Design and mechanisms of antifouling materials for surface plasmon resonance sensors

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ABSTRACT

Surface plasmon resonance (SPR) biosensors have many possible applications, but are limited by sensor chip surface fouling, which blocks immobilization and specific binding by the recognizer elements. Therefore, there is a pressing need for the development of antifouling surfaces. In this paper, the mechanisms of antifouling materials were firstly discussed, including both theories (hydration and steric hindrance) and factors influencing antifouling effects (molecular structures and self-assembled monolayer (SAM) architectures, surface charges, molecular hydrophilicity, and grafting thickness and density). Then, the most recent advances in antifouling materials applied on SPR biosensors were systematically reviewed, together with the grafting strategies, antifouling capacity, as well as their merits and demerits. These materials included, but not limited to, zwitterionic compounds, polyethylene glycol-based, and polysaccharide-based materials. Finally, the prospective research directions in the development of SPR antifouling materials were discussed.

Statement of Significance

Surface plasmon resonance (SPR) is a powerful tool in monitoring biomolecular interactions. The principle of SPR biosensors is the conversion of refractive index change caused by molecular binding into resonant spectral shifts. However, the fouling on the surface of SPR gold chips is ubiquitous and troublesome. It limits the application of SPR biosensors by blocking recognition element immobilization and specific binding. Hence, we write this paper to review the antifouling mechanisms and the recent advances of the design of antifouling materials that can improve the accuracy and sensitivity of SPR biosensors. To our knowledge, this is the first review focusing on the antifouling materials that were applied or had potential to be applied on SPR biosensors.

1. Introduction

Surface plasmon resonance (SPR) biosensors are optical sensors based on the excitation of surface plasmons [1]. Since Nylander and Liedberg et al. [2,3] applied SPR techniques to gas detection and biosensing in 1983, this technology has experienced considerable development and become a useful tool for the characterization and quantification of biomolecular interactions.

The technology has been studied extensively, leading to the commercialization of many SPR apparatus. Since SPR biosensors enable sensitive, label-free, real-time, multiplexed, and high-throughput detection, they are powerful tools useful in many scientific fields, such as antigen-antibody interaction monitoring, immunological identification, medical diagnostics, drug screening, proteomics, environmental monitoring, and food safety and security [4,5]. Recently, SPR biosensors have been applied to several highly complex systems. Table 1 lists some application fields of SPR biosensors.

The fundamental principle of SPR biosensors is the conversion of changes in the refractive index (RI) caused by molecular binding into resonant spectral shifts [24,25]. The adsorption or desorption of nonspecific matter, such as proteins, lipids, cells and

Table 1
Application fields of SPR biosensors.

Application fields	Detection objects	Refs
Biomolecular interaction monitoring	Protein-protein, antigen-antibody, film-drug interactions	[6–11]
Food testing	Food additives, pesticide residues, pathogens and other toxic substances	[6,12–15]
Environmental monitoring	Organochlorine pesticides, PCBs and real-time monitoring of the growth of toxic algae in seawater	[16,17]
Medical diagnosis	Hepatitis B virus, markers of cancers, Alzheimer's psychosis	[18–23]

microorganisms, interferes with RI changes, and consequently disrupt the output signal. This effect is referred to as "fouling" [26]. In SPR detection, particularly in multi-component system analyses, surface fouling of SPR sensor chips is ubiquitous and troublesome, as it related closely to the accuracy and sensitivity of quantitative measurements [27]. For example, the total protein concentration in human blood is 60–80 g/L, and both proteins and blood cells are easily adsorbed onto SPR sensor chips during the detection of specific analyte in human blood. This generates large noise signals, interferes with the interactions between recognition elements and analytes, and inhibits the recognition of very low-concentration analytes [28,29]. Therefore, to suppress nonspecific adsorption on the SPR sensor chip surface, the design and development of materials that resist fouling is necessary to improve the accuracy and sensitivity of SPR biosensing.

Considering the significance of antifouling materials, in this review, we first discuss antifouling mechanisms, including theories and influencing factors, then review the most recent advances (especially those in the past five years) in antifouling materials and applications thereof to SPR biosensors, and finally discuss perspective research and applications of antifouling materials in SPR biosensor.

2. Mechanisms of antifouling surfaces

2.1. Theories of antifouling surfaces

2.1.1. Hydration

Hydration layers, which attach tightly to chip surfaces, are critical for antifouling, as they create a physical energy barrier that inhibit the adsorption of proteins and other contaminants [30] (Fig. 1). Akdogan et al. [31] found that a tightly bound hydration layer could resist the adhesion of fouling onto silica surface; and the removal of hydration layer by hydrophobic residues in mussel foot proteins would result in the protein adhesion to the silica surface. Besseling et al. [32] interpreted the resistance of the hydration layer to protein adsorption using thermodynamic theories. They indicated that interactions between water molecules and the terminal functional groups of proteins increase the system entropy, consequently preventing the protein adsorption onto the chip surface.

The hydration layer is mainly induced by hydrogen bondings or electrostatic forces generated from ion solvation [30]. The former contributes to the antifouling properties of long-chain hydrophilic polymers or short-chain molecular SAMs. When hydrophilic materials are exposed to bulk water, water molecules penetrate the interspaces among the polymers or the SAMs, forming hydrogen bonds that create the hydration layer. Meanwhile, electrostatic forces emerge in zwitterionic polymers, including polypeptides, betaine and its derivatives, and phosphorylcholine and its derivatives [33]. These materials combine with water by ionic solvation to form a hydration layer resistant to protein adsorption and cell adhesion. Some studies have shown that surface hydration depends on the physiochemical properties of antifouling materials, such as molecular weight, surface charge [34], surface chemical components, and the geometric properties of the material

assembly on the chip surface, including thickness, density, and conformation or architecture [35–37].

2.1.2. Steric hindrance

In long-chain polymers, steric hindrance, caused by soft long chains, is another factor contributing to resistance to nonspecific protein adsorption. The steric hindrance hypothesis indicates that, when proteins approach an antifouling surface modified with long-chain polymers, the proteins "squeeze" the polymer, which generates steric hindrance and higher entropy that discourage the adsorption to the surface. Jin et al. [38] summarized and developed models explaining the steric hindrance to effect on the adsorption of molecules to surfaces. Long-chain poly(ethylene glycol) (PEG) is a common kind of "gold standard" antifouling material [39]. Emilsson et al. [40] grafted PEG brushes onto gold surfaces at room temperature (Fig. 2) and found that increases in the grafting density and brush height caused decreased protein adsorption, indicating that steric hindrance was critical to the antifouling properties of the PEG.

2.2. Factors influencing antifouling effect

Nonspecific molecular adsorption onto a surface is influenced by the charge and hydrophilicity of the surface molecules, as well as the properties and microenvironments characterized by interfacial pH and surface roughness. For example, Rodriguez et al. [41] found that acidic interfacial pH values promoted the adhesion of mussel foot proteins to surfaces. For antifouling or the prevention of such adhesion, similar factors must be influential. In the following section, the main factors influencing surface antifouling property, such as molecular conformation, SAM architecture, surface charges, molecular hydrophilicity, and grafting thickness and density are discussed (Fig. 3).

2.2.1. Molecular structures and SAM architectures

Certain molecular structures and SAM architectures formed by antifouling materials offer inhibition of protein adsorption. For example, some self-assembled layers consisting of double-helix chain molecules have better protein-adhesion resistance than layers of other molecular conformations, because molecules with such regularly defined secondary structures tend to form densely packed uniform monolayers that hinder protein adsorption. Grunze and colleagues [29,45–47] found that the antifouling capacity of methoxyl-terminated oligo(ethylene glycol) (OEG) SAMs depended largely on the conformation of the OEG polymer chains. OEG SAMs formed on a gold surface with helical conformation could resist protein adsorption; OEG SAM formation on a silver surface caused conformational changes, which removed the protein adsorption resistance. Through computational modeling, they found that helical SAMs could bind with more water molecules than those containing OEG with the changed conformation. Furthermore, Nowinski et al. [48] synthesized a novel all-in-one oligopeptide with triple functional domains for surface anchoring, ultra-low fouling, and molecular recognition (Fig. 4). They found that oligopeptides with alternative lysine (K) and glutamic acid (E) (EKEKEKE) could form regular secondary structures on gold