL^{-1} and linear range of 0.005–15 ng mL^{-1} along with good selectivity and stability. Malhotra et al. (2010) reported an electrochemical immuno-sensor for interleukin-6 (IL-6) which is involved in head and neck squamous cell carcinoma (HNSCC). The biosensor is developed using anti-IL-6 antibody immobilized on SWCNTs. Here electrochemical sandwich assay using horseradish peroxidase (HRP) enzyme label is employed for detection. The detection limit obtained is 0.5 pg mL^{-1}, and this sensor is tested in HNSCC cells. Similar kind of electrochemical transduction using SWCNTs is also employed by Munge et al. (2010) for the detection of matrix metalloproteinase-3 (MMP-3). Lu et al. (2014) have used silver nanoparticles (AgNPs) decorated with thionine/infinite coordination polymers as sensing platforms for detection of CEA, a type of glycoprotein associated with the development of breast, ovary, pancreas, lung and colon cancer. The sensor showed a detection limit of 0.5 fg mL^{-1} and a wide linear range of 50 fg mL^{-1}–100 ng mL^{-1}. Yang et al. (2012) developed a biosensor based on QDs for simultaneous detection of CEA and also its therapeutic drug, C225. Electrochemical measurements are carried out by stripping voltammetry method. Moon et al. (2014) have reported an immuno-sensor for detection of PSA, in which polypyrrole aided the incorporation of anti-PSA antibody along with Au nanowire array. The biosensor showed a wide linear range of 10 fg mL^{-1}–10 ng mL^{-1} and an extraordinary low detection limit of 0.3 fg mL^{-1}, which is lowest among most of the reported cancer biosensors. Electrochemical PSA biosensors have also utilized MWCNTs as immobilization matrix (Salimi et al., 2013). Apart from PSA, another potential prostate cancer biomarker is alpha-methyl-acyl-CoA racemase (AMACR) for which a biosensor is developed and validated with human blood samples for its reproducibility (Lin et al., 2012).

Since no single biomarker is specific enough for the diagnosis of particular cancer, biosensors capable of simultaneous detection of multiple targets are more accurate, as well as cost and time effective. Several electrochemical biosensors aim simultaneous detection of multiple cancer protein biomarkers. Tang et al. (2007) developed a biosensor for detection of four lung

cancer-associated markers (AFP, CEA, CA125, and CA15-3) using microfluidic magnetic bead-based immunoassay. The biosensor demonstrated a detection limit of less than 0.5 μg mL^{-1} for most of the biomarkers. Wilson and Nie (2006) have developed a chip based immuno-sensor for detection of seven tumor markers namely, CEA, human chorionic gonadotropin (hCG), CA15-3, AFP, ferritin, CA19-9, and CA125, associated with lung, pancreatic, breast, colorectal, and many other types of cancers. They have used electrochemical enzyme-based competitive immunoassay for the detection. Atlintas et al. (2014) have used AuNPs to fabricate a capacitance-based biosensor which can detect CEA, EGFR in a wide linear range of 20–1000 pg mL^{-1} and CA15-3 in a range of 10–200 U mL^{-1}. Two different sandwich-type electrochemical immuno-sensors are developed for simultaneous detection of CEA and AFP using anti-CEA and anti-AFP as biorecognition molecules. One immuno-sensor used amino capped platinum porous nanoparticles whereas, the other exploited biofunctional carboxyl graphene nanosheets as signal probes for making a highly stable biosensor (Chen et al., 2013; Wang et al., 2014b). Apart from these, other electrochemical cancer biosensors for protein biomarkers detection are also reported (Liu et al., 2014; Rezaei et al., 2011; Viswanathan et al., 2012; Yang et al., 2014).

4.2. Optical detection techniques

4.2.1. Fluorescence based detection techniques

Mukundan et al. (2009) have developed a fluorescence-based sandwich detection method for the measurement of CEA, a molecule associated with multiple cancer types. The method used biotinylated anti-CEA antibodies adsorbed on waveguide surface as biorecognition molecules, and also applied to analyze patient's samples. Fluorescence resonance energy transfer (FRET) is also a useful phenomenon used in various kinds of optical assays. FRET involves a nonradiative resonance energy transfer from a photoexcited donor fluorophore to an unexcited acceptor molecule (Zadran et al., 2012). FRET-based biosensors often use nanoparticles such as QDs and upconverting nanoparticles (UCPs) because of their unique optical properties (Chen et al., 2012). Shi et al. (2016) reported a FRET-based biosensor for the detection of epithelial cell adhesion molecule (EpCAM), which shows a high expression in rapidly proliferating tumors of epithelial origin and is a potential prognostic cancer biomarker (Trzpis et al., 2007). This biosensor used EpCAM aptamers labeled with graphene quantum dots (GQDs) as biorecognition molecules. The labeled aptamers are immobilized on molybdenum disulphide (MoS_2) nanosheets which quench the fluorescence signal of GQDs.

The addition of EpCAM leads to fluorescence restoration. This biosensor showed a linear detection range of 3– 54 nM with a detection limit of 450 pM. Also, it has been demonstrated to detect EpCAM-expressed breast cancer MCF-7 cells. Li et al. (2016) also fabricated a similar FRET-based biosensor for CEA detection using CEA aptamers as biorecognition molecules. However, here they have used hexanedionic acid (HDA) modified UCPs and palladium nanoparticles (PdNPs) as donor fluorophores and quencher molecules respectively. The fabricated biosensor showed a linear detection range of 2–100 pg mL^{-1} in the aqueous buffer and 4–100 pg mL^{-1} in diluted human serum. Another highly sensitive FRET-based method is reported by Ding et al. (2016) for the detection of telomerase activity whose upregulation is linked with carcinogenesis. The sensor is successfully tested in crude cancer cell extracts.

4.2.2. SPR based detection techniques

An SPR biosensor is developed by Piliarik et al. (2010) for the detection of hCG and activated leukocyte cell adhesion molecule (ALCAM) in blood plasma. Here, antibodies against hCG and ALCAM are attached to the sensing surface through DNA-directed immobilization. The detection limits are found to be 100 ng mL^{-1} for hCG and 45 ng mL^{-1} for ALCAM. Jang et al. (2009) developed a few-mode fiber SPR based biosensor for the detection of PSA. The sandwich assay used in the detection improved the sensitivity of the sensor to 2.5×10^{-6} refractive index unit (RIU). Another SPR-based biosensor is reported that can detect VEGF in a nanomolar range. Here DNA aptamers are used as the biorecognition molecules (Cennamo et al., 2015). An LSPR based sensor is developed by Zhao et al. (2014) for the detection of a cervical cancer marker, squamous cell carcinoma antigen (SCCa) using an AgNPs array where monoclonal anti-SCCa antibodies are immobilized. This LSPR sensor is tested in human serum samples and showed an extended linear range of 0.1–1000 pM. Yuan et al. (2012) developed a similar type of LSPR sensor for detection of human epididymis secretory protein 4 (HE4), an ovarian cancer biomarker. The anti-HE4 antibody is used as a probe for HE4 detection and immobilized on the nanostructured surface. The shift in extinction maximum of LSPR spectrum is used to detect the interaction between HE4 and probe. This sensor has shown the linear range between 10–10,000 pM with a detection limit of 4 pM.

4.2.3. Chemiluminescence based detection techniques

Chemiluminescence is another optical technique used for sensor design. Here, a photochemical emission takes place during the binding of the biomarker to the recognition element. The advantages of chemiluminescence-based biosensors lie in the fact that they require very simple measurement equipment (Roda et al., 2015). Qu et al. (2013) reported an immuno-sensor for CEA using chemiluminescence immunoassay along with immunomagnetic separation. A portable home-made luminometer is used to detect the optical signals. The linear range of the sensor is found to be 0–50 ng mL^{-1} of CEA with a detection limit of 5.0 pg mL^{-1} and immunoassay time of <35 min. Another similar biosensor for CEA detection is developed by Hao and Ma (2012) using flow injection chemiluminescent immunoassay. This sandwich assay utilized anti-CEA and goat-anti-mouse IgG labeled with AuNPs for CEA detection. Additionally, seed-mediated gold enlargement step is carried out for improving the sensitivity of the analysis. This sensor showed a linear range of 100 pg mL^{-1}–1000 ng mL^{-1} with a detection limit of 20 pg mL^{-1} for CEA. An optical biosensor is reported by Al-Oqaidi et al. (2014) for the detection of CA125, ovarian cancer biomarker through chemiluminescence resonance energy transfer (CRET) using GQDs. In this sensor, GQDs linked with the antibody of CA125 acted as energy acceptors during the interaction of CEA and anti-CEA. With this technique, a wide linear range of 0.1–600 U mL^{-1} with a detection limit of 0.05 U mL^{-1} is obtained for CA125. A chip-based optical sensor is developed by Sun et al. (2004) for simultaneous detection of twelve tumor markers using chemiluminescence principle. This biosensor shows an excellent prospect for multiplex detection of biomarkers in cancer.

4.2.4. Other optical detection techniques

The optofluidic ring resonator (OFRR) is an emerging sensing platform that has been under intensive investigation in recent times. This technology integrates optical ring resonator with microfluidics. In an OFFR, light propagates as whispering gallery modes (WGMs) resulting from total internal reflection inside the ring resonator. Any binding event of molecules captured on OFRR results in the change in the effective refractive index ultimately causing the spectral shift of WGM used as the response signal (Fan et al., 2008). OFFR offers several advantages like label-free sensing, low detection time, portability and multiplex detection (Suter and Fan, 2009). Zhu et al. (2009) have developed a biosensor based on OFRR for detection of CA15-3, a breast cancer biomarker. This OFFR based biosensor has been demonstrated to detect CA15-3 in serum samples. OFFR based biosensor has also been reported for HER2 (Gohring et al., 2010). Lee et al. (2014) reported a SERS-based technique

for multiplex detection of three breast cancer phenotypic markers, i.e. EGFR, HER2, and IGF-1 receptor. They conjugated specific antibodies with SERS nanotags consisting of silica-encapsulated hollow gold nanospheres for enhancing SERS signal intensity. Similar SERS-based methods have also been reported for detection of other protein biomarkers linked to cervical cancer (Narayanan et al., 2015; Wen et al., 2016). Various other optical sensing techniques involving optical microfiber (Li et al., 2014), interferometer (Zhang et al., 2012), and single photon avalanche diode (SPAD) (Pasquardini et al., 2015) are also reported for the detection of cancer biomarkers.

4.3. Mass-based detection techniques

4.3.1. Piezoelectric biosensors

There are a few works reported on piezoelectric biosensors with regards to cancer biomarker detection. A piezoelectric immuno-sensor is reported by Ding et al. (2007) for the detection of AFP using AuNPs coated nano-sized hydroxyapatite. For the fabrication of the sensor, piezoelectric crystals are coated with this hybrid nanomaterial on which anti-AFP antibodies are immobilized. These piezoelectric crystals are immersed into a reaction well where sample solution containing AFP is introduced. The frequency changes observed during the immunoreactions between AFP and piezoelectric probes are calculated followed by electrochemical measurements. This immuno-sensor is able to detect AFP in the range of 15.3–600.0 ng mL^{-1}. It is found that the incorporation of AuNPs increased the reusability of the immuno-sensor. Chou et al. (2002) have developed an immuno-sensor based on quartz crystal microbalance (QCM) for a tumor marker, human ferritin. In this immuno-sensor, antibodies against human ferritin are immobilized on the gold disc of QCM by adsorption and chemical treatment methods. These antibodies interact with ferritin present in the samples. Ferritin is determined in buffer and mouse serum samples in the concentration range of 0.1–100 ng mL^{-1}. Another label-free piezoelectric biosensor is reported by Su et al. (2013) for the detection of PSA and AFP. Here, antibodies of AFP and PSA are immobilized on lead titanate zirconite (PZT) ceramic resonator transducers. Samples are added on the ceramic surface, and the sensor signal of antigen/antibody reactions of AFP and PSA are obtained from the frequency changes in the two ceramic resonator surfaces. This biosensor has shown the sensitivity of 0.25 ng mL^{-1} for both PSA and AFP.

4.3.2. Surface acoustic wave (SAW) biosensors

SAW biosensors are the type of mass sensors in which acoustic waves are generated by the transducer when an electric signal is applied. This wave is again converted back into an electrical signal. Any mass change on the device surface leads to a shift in frequency of the output electric signal. This mechanism can detect any binding event on the sensing surface (Lange et al., 2013). A SAW biosensor is reported by Gruhl and Lange (2012) for the detection of tissue inhibitor of metalloproteinase-1 (TIMP-1) and HER2. This biosensor has shown very low detection limits of 10 ng mL^{-1} for HER2 and 2 ng mL^{-1} for TIMP-1 compared to clinical cut-off values of respective biomarkers.

4.3.3. Microcantilever (MCL)-based biosensors

Apart from piezoelectric and SAW based biosensors, microcantilever (MCL) based biosensors are also gaining importance in the detection of biological and chemical agents. When biomolecules like antibody or antigen bind to the cantilever surface, there will be a change in resonance frequency and amplitude of the cantilever which can be taken as sensor signal (Buchapudi et al., 2011). A few MCL based biosensors are reported for detection of cancer biomarkers. For example, Capobianco et al. (2008) have developed a piezoelectric MCL sensor for the detection of HER2. Instead of using a full-length antibody, a single-chain variable fragment (scFv) specific to HER2 is used as sensing layer. Another MCL based sensor is reported for the detection of ALCAM using suspended microchannel resonators (SMRs). This SMR surface is used as sensing layer for ALCAM detection. This sensor has shown a detection limit of 10 ng mL^{-1} in undiluted serum (von Muhlen et al., 2010).

Different reported cancer biosensors and their characteristics are summarized in Table 1.

5. Conclusion and future outlook

In spite of the continuous discovery of new drugs for cancer treatment, progress in new technology for its diagnosis at an early stage is slow. There is a high demand of efficient biosensors for rapid analysis of cellular alterations to detect cancer at its onset which could ultimately improve the prognosis and treatment strategies, subsequently the patient's survival rate. This review discusses different types of biomarkers and biosensor designs to detect cancer. Some of these cancer biosensors can detect the biomarkers in a wide range from fg mL^{-1}–ng mL^{-1} which shows a good agreement with physiological changes in cancer. However, because of the hold-up in carrying the cutting edge biosensors models under research and development to the clinical rationale, commercial cancer biosensors are still in

their infancy. The major bottlenecks to the commercialization of cancer biosensors are better sensitivity, selectivity, real-time analysis and cost-effectiveness. For clinical use, research on the cancer biosensor development should also focus on their long-term stability. Another major challenge is the high degree of complexity of the cancer cell where a single biomarker may be involved in multiple cellular processes. Therefore, a better understanding of the molecular alterations underlying cancer progression is a pre-requisite. Genomic and proteomic profiling, as well as next-generation sequencing, can aid in the discovery of new cancer-specific biomarkers for biosensors use. Frequently, multiplex detection of several biomarkers is required for the proper diagnosis of particular cancer. Although some efforts have been made to design biosensors for detecting multiple biomarkers simultaneously, the functional validation is still limited. Miniaturization and integration of microfluidics technologies are other challenges to overcome for better multiplex detection and lab-on-a-chip devices.

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Fig. 1. Molecular alterations in cancer: During the onset of cancer, cells undergo tumorigenic transformation due to mutations in various protooncogenes and tumor suppressor genes as well as altered expression of cell surface receptors and secreted proteins. Nucleic acids or proteins undergoing significant alterations during cancer can be used as biomarkers for cancer detection. These biomarkers are classified as diagnostic, prognostic and predictive.

Fig. 2. Biosensor designs for different types of cancer biomarkers: For detecting nucleic acid, receptors, and secretary protein biomarkers, biorecognition molecules such as complementary nucleic acid probes, specific ligands, and specific antibodies are used respectively.

Fig. 3. Transduction systems in biosensors: (A) electrochemical, (B) optical, and (C) mass-based transducers (a detailed description of the figure is given in section 2).

Fig. 4. Schematic representation of an electrochemical sandwich immuno-sensor: (A) nanomaterials used as a biomolecule immobilization matrix, (B) quantum dots of different

sizes used as labels in stripping assay for simultaneous detection of multiple biomarkers. Here, Ab1–Ab5 and Ab'1–Ab'5 represent antibodies with different antigen specificities.

Fig. 5. Schematic diagram of an SPR based biosensor: Biorecognition molecules (such as antibodies) are coated on the gold surface. When an electromagnetic field excites the collective oscillations of free electrons at the metal-dielectric interface, surface plasmon polaritons (SPPs) are created along the metal surface which penetrates into surrounding medium in the form of the evanescent field. Any interaction of biorecognition molecule with the biomarker in the surrounding medium may change its refractive index which further alters the characteristics of the incident and reflected light that acts as a sensing signal.

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Table 1. Characteristics of reported cancer biosensors

Biomarker	Sensing platform	Transduction type	Sensor characteristics	Reference
GSTP1	Carbon graphite	Electrochemical (EIS)	DL: 2.92 pmol	Topkaya et al. (2012)
MDR1	AuNPs-toluidine blue–graphene oxide nanocomposites	Electrochemical (EIS)	LR: 1.0×10^{-11}–1.0×10^{-9} M DL: 2.95×10^{-12} M	Peng et al. (2015)
p53	AuNPs/MWCNTs	Electrochemical (EIS)	LR: 1.0×10^{-15}–1.0×10^{-7} M DL:1.0×10^{-17} M RSD: 2.1%	Fayazfar et al. (2014)
8-OHdG	SiNW	Electrochemical (Resistance changes)	DL:1 ng mL^{-1}	Mohd Azmi et al. (2014)
HER3	AuNPs	Electrochemical (EIS)	LR: 0.2 ng mL^{-1}–1.4 pg mL^{-1}	Canbaz et al. (2014)
HER3	4-ATP SAM	Electrochemical (EIS)	LR: 0.4 ng mL^{-1}–2.4 pg mL^{-1}	Sonuc and Sezginturk (2014)
EGFR	AuNPs	Electrochemical (EIS)	LR: 1 pg mL^{-1}–1 μg mL^{-1} DL: 0.34 pg mL^{-1} (in buffer) & 0.88 pg mL^{-1} (in human plasma)	Elshafey et al. (2013)
ENO1	AuNPs	Electrochemical (SWV)	LR: 10^{-8}–10^{-12} pg mL^{-1} DL:11.9 fg	Ho et al. (2010)
VEGF	MGO composites	Electrochemical (DPV)	LR: 31.25–200 pg mL^{-1} RSD: 2.36%	Lin et al. (2015)
VEGF	Ferrocene monocarboxylic acid	Electrochemical (LSV)	DL: 38 pg mL^{-1}	Prabhulkar et al. (2009)
hTPA	Pd-Pt nanocrystals	Electrochemical (EIS)	LR: 0.0050–15 ng mL^{-1} DL: 1.2 pg mL^{-1}	Wang et al. (2014a)
IL-6	SWCNTs	Electrochemical (RDA)	DL: 0.5 pg mL^{-1}	Malhotra et al. (2010)
MMP-3	SWCNTs	Electrochemical (RDA)	DL:0.4 ng mL^{-1} & 4 pg mL^{-1}	Munge et al. (2010)
CEA	AgNPs decorated thionine/ Infinite coordination polymer particles fibres	Electrochemical (DPV)	LR: 50 fg mL^{-1}–100 ng mL^{-1} DL: 0.5 fg mL^{-1} RSD: 5.5%	Lu et al. (2014)
PSA	Polypyrrole with three-dimensional Au nanowire array	Electrochemical (DPV)	LR: 10 fg mL^{-1}–10 ng mL^{-1} DL: 0.3 fg mL^{-1}	Moon et al. (2014)
CEA, AFP	Platinum porous nanoparticles	Electrochemical (DPV)	LR: 0.05–200 ng mL^{-1} (AFP, CEA) DL: 0.002 ng mL^{-1}(CEA), 0.05 ng mL^{-1} (AFP)	Wang et al. (2014b)
CEA, AFP	Graphene nano composites	Electrochemical (DPV)	LR: 0.5–60 ng mL^{-1} (CEA, AFP) DL: 0.1 ng mL^{-1} (CEA), 0.05 ng mL^{-1} (AFP)	Chen et al. (2013)

			RSD: 2.2% & 3.6%(CEA), 4.9% & 3.4% (AFP)	
IGF-1	AuNPs	Electrochemical (EIS)	LR: 1–180 pg mL^{-1} DL: 0.15 pg mL^{-1}	Rezaei et al. (2011)
CA125	MIP	Electrochemical (EIS)	LR: 0.5–400 U mL^{-1} DL: 0.5 U mL^{-1}	Viswanathan (et al. 2012)
hCG	Gold silicon carbide nanocomposites	Electrochemical (DPV)	LR: 0.1–5 IU L^{-1} & 5–1000 IU L^{-1} DL: 0.042 IU L^{-1} RSD: 1.7–7.0%	Yang et al. (2014)
rHuEPO	4-mercaptophenyl boronic acid /biotin-modified AuNPs	Electrochemical (DPV)	DL: 8 fmol L^{-1}	Liu et al. (2014)
DNA methylation	Laser-wrapped graphene-Ag array	Optical (SERS)	LR: 5×10^{-3}–5 ng μL^{-1} DL: 0.2 pg μL^{-1} RSD: 8.21%	Ouyang et al. (2016)
miRNA	Fe_3O_4@Mg nanoparticles	Optical (SERS)	LR: 0–1000 pM DL: 0.3 fM	Pang et al. (2016)
EpCAM	GQD & molybdenum disulfide nanosheets	Optical (FRET)	LR: 3–54 nM DL: 450 pM	Shi et al. (2016)
CEA	UCPs and Pd nanoparticles	Optical (FRET)	LR: 2–100 pg mL^{-1} DL: 0.8 pg mL^{-1}	Li et al. (2016)
hCG, ALCAM	TCO	Optical (SPR)	DL: 100 ng mL^{-1} (hCG), 45 ng mL^{-1} (ALCAM)	Piliarik et al. (2010)
PSA	EG6-COOH and EG3-OH SAM	Optical (SPR)	OS: 2.5×10^{-6} RIU	Jang et al. (2009)
SCCa	AgNPs	Optical (LSPR)	LR: 0.1–1,000 pM	Zhao et al. (2014)
HE4	AgNPs	Optical (LSPR)	LR: 10–10,000 pM DL: 4 pM	Yuan et al. (2012)
CEA	SPION	Optical (CL)	LR: 0–50 ng mL^{-1} DL:5 pg mL^{-1}	(Qu et al. 2013)
CEA	AuNPs	Optical (CL)	DL:20 pg mL^{-1}	Hao and Ma (2012)
CA125	GQDs	Optical (CRET)	LR: 0.1–600 U mL^{-1} DL: 0.05 U mL^{-1}	Al-Ogaidi et al. (2014)
CA15-3	3-APS	Optical (OFRR)	DL: 1 U mL^{-1}	Zhu et al. (2009)
HER2	Protein G	Optical (OFRR)	LR: 13–100 ng mL^{-1}	Gohring et al. (2010)
AFP	AuNPs	Optical (EWA)	DL: 0.2 ng mL^{-1} and 2 ng mL^{-1}	Li et al. (2014)
fPSA	Au-coated nanostructures	Optical (FPI)	DL:10 pg mL^{-1}	Zhang et al. (2012)

VEGF	MPTMS	Optical (CL)	DL: 60 pg mL^{-1}	Pasquardini et al. (2015)
AFP	AuNPs & nano-sized hydroxyapatite	Mass-based (Piezoelectric)	LR: 15.3–600.0 ng mL^{-1}	Ding et al. (2007)
FERRITIN	Gold disc	Mass-based (QCM)	LR: 0.1–100 ng mL^{-1}	Chou et al. (2002)
AFP, PSA	PZT	Mass-based (Piezoelectric)	DL: 0.25 ng mL^{-1}	Su et al. (2013)
TIMP1, HER2	Parylene C	Mass-based (SAW)	DL:10 ng mL^{-1} (HER2), 2 ng mL^{-1} (TIMP1)	Gruhl and Lange (2012)
HER2	PZT	Mass-based (Piezoelectric)	DL: 5 ng mL^{-1}	Capobianco et al. (2008)
ALCAM	CBDPs	Mass-based (SMR)	DL: 10 ng mL^{-1}	von Muhlen et al. (2010)

*LR: linear range, DL: detection limit, RSD: relative standard deviation, fPSA: free prostate-specific antigen, rHuEPO: recombinant human erythropoietin, LSV: linear sweep voltammetry, RDA: rotating disk amperometry, CL: chemiluminescence, FPI: fabry perot interferometer, 4-ATP: aminothiophenol, SAM: self-assembled monolayers, MGO: Magnetic graphene oxides, MIP: molecular imprinted polymers, TCO: thiolated complimentary oligonucleotides, CBDP: carboxy betaine derived polymers, OS: Optical sensitivity, SPION: super paramagnetic iron oxide nanoparticles, 3APS: (3-aminopropyl) trimethoxysilane, MPTMS: mercaptopropyltrimethoxysilane, EWA: evanescent wave absorption, parylene C: poly(2-chloro-p-xylylene)

Highlights

- The importance of different cancer biomarkers and how their detection with biosensors may help in the early diagnosis of cancer is enlightened.
- Different strategies used to fabricate cancer biosensors including different transduction systems and biorecognition molecules are discussed. Here, we have also tried to enlighten how the incorporation of nanomaterials in the biosensor design can improve the performance of the cancer biosensors.
- Various nucleic acid and protein biomarkers based cancer biosensors reported in the literature as well as the performance of these biosensors are reviewed in detail.