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Rapid biosensing tools for cancer biomarkers

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ABSTRACT

The present review critically discusses the latest developments in the field of smart diagnostic systems for cancer biomarkers. A wide coverage of recent biosensing approaches involving aptamers, enzymes, DNA probes, fluorescent probes, interacting proteins and antibodies in vicinity to transducers such as electrochemical, optical and piezoelectric is presented. Recent advanced developments in biosensing approaches for cancer biomarker owes much credit to functionalized nanomaterials due to their unique opto-electronic properties and enhanced surface to volume ratio. Biosensing methods for a plenty of cancer biomarkers has been summarized emphasizing the key principles involved.

1. Introduction

At present, human mortality due to cancer is next to heart ailments. Moreover, it has been projected that the fatality rates from cancer may surpass heart attacks in the near future (Siegel et al., 2015). Various strategies that are currently being implemented to identify and fight against this disease include therapeutic approaches, molecular imaging techniques and ultrasensitive monitoring of cancer biomarkers using innovative biosensing tools. Therapeutic approaches mainly investigate potential inhibitors against cancer promoting factors. However, this approach is rather remedial instead of preventive. Difficulties in combating cancer in advanced stages strongly recommend precautionary approach via upcoming quick and reliable cancer diagnostics.

Therefore, focus on early monitoring of cancerous tumor is as important as the discovery of lifesaving anticancer drugs and treatments (Hussain and Nguyen, 2014).

Necessity of early cancer prognosis through convenient and economical in vitro diagnostic tests motivates to devise miniaturized, robust and rapid multiplexed analytical platform based point-of-care (POC) devices (Gubala et al., 2012) for monitoring various forms of cancer at preliminary stages. Presently, popular methods for cancer diagnostics include biopsy analysis, tumor imaging, cancer biomarker monitoring through approaches such as enzyme-linked/radio/electrophoretic immunosorbent assay (ELISA) and mass spectrometry based proteomics (Jin et al., 2014).

These complicated, expensive and cumbersome diagnostic methods discourage patients to undergo routine investigative consultation for early signs of cancer which often results in its progression, ultimately reaching incurable advanced stages. To eliminate this diagnostic delay, researchers are investigating auspicious cancer biomarkers and their ultrasensitive monitoring via different novel biosensing approaches. Monitoring of these biomarkers, whose abnormal concentration in blood or serum indicates early warning signs of cancer will prove highly useful in adopting preventive measures. Considering these points, multi-channeled microfluidics based diagnostic automation may result in miniaturized and smart POC devices for mass utility (Raamanathan et al., 2012). Microfluidics allows controlled laminar flow of participating reactants through microchannels during a diagnostic assay and offers benefits such as low material consumption, reduced sample size, real time analysis and high throughput screening (Zhang and Nagrath, 2013). Measurement of altered gene expression during the onset of cancer can be performed through the development of rapid DNA sequencing methods. Use of capillary array electrophoresis in form of microfluidic chip for building multiplexed analytical platform is one of

AbbreviationsAPTMS3-aminopropyltriethoxysilane8-OHdG8-hydroxydeoxyguanosineBREBio-recognition elementBRCA-1Breast cancer 1 geneCNTsCarbon nanotubesCLLChronic lymphocytic leukemiaEISElectrochemical impedance spectroscopyELISAEnzyme linked immunosorbent assayEGFREpidermal growth factor receptorFETField-effect transistorFPsfluorescent probesFRETFluorescence resonance energy transferGOxGlucose oxidaseGAGlutaraldehydeAuNCsGold nanoclustersAuNPsGold nanoparticlesAuNRsGold nanorodsGOGraphene oxideHERHuman epidermal growth factor receptorIL-6Human interleukin-6LODLimit of detectionLSPRLocalized surface plasmon resonancemiRNAsMicro RNAsOFRROpto-fluidic ring resonatorPDACPancreatic ductal adenocarcinomaPTHrPParathyroid hormone-related peptidePEMSPiezoelectric microcantilever sensorsPQCPiezoelectric quartz crystalsPtNPsPlatinum nanoparticlesPOCPoint-of-carePSAProstate specific antigenQDsQuantum dotsQCMQuartz crystal microbalanceRSRaman spectroscopyAgNPsSilver nanoparticlesSWSVSquare wave stripping voltammetrySERSSurface enhanced Raman scatteringSWVSquare wave voltammograms

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the prime interests in cancer research (Ying and Wang, 2013). Presently, popular POC devices are based on lateral flow immunological or colorimetric strips and glucose sensors. Recently, Su et al., 2012 came up with an innovative solution towards designing POC devices in cancer monitoring via the use of personal glucose sensors for detecting carcinoembryonic antigen. Magnetic beads labeled with secondary antibody were used as carriers for invertase enzyme to perform sandwiched immunoassay.

The present review in general is an attempt to explain the most recent advancements in the field of biosensors for cancer diagnostics and impeccable role of functionalized nanomaterials in improving the biosensor research.

2. Biosensing approach for cancer biomarkers

Recent years have witnessed extensive research in fabricating miniaturized biosensors for monitoring cancer biomarkers. Quick evaluation of biological fluids for probing potential disease biomarkers requires advanced analytical techniques.

In this aspect, bioluminescence based rapid approaches for evaluation of endotoxicosis in human serum was investigated more than a decade ago (Esimbekova et al., 1999). Monitoring the course of diseases viz. chronic cholecystitis, bronchitis or ulcerous disease in human beings through the analysis of biological fluid was an important study which markedly promoted the area of rapid bio-diagnostics. The adopted method was based on studying the bioluminescence decay pattern (A: normalized luminescence in control; B: observed difference of luminescence in test sample with respect to control) from bacterial luciferase system when incubated with blood serum of afflicted patients. Though the method could not justify disease type, nevertheless high sensitivity, ease of usage and rapidity of the method played a pivotal exploratory role for witnessing new horizons in rapid biosensing. Lately, a detailed review on various applications on bacterial coupled enzyme systems: NADH: FMN-oxidoreductase and bacterial luciferase is presented by Kratasyuk and Esimbekova (2015). The emphasis was laid on development of economic biosensors for environmental, medical and industrial applications. In medical field, this methodology was used to evaluate the state of patient's illness and usefulness of luciferase index as prognostic plan in diseased personnel.

Lately, functionalized nanomaterials inheriting overwhelmingly high surface to volume ratio, conductivity and opto-electronic properties such as localized surface plasmon resonance (LSPR) and surface enhanced Raman scattering (SERS) is being investigated for their widespread application in fabrication of smart biosensor systems and minimizing signal interferences during real sample analysis. Further, concerns associated with biorecognition element (BRE) such as instability and non-reusability invites ample scope and motivation for continuous improvements in biosensor research (Arya and Bhansali, 2011).

The BRE often employs antibody, enzyme, short DNA strand or aptamer against specific cancer biomarker in close association to a physical transducer (electrochemical, optical and piezoelectric) which amplifies the signal response manifold after which the data is digitalized to give results in form of display readout (Fig. 1). Therefore, research involved in this area is highly interdisciplinary and encourages close associations among researchers from the field of biochemistry, biotechnology, medical sciences, material sciences, computer programming and electronics, chemical sciences and nanotechnology.

The role of physical transducers in biosensor research is indeed, very crucial. Prime desired features of transducing electronic components include high signal to noise ratio, requirement of low input voltage, inexpensiveness and provision for their fabrication into a handheld sleek design. In cue of this, electrochemical transducers offer cost effective and portable biosensing of analytes. In one of such sensitive electrochemical sensing strategies; the voltage across the working electrode (fabricated bioprobe) is gradually increased in a cyclic manner and concomitant current measurement is taken during assay. However, precise functionalization of working electrode with biological component is a challenging task which often involves multiple layering with conductive chemical agents and nanomaterials for enhanced current measurement. Optical transducers have gained significant attention after the introduction of functional nanomaterials for biosensing purposes, which have greatly improved the assay sensitivity due to plasmonic interactions between nanomaterials and light waves (Rusling et al., 2010; Abhijith et al., 2014; Swierczewska et al., 2012). However, fine tuning of the multiple experimental conditions (e.g. distance between luminescence response and the nanomaterial, dielectric constant of the surrounding medium, shape, size and opto-electronic properties of the metal nanomaterial) for observing such phenomena is a perplexing task. Recently, ring resonator sensing technology is being investigated for its potential in biosensor research. A subclass of this technology, opto-fluidic ring resonator (OFRR) promises an inexpensive and multiplexed optical biosensing of cancer biomarkers (Gohring et al., 2010).

Another class of sensors, generally made from quartz crystals inheriting piezoelectric (mechanical stress induced electric charge) properties respond to mass changes at their surface and are used for biosensing purposes.

Further, biosensing automation via incorporation of microfluidics and multiplexed analytical platform is currently being the thrust area of biosensor research; will aid in revolutionizing POC devices for early cancer monitoring (Malhotra et al., 2012; Miyamoto et al., 2014).

2.1. Electrochemical biosensors for cancer biomarkers

Fabrication of biosensors using the techniques of field-effect transistor (FET), square wave voltammograms (SWV), square wave stripping voltammetry (SWSV), electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV) allow rapid biosensing of key analytes for different types of cancer. An electric field dependent transistor, FET sensors for biological applications allow interaction of biomolecules with the gate of the transistor resulting in re-distribution of charge, which leads to measurable conductance change in FET channels. In yet another electrochemical approach, quantitative analysis using SWV has received tremendous attention in the fabrication of biosensors due to their ability to perform experiments at much faster scan rate when compared to pulse voltammetric techniques. Meanwhile, to introduce, sensitivity of pulse voltammetric techniques towards faradic currents is more than direct current (dc) voltammetry due to their ability to discriminate against charging (capacitance) current which also obtain peaks for faradic currents instead of sigmoidal waveforms in case of normal pulse or dc voltammetric techniques. SWSV, an even more sensitive answer for rapid biosensing involve deposition of an analyte on the working electrode leaving its concentration lesser in the sample solution. After sufficient concentration, application of electrode potential strips the overladen analyte into the solution leading to increased current yielding higher sensitivity during electrochemical biosensing of analytes.

A sandwiched immunosensor based on the principle of SWSV was described by Zhu et al. 2013 in which they reported monitoring of human epidermal growth factor receptor-2 (HER-2) and cancerous breast cells expressing HER-2. Anti HER-2 antibodies were covalently immobilized on self-assembled nanocomposites of 2,5-bis(2-thienyl)−1*H*-pyrrole-1-(*p*-benzoic acid) and AuNPs which in the presence of HER-2/HER-2 overexpressing cells and hydrazine-AuNPs-aptamer conjugate; formed a sandwich-type format. Hydrazine could specifically and uniformly reduce silver ions during stripping voltammetric assay. The deposited silver was detected under microscope and the level of these analytes was quantified using SWSV.

High counts of B-lymphocytes may indicate chronic lymphocytic leukemia (CLL) and unfortunately, are detected only at advanced cancer stages. In this direction, a single stranded DNA probe