Talanta 132 (2015) 162–174

Contents lists available at ScienceDirect

Talanta

journal homepage: www.elsevier.com/locate/talanta

Review

Applications of electrochemical immunosensors for early clinical diagnostics

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ARTICLE INFO

Article history:
Received 4 July 2014
Received in revised form
18 August 2014
Accepted 27 August 2014
Available online 6 September 2014

Keywords:
Biosensor
Cancer biomarkers
Immunosensor
Electrochemical biosensors
Early diagnosis

ABSTRACT

Cancer and cardiovascular diseases are the major threats to global health. Hence, there is a growing demand for a range of portable, rapid and low cost biosensing devices for the detection of these diseases. Electrochemical immunosensors are simple, rapid, reliable and inexpensive devices and they have sensitive detection limits to monitor both levels of the biomarkers in normal and patient serum. Due to the specific binding of antibody to its corresponding antigen, immunosensors based on antibody–antigen interaction are one of the most widely used analytical techniques in the quantitative detection of these diseases. The changed levels of markers in patients are associated with diseases. In this article the biosensors and biomarkers, which were commonly used in terms of monitoring the diagnosis and treatment of cancer and cardiac diseases, are reviewed. In addition, the developed biosensors are compared in terms of precision, reproducibility, regeneration, stability and specificity.

Contents

1. Introduction

The pioneering study of Clark and Lyons, more than four decades ago, shed light on some analytical researchers in designing of biosensors, which perform as economical and fast tools for clinical, chemical, environmental and pharmaceutical studies. Because of its simple use and portability in relatively complex samples, biosensors offer a potential alternative to advanced bioanalytical systems [1].

A biosensor is composed of two components, a bioreceptor and a transducer. First part, the bioreceptor is a biomolecule that recognizes the target analyte, and second part the transducer converts the recognition event into a measurable signal [2]. Immunosensors are antibody–antigen based affinity biosensors, in which the detection of antigen as a target analyte is a result of the specific binding of the antigen to particular region of an antibody on the electrode surface [3]. Also, in electrochemical immunosensors antibody acts as a bioreceptor and antigen acts as a target analyte and transducer can be able to quantify the antigen concentration by using amperometric, potentiometric, impedimetric or conductometric signals. Fig. 1 shows a schematic presentation of an electrochemical immunosensor.

In recent years, optical and electrochemical detection methods have been used in early clinical diagnosis. Optical detection transduction method is less sensitive when coupled with radioimmunoassay, has short half-life of radioactive agents, concern of health hazards, and has disposal problems. On the other hand, electrochemical

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http://dx.doi.org/10.1016/j.talanta.2014.08.063
0039-9140/

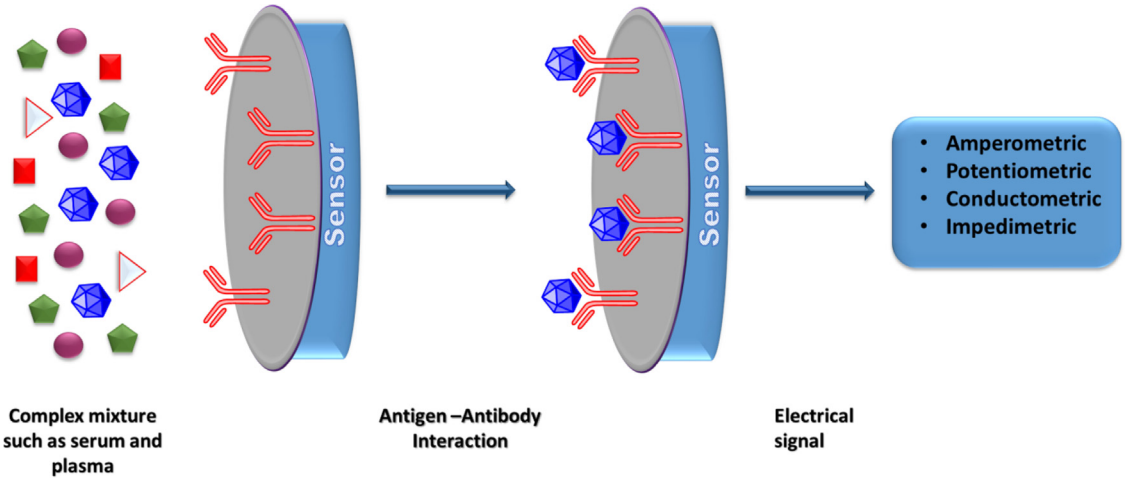

Fig. 1. Schematic representation of electrochemical immunosensor.

detection method shows no similar problems and electrochemical immunoassays and immunosensors enable fast, simple, and economical detection [4].

Electrochemical immunosensors are used as care devices since they are portable, simple, easy to use, cost effective and disposable in most cases [5,6]. Compared with traditional immunoassay methods, electrochemical immunosensors are specific, simple and convenient, and can offer multitarget analyses and miniaturization. They can perform in situ, real-time, automation detection [7].

Specificity for any given biomarker is often achieved by use of antibodies. The specific binding of an antibody to its target antigen in a complex mixture such as serum and plasma provides the detection and quantification of diseases at levels as low as picograms (pg) [8]. Also, this is another advantage of immunosensors.

In this study the biosensors and biomarkers, which were commonly used in terms of monitoring the diagnosis and treatment of cancer and cardiac diseases, are reviewed. And also, it focuses on recent development for tumor markers and cardiac markers testing and monitoring in clinical diagnosis. However, a wide range of researches have been published in this area. This review is limited to recent publication within the past nine years. Most reviews have been organized around only tumor or cardiac biomarkers and their diagnosis of biosensors. Herein we present different biomarkers used in several publications of electrochemical immunosensors for tumor and cardiac diseases and highlighted the major clinically relevant parameters, such as their detection limit/range and designing of bioassay. Moreover, in this review, we emphasize on the opportunities for further improvement in tumor and cardiac diseases diagnostic and treatment monitoring.

2. Electrochemical immunosensors

An antibody based biosensor was applied for the first time in the 1950s, leading the possibility of immune-diagnosis [4]. These types of biosensors have high specificity and low limit of detection due to their extreme antibody affinity to their antigen. Antibodies are proteins produced by the immune system. However, antigens can be a variety of different molecules, from protein to DNA, lipids, etc [6].

In developing immunosensors, the immobilization of antibody is an important step because antibody acts as the recognition element for antibody–antigen reaction. The performance of the detection and antigen binding capacity can be increased by a proper antibody surface. Thus the choice of the antibody immobilization method is very important in the design of an immunosensor. Several methods including physical [9–10] and chemical adsorption have been used for the preparation of oriented antibody molecular layers on the surface of the transducer. Self-assembly (SAM) technique has been used as chemical adsorption method for immobilization of antibody [11–13]. In this technique, a self-assembly monolayer is fixed on the surface through chemical bonds. Then the antibody is covalently attached to the monolayer by using cross-linkers.

Transducer types used in immunosensors are electrochemical (amperometric, potentiometric, conductometric, capacitative), optical (fluorescence, luminescence, refractive index), piezoelectric or calorimetric. The electrochemical immunosensors rely on the measurements of currents and/or voltage to detect binding between antibody and antigen.

In potentiometric measurements, the potential difference between a working and a reference electrode is determined by a voltammeter when there is no significant current flowing through them. The potential difference is measured due to the oxidation and reduction of the species in sample solution. The transducer may be an ion selective electrode (ISE) based on thin film or selective membranes as recognition elements. Analytical information is obtained when the ISE convert the biorecognition process into a potential signal.

In amperometric measurements, a current occurs as a result of electrochemical oxidation or reduction of an electroactive species. This type of measurement is taken by maintaining a constant amplitude voltage at working electrode (gold, platinum, and carbon) related to reference electrode, under a fixed potential, current pass through sample [8].

In impedimetric measurements, when biorecognition elements occur at the modified surfaces, the interfacial properties change. Thus impedimetric immunosensors can be used to determine quantitative parameters of electrochemical properties. Electrochemical reactions, known as electron transfers at the electrode surface, involve electrolyte resistance, adsorption of electroactive species, charge transfer at the electrode surface, and mass transfer from the bulk solution to the electrode surface. Each reaction process represented by an electric circuit consists of resistance, capacitors, or constant phase elements combined in parallel or in series. The most favorite model of electric circuit for a simple electrochemical reaction is the Randles–Ershler electric equivalent circuit model, consisting of electrolyte resistance (R_s), charge-transfer resistance (R_{ct}) at the electrode/electrolyte interface, double-layer capacitance (C_{dl}), and mass transfer resistance (R_{mt}), also Warburg impedance (W) [2,14].

In conductometric measurements, there is a relationship between a biorecognition event and conductance. While a reaction, a change in the ionic species concentration leads to change