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Electrochemical immunosensors: Critical survey of different architectures and transduction strategies

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ABSTRACT

This review describes the most popular architectures and transduction strategies that have been proposed for the development of electrochemical immunosensors. Relative published work has been classified into four main categories: i) enzyme-labelled immunosensors, ii) metal nanoparticle- and quantum dot-labelled immunosensors, iii) capacitive and (faradic) impedimetric immunosensors, and iv) magnetoimmunosensors. The principle of operation, analytical features, various signal amplification strategies as well as the adaptability of the afore-mentioned types of immunosensors to multiplexed formats, (micro) fluidic platforms and paper-based approaches are critically discussed. Perspectives in point-of-care analysis and commercialization opportunities are also discussed.

Contents

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1. Introduction

Specific non-covalent binding between antibodies (commonly used as analyte-specific probes) and antigens (analytes) constitutes the keystone of immunoassays, a widespread family of analytical methods for the selective and sensitive detection of substances of great interest in clinical analysis and diagnostics, food safety control, drug screening and development, environmental monitoring, forensic analysis, managing of biological threats, the prevention and control of epidemic diseases, personalized medicine, etc. [1–5]. As a result, immunoassays represent an important, continuously growing, scientific industry; analysts forecast that the immunoassay market is expected to reach $23,712.4 million by 2019 from $14,926.3 million in 2014, at a mean annual growth rate of 9.7% [6].

Nowadays, enzyme-linked immunosorbent assay (ELISA) approaches (which fall into two major formats; sandwich (Fig. 1A) and competitive (Figs 1B, 1C)) represent the most popular technology for the implementation of the afore-mentioned immunoassays offering low detection limits (around 10^{-12}–10^{-9} mol L^{-1}). Limiting factors in ELISA assays include the complexity of the assay workflow, the use of costly reagents, the bulky ELISA readers, and the time-consuming operation [3,7].

As illustrated in Fig. 1A, the ELISA sandwich format is applicable only to antigens (Ag) that have at least two binding sites (epitopes) for their specific antibody (Ab). The interaction between the (immobilized) capture antibody and the antigen cannot be directly monitored and thus quantification of the analyte requires an extra labelling step and appropriate compounds (enzyme-labelled reporting antibody and the enzyme's substrate) to produce a detectable response (e.g. absorbance, fluorescence, current), the magnitude of which is proportional to the concentration of the analyte. In the ELISA competitive formats, the magnitude of the response is inversely proportional to the concentration of the analyte (sample antigen). In the format illustrated in Fig. 1B, the molecules of the antigen in the sample compete with the enzyme-labelled reporting antigens added in the sample for binding with the immobilized antibodies. In the ELISA competitive format illustrated in Fig. 1C, the antigens in the sample compete with the immobilized antigens for binding with the enzyme-labelled reporting antibodies [8].

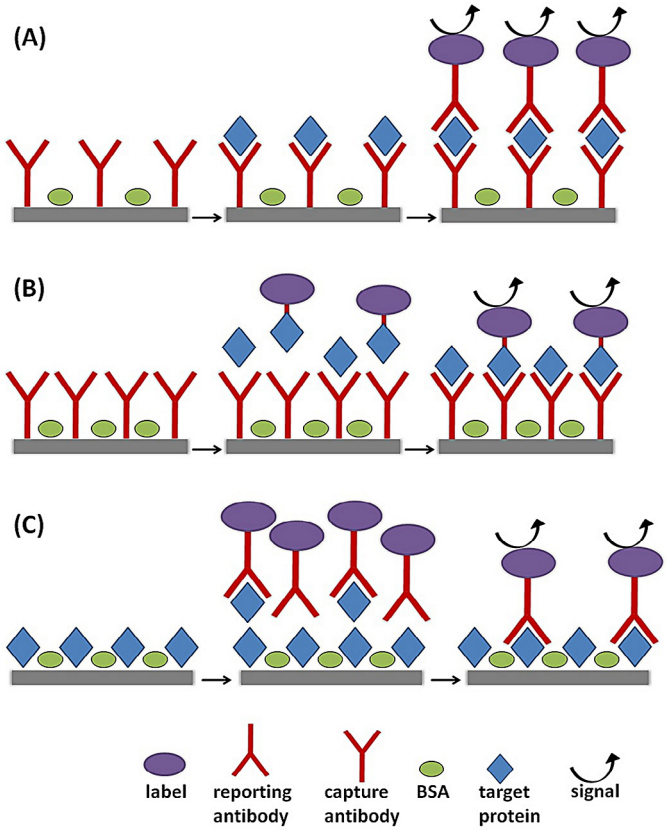

Fig. 1. Schematic representation of different ELISA formats: (A) sandwich, (B) competitive antibody coating and (C) competitive antigen coating.

Developments in various fields of chemical analysis since the early 1980s prompted the integration of the biochemical (i.e. the Ab-based sensing layer) and the physical (measuring property-to-signal converter) transducers into a single device known as an immunosensor. Depending on the physical transducer technology, immunosensors could be categorized into three major classes: electrochemical, optical and piezoelectric. Amongst them, the electrochemical ones are of particular interest thanks to their fabrication simplicity, low cost of instrumentation, scope for mass fabrication, short response time, high sensitivity and amenability to miniaturization. For a detailed description of optical (colorimetric, fluorescence, chemiluminescence, surface plasmon resonance), piezoelectric (quartz crystal microbalance, surface acoustic wave) and other types of immunosensors based on surface-enhanced Raman spectroscopy and cantilever-based immunosensors, which are out of the scope of this review, the reader is referred to Refs. [9,10].

This review focuses on the description of the most popular types of electrochemical immunosensors, which have been classified as i) enzyme-labelled immunosensors, ii) metal nanoparticle- and quantum dot-labelled immunosensors, iii) capacitive and (faradic) impedimetric immunosensors, and iv) magnetoimmunosensors. As shown in Fig. 2A, enzyme-labelled and electrochemical impedance spectroscopy (EIS)-based immunosensors (i.e. capacitive and (faradic) impedimetric immunosensors) represent the most studied types over the period from 2000 to 2015. The number of publications related to quantum-dot-labelled immunosensors (data not shown) and magnetoimmunosensors, which had scarcely appeared in the period 2000–2005, shows an ascending trend with these two types of immunosensors collectively representing 9% of the total published work on the topic of electrochemical immunosensors during the last half-decade (Fig. 2B). Finally, the large number of publications related to nanoparticle-modified immunosensors is justified by the unique properties of nanoparticles compared with their bulk materials and reflects the recent emergency of nanomaterials in the design of advanced immunosensors in terms of selectivity and sensitivity and their use as electrode modifiers, as immobilization platforms and as electrocatalysts in addition to labels, which is the objective of this review.

This review highlights and critically discusses the most efficient signal amplification strategies, as well as the adaptability of the afore-mentioned types of immunosensors to multiplexed formats, (micro) fluidic platforms and paper-based approaches, by using selected examples illustrating novel concepts and promising applications in the field; however, some interesting articles may not be included because of space constrains. To this end, if the progress in a particular topic has been sufficiently and comprehensively reviewed, for a wider and more detailed description the reader is referred to Table 1 which lists the review articles of the topics presented here along with the number of the references cited in each review and the year of publication. Finally, perspectives in point-of-care (POC) analysis and commercialization opportunities of the afore-mentioned types of immunosensors are also discussed.