Talanta 205 (2019) 120122

Contents lists available at ScienceDirect

Talanta

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

A brief review on the strategy of developing SPR-based biosensors for application to the diagnosis of neglected tropical diseases

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ARTICLE INFO

Keywords:
Surface plasmon resonance
Biosensor
Immunosensor
Neglected tropical diseases
Visceral leishmaniasis
Antigen-antibody interaction

ABSTRACT

The phenomenon of surface plasmon resonance (SPR) through optical sensors was developed from initial studies involving excitation of surface plasmons on metallic substrates. From the beginning, these optical systems have attracted increasing interest for application in different areas, ranging from physics, chemistry, and materials science to biology. Although numerous applications have been explored, the use of SPR in the development of biosensors is by far the most prominent. This review provides a brief account of fundamental aspects related to the recent applications of SPR as a tool for the development of new clinical diagnosis methods. The applications of SPR biosensors were illustrated through recent studies published in the field of neglected tropical diseases, with an emphasis on the contributions achieved in visceral leishmaniasis. It was possible to demonstrate the real benefits and the difficulties that the SPR biosensors have encountered in this important and complex system. Finally, future trends in the use of nanomaterials for the development of SPR-based portable devices for application to neglected tropical diseases have been demonstrated.

1. Introduction

Chemical sensors are devices that transform chemical information, such as the concentration variation of a specific component in a sample, into a useful or measurable analytical signal [1,2]. Sensors have unique characteristics that distinguish them from large-scale instrumental methods (including high-performance liquid chromatography, gas chromatography, mass spectrometry, infrared, and nuclear magnetic resonance). Unlike these instrumental methods, chemical sensors allow the acquisition of information *in situ* and in real time. In addition, the low cost, portability, ease of automation and possibility of miniaturization are other important features of sensing systems [3].

Biosensors are a subclass of chemical sensors that merge high sensitivity, as indicated by their low detection limits, with high specificity obtained from a biological recognition process [4]. Therefore, they consist of analytical devices that involve a biological component of recognition (such as enzymes, cells, tissues, receptors, antibodies and antigens) making close contact with a transducer's surface. When the component is bound, the transducer converts the biological signal into a quantifiable signal [5–7]. Affinity biosensors are included in a subclass of biosensors that rely on the strong and selective binding of biomolecules, such as antibodies, membrane receptors, and oligonucleotides [8,9]. The molecular recognition in these systems is mainly determined by the complementary size and shape of the binding site for the analyte. For instance, an immunosensor is an affinity biosensor that benefits from the ability of an antibody to very specifically recognize an antigen present in a complex environment [8,10]. The immunoassay principle was first established by Yalow and Berson (1959) [11], and later, Clark and Lyons (1962) [12] developed the concept of an immunosensor. Currently, immunosensors are widely applied in several areas, including clinical medicine (where they are used for the development of new diagnostic methodologies), food industry, and environmental analysis [2,13–15].

Overall, the basic premise involved in the development of chemical sensors (which include biosensors) is their ability to evaluate surface and interfacial processes. Even though different transduction systems (such as piezoelectric, electrochemical, acoustic, impedimetric and optical) have been used for this purpose [15,16], in this review, the focus is the use of the surface plasmon resonance (SPR) technique for the construction of biosensors. Conceptually, SPR-based biosensors

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https://doi.org/10.1016/j.talanta.2019.120122
Received 16 April 2019; Received in revised form 3 July 2019; Accepted 5 July 2019
Available online 11 July 2019
0039-9140/

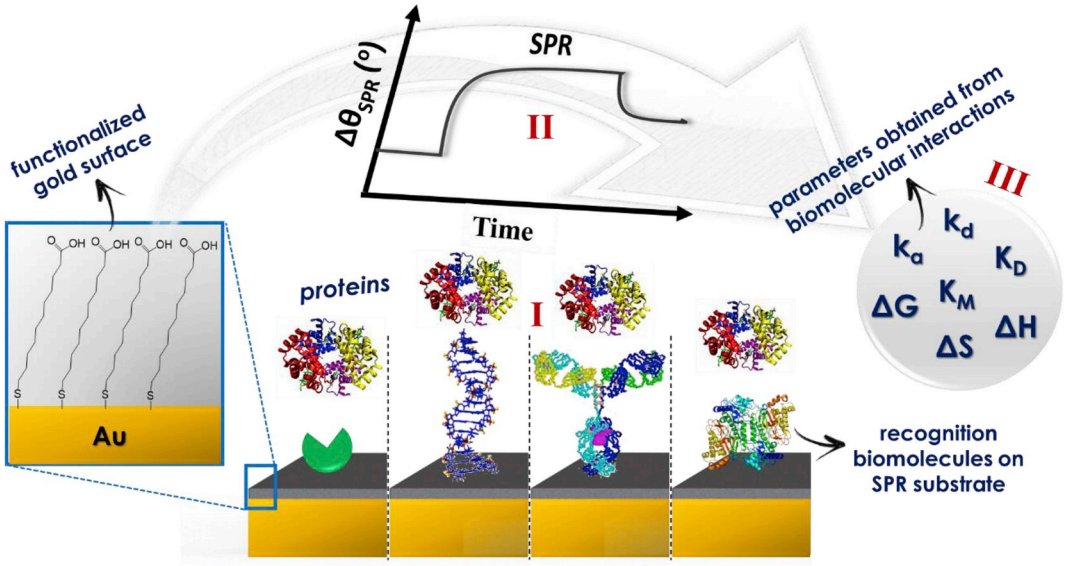

Fig. 1. Schematic representation of a SPR biosensor, showing (I) interaction of analytes (e.g. proteins): with recognition biomolecules immobilized on a functionalized metallic surface; (II) real-time monitoring of the interactions by SPR biosensors; (III) kinetic and thermodynamic parameters measured through the results obtained by SPR biosensors.

(SPR biosensors) belong to a subclass of optical sensors that consist of a biological recognition component (enzymes, antigens, antibodies, DNA, RNA, receptors, cells, tissues) in intimate contact with the surface of a transducer, which is able to transform the information of biological interaction into a signal based on characteristics of the wavelength of light [1,17] (see the schematic representation in Fig. 1).

As discussed these analytical devices combine the high sensitivity achieved by advanced technologies available for transduction systems with the high selectivity found in biological recognition systems [18]. The main advantages in the use of SPR biosensors are as follows: (1) high sensitivity for the investigation of biomolecular interactions, which is very important, for example, for the detection of very low concentrations of parasites in the bloodstream of infected people; (2) decreased number of experimental steps, making them a fast diagnostic method; (3) the possibility of sensor surface regeneration, which allows the use of the same device for the evaluation of several samples; and (4) the ability of analysis performed in an SPR sensor to be used for the acquisition of information in real time without the need for chemical or biological probes. The last of these four properties makes it possible to assess kinetic (i.e., stoichiometry and number of elementary reaction steps, association and dissociation constants) and thermodynamic (e.g., affinity constant, free energy, enthalpy, and entropy) aspects of the biomolecular interaction in many diversified systems (see Fig. 1) [17]. SPR technique has been used for diagnostic purposes and for the evaluation and elucidation of biological events and is considered by the plasmonic field as one of the main tools for the investigation of biochemical events that take place as a result of biomolecular interactions, such as protein-protein, enzyme-substrate, peptide-membrane, or DNA or RNA-protein, etc. [19,20].

The neglected tropical diseases were given their name because they affect low-income populations and consequently have not received due attention from government agencies and drug industries. Although visceral leishmaniasis (VL) is a very important type of tropical disease, few studies involving biosensor development and VL have been published thus far. Therefore, the choice of VL as the focus of the discussion is due to the importance of the subject and for the purpose of demonstrating the real contribution that the SPR biosensors have made to this topic.

As originally described by Ross (1903), leishmaniases are infectious diseases caused by protozoan parasites from the genus *Leishmania* [21]. These infections represent a significant problem for public health since approximately 2 million people are infected annually in more than 90 countries [22]. VL (also known as “calazar”) is the most severe form of the disease because the parasites penetrate into vital organs of the human physiological system, resulting in a high mortality rate due to the lack of access to proper treatments [23,24]. The most common etiologic agent found in America and North Africa is *Leishmania infantum* (or *Leishmania chagasi*). The transmission route generally involves the bite of female phlebotomine sandflies (genus *Lutzomyia*), while dogs and other canidaes act as hosts of the parasite [25–28]. Although more than 90% of VL infections are concentrated in India, Brazil, Bangladesh, Nepal and Sudan, studies have shown that the number of cases worldwide is increasing, which is concerning considering the expected climate change in the near future in Europe and other regions situated in temperate zones [29].

Reliable diagnostic tests for VL are very important for parasite monitoring programs aimed at preventing unnecessary sacrifice of dogs [30,31]. VL diagnosis is mainly made through serological methods in clinical routine analysis [32], and the most common methods are the enzyme-linked immunosorbent assay (ELISA) and the indirect immunofluorescence antibody test (IFAT) [33]. However, these tests present limitations, such as low sensitivity for the detection of asymptomatic cases and the existence of cross-reactions with diseases caused by other similar parasites [34]. In this context, there is a great incentive for scientific research towards developing new methodologies for VL serological diagnosis [35,36].

In this brief review, the discussion is focused on the use of SPR for the development of both new clinical diagnostic methodologies and elucidation of different types of biological events related to the VL. The contributions of studies on SPR immunosensors received thus far to diagnosing this serious disease were discussed, as well as the main perspectives and difficulties in this field of study.

2. SPR-based biosensors: an efficient tool for biomolecular interaction studies in highly important and complex systems - visceral leishmaniasis

2.1. SPR-based immunosensor for diagnosis of visceral leishmaniasis

In agreement with the necessity of developing new methodologies for the serological diagnosis of the VL, our group worked on the first immunosensor employing the SPR technique as a new tool for the

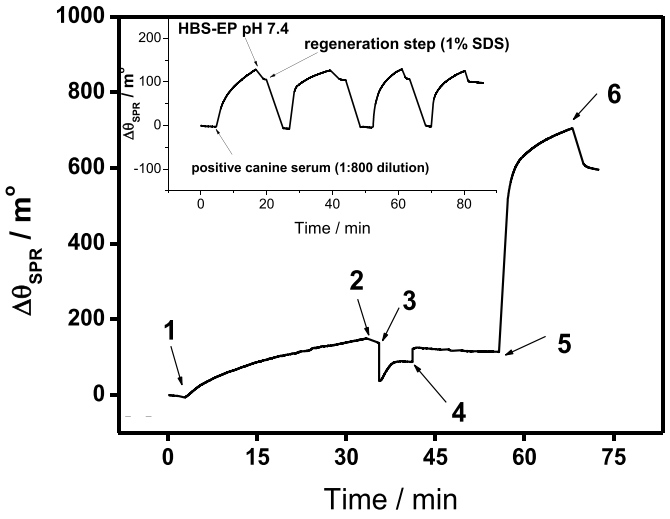

Fig. 2. SPR-based immunosensor. Sensorgram showing the immobilization and immunoreaction of L. infantum antigen onto the activated 11-MUA modified gold surface [1: injection of L. infantum antigen (50 μg mL^{-1}); 2, 4 and 6: HBS-EP pH 7.4 buffer flow; 3: injection of ethanolamine; 5: injection of positive canine serum at 1:50 dilution]. Inset: SPR sensorgrams observed when positive canine serum of L. infantum antibody was injected repeatedly after a regeneration step carried out by using 1% (w/v) SDS.
Figure reprinted from Ref. [37] with permission; copyright (2019) Elsevier.

diagnosis of VL [37]. In that study, an SPR-based immunosensor was developed for the direct and highly sensitive detection of anti-*Leishmania infantum* antibodies. The method was developed by using soluble crude antigens of *L. infantum* that were covalently immobilized on a self-assembled monolayer (SAM) formed by the binding of 11-mercaptoundecanoic acid (11-MUA) on a gold surface (SPR sensor chip). Consistent with its extensively use in recent decades, the use of thiols in the functionalization step still represents one of the most convenient, simple and flexible methods since it is versatile towards the interfacial properties of metals, oxides and semiconductors. Moreover, another advantage of these organized films is based on their ability to control the accessibility and orientation of bound molecules, which enables excellent control at molecular level [38,39]. The sensorgram in Fig. 2 shows the responses obtained from the assembly of the immunosensor to the detection of specific antibodies present in a diluted sample of canine serum and successive cycles of immunosensor regeneration are shown in the insert.

This work has made extraordinary contributions towards the advancement of biosensors. First, the proposed immunosensor showed a much higher sensitivity for the detection of VL antibodies (anti-*L. infantum*) in real samples than the ELISA assay. Second, real time interaction analysis with no previous probing requirement was achieved. Finally, it was also possible to perform successive cycles of sensor regeneration. Therefore, this study demonstrated for the first time the successful applicability of an SPR-based immunosensor to VL diagnosis.

However, there is still room for improvements. One of the factors that contributes to the limitations of conventional assays for VL detection is the form of the antigen used, since crude antigens or their soluble extracts are still employed in immunodiagnostics [40]. Nonetheless, recent studies show that the use of synthetic peptides or recombinant antigens, instead of crude antigens, improves the specificity of the tests for the diagnosis of VL, which significantly decreases cross-reactions with other diseases [41–44]. Despite the progress achieved in recent years, developing a 100% effective diagnosis for VL is still a challenge [43]. Consequently, the production of new *L. infantum* antigens by using recombinant DNA technology to generate recombinant proteins with high antigenic potential is a very promising area to improve diagnosis [42,45,46].

2.2. Evaluation via SPR of the viability of new recombinant proteins in immunoassays of the VL

Recombinant (r) proteins are developed by recombinant DNA technology and expressed in bacteria (the most common is the expression system using *Escherichia coli*) or other organisms. In recent decades, this method has become well established and widely used to generate proteins with different sensitivities and specificities for VL immunodiagnostics [43]. The antigenic proteins derived from *Leishmania* are now distributed into the following classifications: (1) proteins related to kinesin, notably rK39 and rK26 [47,48]; (2) heat-shock proteins, such as rHSP70 [49]; (3) enzymes, with emphasis on rLACK [50]; and (4) proteins with unknown functions, such as rA2 [51]. Another alternative used by different research groups as a methodology to produce antigens for immunodiagnostic tests consists of utilizing an ensemble of different peptide fragments to create an artificial protein (usually a chimeric protein). This type of protein carries different antigenic determinants, resulting in an increase in sensitivity for diagnostic tests. In this context, in the following studies our group used recombinant proteins to integrate the sensor recognition system in order to improve the analytical performance of the developed SPR-based immunosensors, especially their specificity [52]. Ten peptides derived from nine proteins of *L. infantum,* as promising antigens for use in serological VL diagnosis, were identified [53] and used to generate an artificial DNA fragment coding for a new recombinant chimeric protein (C10) [53]. The capacity of CP10 to identify infected, yet asymptomatic dogs (approximately 80%), was remarkable and it was very impressive considering the difficulty in detecting these cases by well-documented antigens [54]. With the intent of measuring the binding affinity between CP10 and specific VL antibodies, we developed SPR-based and quartz crystal microbalance (QCM)-based immunosensors for the detection of anti-*L. infantum* antibodies (Fig. 3). The low limits of detection found for SPR (LOD = 4.23 nmol L^{-1}) and for QCM (LOD = 4.61 nmol L^{-1}) demonstrate the viability of the SPR and QCM immunosensors for the diagnosis of VL. Additionally, quantitative analysis of the CP10 antigenic potential obtained from SPR and QCM identified a high binding affinity between CP10 and the anti-CP10 antibody (SPR: $K_D = 8.27 \times 10^{-10}$ mol L^{-1}; QCM: $K_D = 2.42 \times 10^{-10}$ mol L^{-1}), which quantitatively indicated the strong immunogenic character of this new recombinant chimeric protein. The results reported in this study, together with results acquired using ELISA for the detection of infected asymptomatic dogs, constitute strong evidence for the potential contribution of this novel protein in immunodiagnostics and, as a consequence, in control programs of VL.

Once the viability of the developed immunosensors for *in situ* evaluation of antigen-antibody interaction was determined, our next work turned towards the amplification of the recognition interface during the sensor construction step. For this purpose, the "*layer-by-layer*" method was explored using a thiol SAM (cysteamine) combined with dendrimer molecules [55]. Among several existing systems, the large and well-established family of dendrimers derived from polyamidoamine (PAMAM) stands out [56,57]. In this study, a 4th-generation dendrimer with 64 terminal amino groups (polyamidoamine – PAMAM(G4)) was used to construct a multivalent platform (PAMAM-SAM) (see schematic representation in Fig. 4).

In this study, the recognition biomolecule used to construct the immunosensor was a protein with unknown function in *L. infantum* (hypothetical C1 protein or C1 protein) [58]. Among the different classes found in *L. infantum*, the hypothetical proteins are interesting targets for research because of the little information regarding them and because of the identification of the high expression and reproducibility of these proteins in the evolutionary forms of *L. infantum* (amastigotes and promastigotes) [58,59]. According to Peacock et al. (2007), *L. infantum* is a diploid unicellular organism that has 36 pairs of chromosomes and approximately 8300 genes, of which 27 are species-specific [22], but from which only ten have predicted functions. Ten of

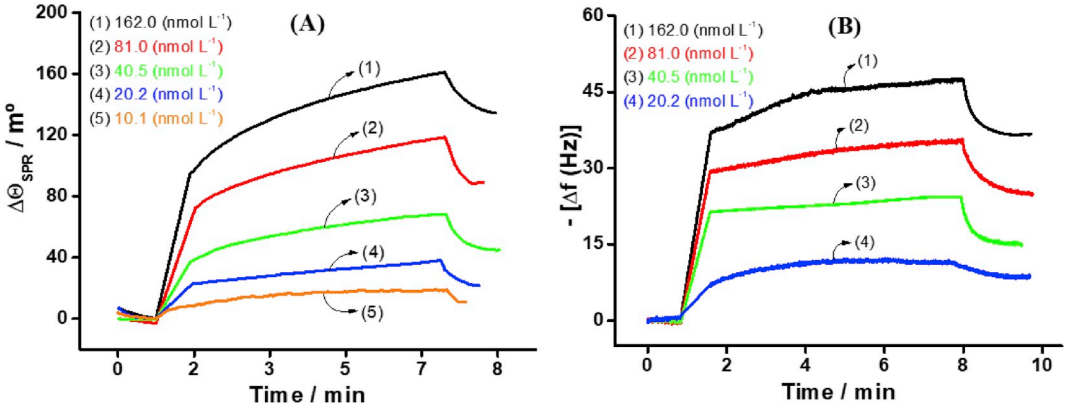

Fig. 3. SPR (A) and QCM (B) immunosensor curves showing the association and dissociation steps by the addition of different concentrations of antibody anti-CP10 (10.1; 20.2; 40.5; 81.0; and 162 nmol L^{-1}) over the CP10 protein immobilized on SAM/Au. Binding affinity between CP10 and the antibody anti-CP10 was SPR: $K_D = 8.27 \times 10^{-10}$ mol L^{-1} and QCM: $K_D = 2.42 \times 10^{-10}$ mol L^{-1}.
Figure reprinted from Ref. [52] with permission; copyright (2019) Bentham Science Publishers LTD.

these genes have predicted functions. Considering that 50% of the genes in the whole genome of *L. infantum* do not have an identified function, the choice of C1 protein as the focus for this study is an interesting and important investigation. Immunoassays showed that the hypothetical C1 protein from *L. infantum* was exclusively reactive with the serum of dogs infected with this parasite, while no reactivity with the serum of dogs infected with *Trypanosoma cruzi* was detected (Fonseca et al. (2014)) [58]. Furthermore, all the samples of asymptomatic dog serum were also detected by assays using the C1 protein, a result that is very promising when taking into account the restrictions against efficient diagnosis in these cases. Considering the high motivation to continue with this study, the immobilization of the recombinant C1 protein on a multivalent platform was performed to construct an SPR-based immunosensor for the detection of anti-*L. infantum* antibodies. The results showed that the immobilization of the C1 protein on the platform formed by the combination of a thiol SAM (cysteamine) and the PAMAM(G4) dendrimer caused an amplification of the SPR signal (Fig. 5), suggesting that there is a greater number of immobilized biomolecules since the tridimensional structure of the dendrimer molecules provides a broader surface area for interaction with the C1 protein. These findings indicate increased efficiency of the multivalent film used for the construction of the SPR immunosensor.

Based on the results found for the interaction of C1 protein with its specific IgGs, a kinetic study was proposed to elucidate the mechanism of the reaction between these biomolecules. The existence of two immunodominant sites in the protein for the binding of the antibody was suggested, with a global reaction consisting of two elementary steps. The values of the dissociation constant measured via SPR immunosensors for the first and second reactions ($K_{D1} = 6.79 \times 10^{-9}$ mol L^{-1} and $K_{D2} = 2.41 \times 10^{1}$ mol L^{-1}, respectively), as well as the K_D for the global reaction (K_{D1} x K_{D2}: 1.64×10^{-7} mol L^{-}), showed high binding affinity between the biomolecules, which demonstrates a favorable applicability of C1 protein to VL diagnosis. The high sensitivity of the proposed methodology was also demonstrated by the low limits of detection (LOD = 7.37 nmol L^{-1}) and quantification (LOQ = 7.83 nmol L^{-1}) obtained using the SPR-based immunosensor. Finally, samples of dog serum, either positive or negative for the infection of VL, were used to confirm the viability of the proposed SPR-based immunosensor. The results revealed that the SPR-based immunosensor allowed fast analysis that did not require probing to achieve sensitive and selective detection of anti-*L. infantum* antibodies.

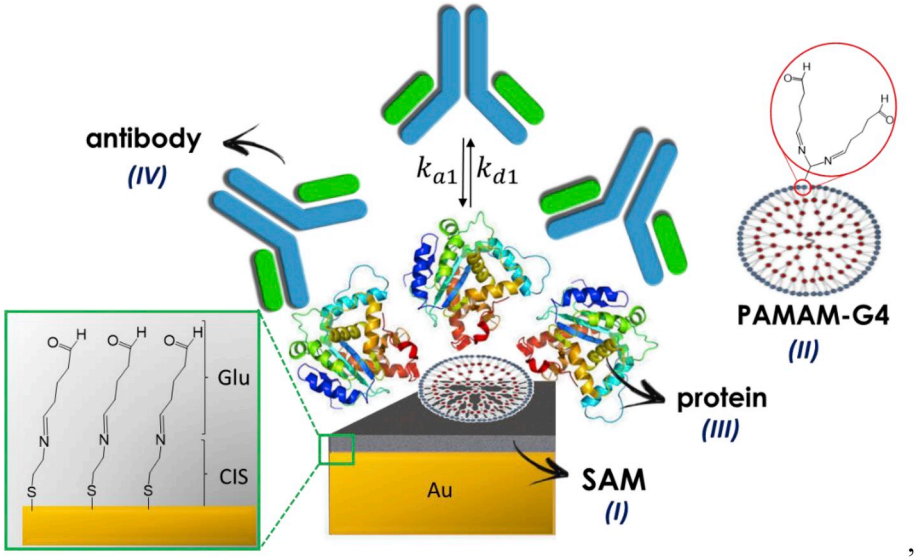

Fig. 4. Steps involved in the SPR immunosensor construction and evaluation (I) CYS-SAM formation on the gold; (II) formation of PAMAM(G4)/CYS-SAM; (III) Immobilization of the C1 protein. (IV) interaction between IgGs anti-C1 and the protein C1.

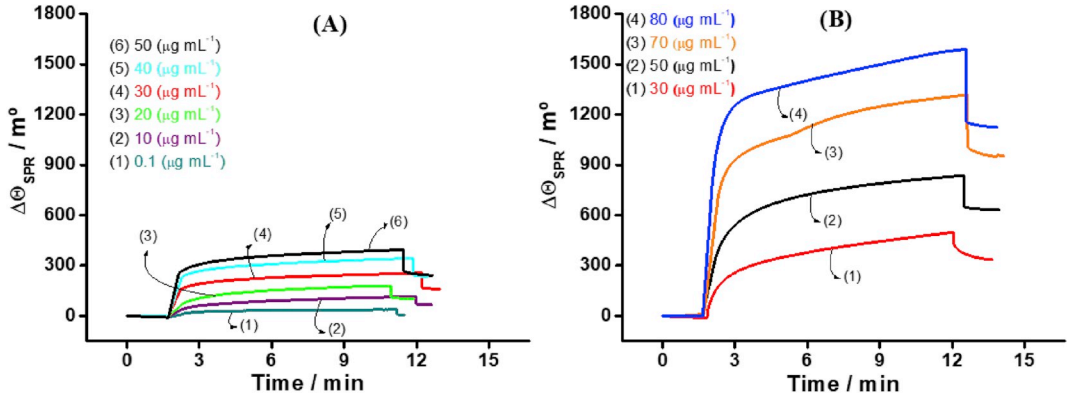

Fig. 5. SPR measurements. Sensorgrams showing the effective $\Delta\theta_{SPR}$ obtained for the addition of different concentrations of the recombinant protein C1. Immobilization of the protein over CYS–SAM/Au (A) and PAMAM(G4)/CYS-SAM/Au (B). Figure reprinted from Ref. [55] with permission; copyright (2019) Elsevier.

2.3. Other contributions of the SPR technique to visceral leishmaniasis diagnosis

Earlier studies on SPR showed possible uses of this technique for quantitative analysis of antibody or antigen-antibody binding [60]. Likewise, SPR can be used for the early diagnosis of parasite diseases, for the development of new medications for their treatment, and for the design of possible vaccines, and thus, it is very helpful to resolve this problem [61–63]. There are widespread possibilities for the technique that are likely to overcome the challenges Leishmaniosis sets up since SPR presents important information about selectivity, binding affinity and kinetics [60,61]. In 2014, Roy K. et al. [63] studied interactions of proteins from *Leishmania donovani* implicated in vaccine design using a disease model in which the parasite replicates inside the macrophages and probably in dendritic cells and in their intracellular cycle, *L. donovani* parasites can cause several defects in cellular homeostasis. The authors proposed as target the major histocompatibility complex peptide class II (MHC-II) since a MHC-II-restricted immune response might be essential to control the infection. In this case, the membrane was fixed on the LI sensor chip, and up to 2500 response units of normal and previously infected macrophages were immobilized on the chip. The analysis of the affinity of p-MHC-II for the APC membrane (plasma membrane-associated protein amino acids conserved in vertebrates) was carried out by varying the concentration of OVA peptides (restricted peptide epitope of ovalbumin) from 1 to 2000 nmol L^{-1}. The analyses of the equilibrium constants showed that MHC-II complex formation is more compromised in infected macrophages than in normal macrophages. The kinetic parameters were calculated based on a Langmuir 1:1 binding isotherm, and the values of k_{on} (association rate constant) and k_{off} (dissociation rate constant) were 67.3 mol $L^{-1}s^{-1}$ and 9.32 μs^{-1}, 5.6 mol $L^{-1}s^{-1}$ and 32.2 μs^{-1}, and 55.9 mol $L^{-1}s^{-1}$ and 10.2 μs^{-1} for $OVA_{323-339}$ with the normal macrophage, infected macrophage, and the 6-h infected macrophage, respectively, and 1.7 mol $L^{-1}s^{-1}$ and 192 μs^{-1} for $OVA_{scramble}$ with the normal macrophage, respectively. In conclusion, the k_{on} of the complex was approximately 12-fold slower in infected macrophages than in normal ones, and the k_{off} was 3.5-fold faster in normal macrophages than in infected ones. The values of the dissociation and association rate constants of the 6 h infected macrophages were close to those of the normal macrophages [63].

In 2017, S. Prakash et al. [64] reported studies using the SPR technique to investigate proliferating cell nuclear antigen (PCNA) of *Leishmania donovani* (LdPCNA). PCNA acts as a sliding clamp by supporting the replication and repair of DNA and is a potential target of modern antiprotozoan drugs because current treatments are based on toxic and low efficacy drugs such as Pentostam and amphotericin B. SPR was then employed to investigate the binding of LdPCNA to two peptides and two inhibitors at five different concentrations (between 0.2 μM and 3.2 μM) to determine their equilibrium binding constants. The two peptides were P1 141-Lys-Arg-Arg-Gln-Thr-Ser The Met-Thr-Asp-Phe-Tyr-Hia-152 from human cyclin kinase inhibitor and P2 338-Lys-Thr-Gln-Gly-Arg-Leu-Asp-Ser-Phe-Phe-Thr-Val-350 from flap endonuclease from *Leishmania donovani*. The small-molecule inhibitors used were (S)-4-(4-(2-amino-3-hydroxypropyl)-2-6-diiodophenoxy) phenol hydrochloride – ADPH, and N-(3-methylthiophene-2-carboxylcacid)-N'-((3-hydroxy-2-naphthalenyl)methylene)hydrazine - MCMH. Immobilization of LdPCNA on a CM-5 chip was performed using an amine coupling kit with a buffer (PBS at pH 7.4), and the activation was performed using a 1:1 mixture (v/v) of the immobilization reagents N-hydroxysuccinimide and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide. The rising curves indicated the binding of the compounds to the immobilized protein, and the dissociation constants for the four compounds were determined, indicating a 1:1 binding model and more affinity between the two peptides and one of the inhibitors than the other inhibitor used. The dissociation constants determined for the inhibitors ADPH and MCMH and the peptides P1 and P2 were 0.35 ± 0.09 μmol L^{-1}, 1.20 ± 0.08 μmol L^{-1} 0.29 ± 0.09 μmol L^{-1} and 0.37 ± 0.08 μmol L^{-1}, respectively. The results of this study can be a good starting model for the design of more potent inhibitors of LdPCNA [64].

2.4. Portable devices and recent strategies to enhance the sensitivity of SPR-based biosensors

The SPR biosensors discussed above are related to direct assays, which are based on the detection of the interaction between an analyte (target molecule) and a surface-functionalized biomolecule (receptor). This detection format requires a small number of steps, which is an advantageous feature of SPR-based assays. Typically, the optical sensors based on surface plasmon excitation can be divided into two categories: the propagating SPR (namely, SPR, discussed throughout the text) and localized SPR (LSPR) [65,66]. Both detection mechanisms are sensitive to changes within their associated plasmon decay lengths. SPR are usually excited on continuous metal thin films through prism couplers, diffraction gratings or wave guides, and the surface plasmon resonance can propagate along the metal-dielectric interface [65]. In turn, in LSPR the conduction electrons in metallic nanoparticles undergo collective harmonic oscillations under an applied electric field, which result in a dipolar response. Thus, the LSPR are nonpropagating surface plasmons excited on nanostructured metal surfaces, and the plasmon resonance can be adapted by their size, shape and composition [67]. Although LSPR sensors have much better spectral adaptabilities than SPR sensors, their sensitivities are orders of magnitude lower. In general, the main challenges for both SPR and LSPR sensors, as well as for electrical and mechanical sensors, are to detect low-molecular-weight (less than 400 Da) chemical and biological analytes under highly dilute conditions

[68]. For this reason, the sensitivities of these systems have been insufficient to detect low quantities of low-molecular-weight biomolecules, such as cancer biomarkers and numerous antigens, which are important for early-stage disease diagnosis [69].

To overcome this challenge in SPR sensors, through the rapid development of nanotechnology in the past few years, nanomaterials have been developed for enhancing the sensitivity of surface plasmon resonance sensors, which allowed the detection of biomolecules within the concentration range between pmol and amol. For these systems, the adopted strategy was based on nanomaterials, such as metallic nanoparticles (e.g., Au and Ag nanoparticles), magnetic nanoparticles, carbon-based nanostructures (e.g., graphene) [67]. The involved mechanism consists in the use of these materials to increase the sensitivity both of the sensor substrates and the amplification tags, which can be further combined to achieve improved SPR sensing performance [69].

It has been demonstrated that SPR sensitivity is intimately related to the excited electric field: the larger the electric field is, the more sensitive the SPR sensors are to the changes in its surrounding medium. Noble metal nanoparticles, especially gold nanoparticles (AuNPs), also called plasmonic nanoparticles, exhibit strong absorption in the visible and near-infrared wavelength regions and present a large electric field due to LSPR excited on the surface of the particles [67]. Therefore, coupling the LSPR with surface plasmon waves generated from a metal thin film on a conventional SPR sensor may be the largest field enhancement, increasing the sensitivity of the sensor. The ease of functionalizing the surface of metallic nanoparticles with numerous functional molecules allows modification of the surface coverage and binding efficiency of target molecules on the surface of the particle for specifically interacting with the sensing film [18]. The sandwich detection format is another strategy commonly employed for improving the sensing of lower-molecular-weight biological compounds. Typically, the targeted analytes flow over an SPR sensing film that has been previously modified with capture receptors followed by flowing a solution of AuNPs functionalized with a detecting unit. In this way, the sandwich format is formed with targeted analytes between the AuNPs and the sensing film [70].

In another very interesting approach, functionalized magnetic nanomaterials (MNPs), such as Fe_3O_4 nanoparticles, are employed for signal amplification of SPR sensors. For these systems, a magnetic field is generally applied to form a dense layer with a strong refractive index on the metallic sensing film that leads to an increase in the SPR signal. Additionally, the applied magnetic field increases the kinetic efficiency of biomolecule mass transport. Compared with that of the plasmonic nanoparticles, the production cost of the MNPs is lower, and the step for initial receptor immobilization onto the SPR sensing film is not needed [71].

Discussion about the use or not of the mentioned nanomaterials is something that should be taken into account in accordance with the desired application. Through this discussion, it is possible to verify the efficiency of the AuNP and MNP nanomaterials for the considerable increase in the sensitivity of the sensors of SPR. On the other hand, one of the great advantages of the SPR technique is that it allows direct detection of the interaction between analyte and receptor, which greatly simplifies the method. In this context, the use of nanomaterials is justifiable when it is desired to detect molecules with smaller molar masses or if very low detection limits are required for the system being studied. Therefore, depending on the application, the direct assay using simpler methodologies for modification of the SPR sensing substrate may be sufficient, in which case there is no need to make the method more laborious and costly through the use of AuNP and MNP nanomaterials.

Another factor that should be taken into account in relation to SPR biosensors is the use of the on-site analysis technique [70]. Termed point-of-care (POC) diagnostics, this assay method enables rapid disease detection to make an instantaneous clinical decision, which facilitates early treatment. A POC diagnostic must be affordable, sensitive, specific, user-friendly, rapid, robust and equipment-free [72]. However, the size and cost of traditional SPR-based sensors are viewed as enormous difficulties for on-site diagnosis. Recent strategies have shown the real possibility of confining light at dimensions smaller than the incident wavelength, which has opened up new routes for integrated nanophotonic and optoelectronic devices [73]. These characteristics make plasmonic platforms suitable for low-cost POC diagnostic devices, mainly due to their integration into microfluidic systems and high sensitivity to changes in the refractive index at metal-dielectric interface proximities [74]. Despite the extensive research efforts on SPR biosensing, the detection of small analytes or analytes dispersed in solutions at very low concentrations, in both traditional and miniaturized SPR devices, remains challenging [75]. The limitations associated with LSPR for building POC devices have motivated other strategies to enhance SPR sensing. Thus, one strategy is to amplify the SPR signal using magnetic nanoparticles, metamaterial surfaces, and magnetooptical (MO) structures [74]. Such developments should benefit from the various features of plasmonics, including label-free, nondestructive, high sensitivity, and high miniaturization capabilities. The combination of quantum plasmonics with metamaterials could provide increasing phase change sensitivity for improved limits of detection. In fact, plasmonic lab-on-a-chip biosensing devices have already been developed [74]. It is very possible that research on next-generation POC diagnostics is focused on the development of portable smart devices towards personalized healthcare monitoring and management [76,77].

Although numerous applications demonstrate the feasibility of using nanomaterials to amplify the signal in SPR sensors, no study has been performed using the nanomaterials discussed in SPR-based biosensors dedicated for visceral leishmaniasis diagnosis.

3. Conclusions and future trends

Plasmonics is a well-established field of research and the SPR technique is one of the main tools for biomolecular interaction studies. The analysis performed in an SPR-based biosensor can be used for the acquisition of information in real time without needing chemical or biological probes, which makes it possible to assess kinetics aspects of interaction events in diversified systems. The SPR technique has been used for diagnostic purposes and for the elucidation of biological events that take place as a result of biomolecular interactions (such as protein-protein, enzyme-substrate, peptide-membrane, DNA or RNA-protein, bacteria, protozoa, and viruses).

We believe this is an excellent time to draw the attention of the world population towards the importance of the insertion of new technologies, both as new methods of diagnosis for neglected tropical diseases and to evaluation of new antigenic candidates to be explored in immunodiagnostics. It is important to emphasize that although the vast majority of visceral leishmaniasis (VL) infections are still concentrated in India, Brazil, Bangladesh, Nepal and Sudan, studies show an increase in the VL cases worldwide, which is a matter of concern considering the expected climate change in the near future in Europe and in other regions situated in temperate zones. Another point to highlight is that a recent Nobel Prize in Physiology and Medicine, 2015, was related to neglected diseases. William Campbell and Satoshi Omura whom created new therapies for verminoses, and Youyou Tu, who developed a new therapy against malaria.These factors increase our expectation of greater investments from governments and companies in this area.

Concerning the results obtained from the studies involving SPR and VL, the developed biosensors allowed detection in real time and more sensitive analyses of LV antibodies compared to the analyses of routines used in clinical laboratories. In addition, the viability of the kinetic and thermodynamic studies performed via the SPR immunosensors quantitatively demonstrated the high binding affinity between novel biomolecules, such as recombinant proteins against VL antibodies. It was another very important aspect to be considered. For all the reasons described, it is possible to safely affirm that new and well-established

methodologies were developed as immunodiagnostics for VL and in the elucidation of biochemical mechanisms and evaluation of new antigenic candidates to be used in immunodiagnostics. However, a considerable disadvantage of the SPR technique is the high price of the commercial device. Therefore, a very promising perspective is centered on the application of these methodologies in miniaturized and low-cost devices, which would allow the real application in the field (endemic areas of LV, for example) of SPR biosensors. In this context, we strongly believe that studies focused on the use of nanomaterials (AuNPs and MPNs), miniaturization and the design of multisensory arrays should be explored for on-site diagnosis involving neglected tropical diseases.

Acknowledgements

The authors thank the São Paulo State Research Foundation (FAPESP, 2017/26058-6, 2017/26131-5, 2014/50867-3 and 2013/22127-2) and the National Institute of Science and Technology in Bioanalytics (INCTBio) for financial support and fellowships.

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