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Antibodies as target for affinity biosensors

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ABSTRACT

Antibodies or immunoglobulins (Ig) are proteins produced by the immune system to protect the body by identifying and neutralizing pathogens. The determination of antibodies is an important area in bioanalysis because their presence provides information about pathologies such as infections, allergies, auto-immune diseases and cancers. Antibodies can be readily detected and quantified by using immunosensors. This review provides an up-to-date overview of immunosensors for the determination of antibodies which can be implemented in the clinical area, for point-of care applications or in routine laboratories.

Contents

In memory of Prof. M. Mascini.

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1. Introduction

Marco Mascini highlighted in 1992 the interest of applying biosensors in medical fields: "Electrochemical biosensors have found wide interest in clinical chemistry and medicine. Physiologists, cardiologists, diabetologists dreamt for years about the possibility of continuously monitoring chemical parameters to feedback appropriate action to restore the values to normal levels [1]." This dream is still relevant today and allergologists, infectiologists and gastroenterologists can be added to the potential users of biosensors and particularly biosensors for antibodies determination.

Biosensors can be classified either as a function of the biological recognition element or as a function of the transducer. A distinction can also be made between (i) biocatalytic biosensors (i.e. comprising an immobilized enzyme, whole cell, organelle) for which the recognition and binding of the analyte are inducing chemical change(s) and (ii) affinity biosensors (i.e. comprising an immobilized antibody, antigen, DNA, aptamer, membranous receptor) for which the binding event does not involve a chemical reaction [2]. Immunosensors faced the most important research trends in affinity biosensor development. They correspond, generally, to a combination of an immobilized antibody used for the detection of a target antigen and a transducer to convert the immunological reaction into a measurable signal. The antibody is selected as a function of the target. Immunosensors exploit the same transducers as biosensors. They can be differentiated into electrochemical, optical, piezoelectric, magnetic, calorimetric, mechanical, i.e. atomic force miscrocopy (AFM) cantilever immunosensors [3].

A vast number of immunosensors have been developed for the determination of drug compunds [4], pesticides [5], biomarkers [6,7], pathogens [8] or toxins [9] with the antibody being used as immobilized probe [10]. It is interesting, however, to consider the antibody as the target of an immunosensor. Indeed, an antibody is a biological protein giving informations about the immunological status, infection, allergy, auto-immune diseases etc. . . An antibody is traditionally detected by immunoprecipitation, agglutination or neutralization assays (use of an animal) and, more frequently, by applying an enzyme immunoassay such as an enzyme-linked immunosorbent assay (ELISA). ELISAs are time consuming, and need a qualified technician and a relatively sophisticated instrumentation. In contrast, immunosensors are miniaturized integrated devices which allow rapid, easy-to-use and on-site detection (point of care) [11].

Antibodies or immunoglobulins (Ig) are subdivided into classes or isotypes according to the structure of the constant domains of the heavy chains: IgG (70-75%), IgA (15%), IgM (10%), IgE (less than 1%), IgD (less than 1%) [12]. IgGs are the main class of antibodies circulating in blood (12 mg/mL in serum). They are synthesized by plasma cells as humoral immune response to a contact of the immune system with antigens. IgGs are glycoproteins of 150 kDa containing two identical heavy chain polypeptides and two identical light chains. IgMs are the first antibody synthesized by the plasma in primary reaction after initial exposure to an antigen. The IgAs are produced under secretory form in mucosal tissues (i.a. in the intestinal lumen, the respiratory tract and the saliva) where they neutralize toxins. IgEs are utilized during immune defense against parasitic infestation. IgEs also play a role in various allergic diseases [12]. Generally, an antigen has several epitopes which cause several antibodies formation, these are polyclonal antibodies. In clinical biology, the search of an antibody is always a search of polyclonal antibodies.

The strategy applied with immunosensors is based, most of the time, on a sandwich-type format. The antigen corresponding to the target antibody is immobilized onto the transducer. After sample incubation, a labeled antibody against IgG or IgA (depending on the isotype of the target antibody) is added in order to allow the detection (Fig. 1A). Label-free biosensors allow a direct detection of the affinity event such as in surface plasmon resonance (SPR) biosensors, piezoelectric sensors or impedimetric based sensors. Such configurations allow real time detection with a reduced number of steps and with reduced time of analysis (Fig. 1B). SPR biosensors measure a refractive index change due to the binding of an analyte to its biospecific partner immobilized onto a gold surface [13]. Piezo and impedimetric sensors are built with the antigen immobilization onto a quartz crystal microbalance or an electrode substrate, respectively. After antigen-antibody binding, the former measures a mass change and the latter a modification of the impedance at the electrode-solution interface [10].

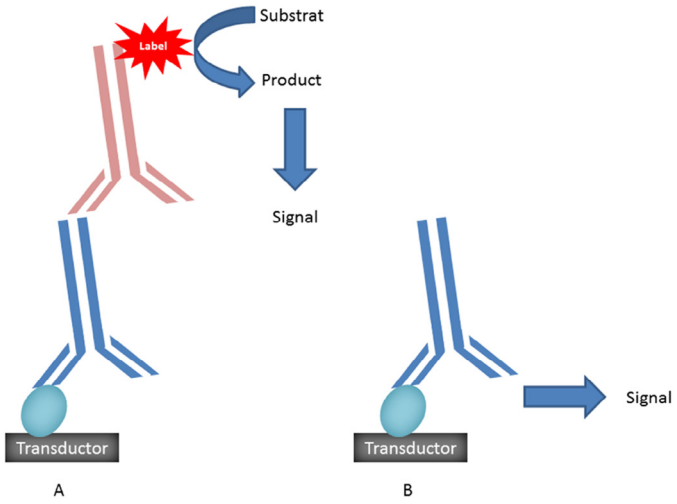

Fig. 1. Some strategies at immunosensors. A. Sandwich-type immunosensor measurement in multi steps, the reaction between the label and reagent causes the signal. B: Label free immunosensor measurement in one step, the antigen-antibody binding induces the signal.

To the best of our knowledge, there are no immunosensors for antibody assay on the market yet. Several commercially available transducers using a screen printed electrode (SPE) or the SPR technology can be customized for antibody assays. Semi quantitative immunochromatographic assays are available, however, such as the immunochromatography stick for the detection of tetanus antibodies (Quick TetanCheck®, Tétanos Quick Stick® [14]).

In this review, we have chosen to present different immunosensors classified by their application and not by the transducer. Immunosensor applications will be dedicted (i) to an IgE boost (allergy) (ii) to antibodies raised in autoimmune diseases, during bacterial, viral and parasitic infections, (iii) to monitor levels of antibodies in the context of a vaccination and (iv) to antibodies developed in response to some cancers.

2. Applications

2.1. Immunoglobulin E (IgE)

Some electrochemical immunosensors are dedicated to the determination of IgEs. Because the IgEs play an important role in type I hypersensitivity, their presence in blood is considered as a marker of allergy. Kreuzer *et al.* have developed an immunosensor for measurement of allergy related IgEs in human blood samples. The immunosensor is based on a competitive immunoassay using an anti-IgE modified screen-printed carbon electrode (SPE) and amperometric detection of p-aminophenol produced by alkaline phosphatase (AP). The immunosensor measures the IgE level within a 30 min time interval [15].