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Thin hydrogel films based on lectin-saccharide biospecific interaction for label-free optical glucose sensing

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ABSTRACT

Concanavalin A (Con A) has been widely used as glucose recognition element in glucose sensors, however, these sensors typically detect glucose by fluorescence, and suffer from laborious labeling processes. Here a new label-free optical Con A-based glucose sensor was designed. The sensor uses Con A-containing thin hydrogel films as sensing material and Fabry-Perot cavity simultaneously, which were fabricated by layer-by-layer assembly of Con A and dextran, using lectin-saccharide biospecific interaction as driving force. These films display Fabry-Perot fringes on their reflection spectra, from which optical path length of the films can be calculated. The films swell upon addition of glucose, which causes a shift of Fabry-Perot fringes on the reflection spectra of the film, from which the glucose concentration can be reported. The glucose-induced swelling is reversible, and the increase in optical path length increases linearly with glucose concentration over a wide range of glucose concentration. The sensor works well at physiological temperature, pH and ionic strength. Other sugars, which may present in blood, do not interfere with glucose detection, because of their very low concentrations in the blood. Particularly, unlike other hydrogel-based sensors, this sensor responds quite fast, because the hydrogel films are very thin. The new sensor may have potential for real time, continuous glucose monitoring.

1. Introduction

Diabetes mellitus is one of the largest health concerns in the world. It was well-documented that tight glucose control would reduce the complications of diabetes [1]. For better glycemic control, frequent blood glucose testing is needed to detect hyper- and hypoglycaemia, and to adjust treatment accordingly to maintain long-term near-normoglycaemia. For this purpose, various glucose sensors were designed. Usually, glucose oxidase, boronic acids, or concanavalin A (Con A) were used as glucose recognition elements in these sensors.

Con A is a typical lectin protein found in Jack beans. Under physiological conditions, Con A exists as a tetrameric protein with a molecular weight of 104,000. Each of the four subunits has one mannose- or glucose-specific binding site. The ability of Con A to specifically bind glucose has been widely exploited to design glucose sensors using various signal-transducing mechanisms, including electrochemical [2], mechanical [3,4], and optical ones [5–10]. For example, Sato et al. [2] designed an electrochemical glucose sensor in which glassy-carbon electrode was modified with layer-by-layer deposited films of Con A and ferrocene-appended glycogen. The peak current in the cyclic voltammogram decreases with increasing glucose concentration in the solution. Ballerstädt and Ehwald [3] detected glucose concentration by measuring the glucose-induced changes in the viscosity of a homogeneous aqueous dispersion of dextran and Con A. Sato and Anzai [10] determined glucose concentration based on the fact that glycogen quenches the fluorescence of fluorescein isothiocyanate-labeled Con A (FITC-Con A) as a result of the formation of FITC-Con A/glycogen complex and the fluorescence can be restored upon addition of sugars. As for fluorescent glucose sensors, Förster Resonance Energy Transfer (FRET) has been identified as an ideal transduction mechanism [7]. Many other Con A-based glucose sensors were designed using this mechanism [5–9]. Very recently, Zhang et al. [5] designed a nanostructured glucose sensor in which the FRET pair, including the donor, CdSe/ZnS quantum dots, and the acceptor, dextran-binding malachite green, was conjugated to Con A. Addition of glucose will displace the dextran from Con A and thus restore the quenched emission of quantum dots.

Compared to other sensors, optical sensors have a lot of advantages.

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They are immune to electromagnetic interference, easy to miniaturize, and require low or no power supply [11,12]. However the fluorescence-based optical sensors require laborious labeling processes. The fluorophores are usually photochemically instable. In addition, in vivo fluorescence measurements may be complicated by background fluorescence, low fluorophore solubility and oxygen interference [13].

Here we reported a new optical glucose sensor using Con A-based hydrogels as sensing materials. Hydrogels are three-dimensional networks of hydrophilic polymers which swell but do not dissolve in water. Previously various glucose-sensitive hydrogels were constructed from Con A and a glycopolymer [14–22]. These hydrogels are characteristic for reversible lectin–saccharide crosslinking, which can be disconnected by the addition of free glucose. As a result these hydrogels exhibit various glucose-responsive behaviors, including reversible gel-sol phase transition [21], changes in permeability [19,22] and/or swelling degree [15,17,20]. This property has been widely exploited for self-regulated insulin release [16–19,21,22]. Here this property was exploited to design optical glucose sensors. For this purpose, thin hydrogel films were fabricated by layer-by-layer assembly of Con A and dextran based on specific lectin-saccharide recognition. It is noteworthy that Con A/dextran LBL films and other Con A-containing LBL films were reported previously, however, glucose-induced swelling behavior of these films was not revealed [8,23–29]. We chose to report the glucose-induced swelling of the gel films by the shift of Fabry-Perot fringes in its reflection spectra (i.e., oscillations in the spectra, a result of thin-film interference) [30]. Like other optical transducing methods based on light interference or diffraction [12,13,31–34], this method is label-free. However this method does not require the introduction of ordered structures. Instead, this method uses the hydrogel film itself as Fabry-Perot cavity [11,30,35]. More importantly, because the hydrogel films were very thin, a fast response was achieved, making the new sensor potential for true applications [30].

2. Material and methods

2.1. Materials

Concanavalin A extracted from Jack beans (Con A, type V, $M_w \approx 104{,}000$) was purchased from Heowns. Dextran (Dex, M_w 20 K, 40 K, 70 K, 150 K, and 250 K), D-fructose and dimethyldichlorosilane (99%) were purchased from Aladdin. Tris-HCl buffer, D-glucose, D-sucrose, D-galactose, D-xylose, D-ribose were purchased from local providers. All chemicals were of analytical grade and were used without further purification.

2.2. Preparation of Con A/Dex hydrogel films

The hydrogel films were fabricated by layer-by-layer assembly using silicon wafers as substrates. Before use the substrates were first cleaned in boiling piranha solution (3: 7 v/v H_2O_2—H_2SO_4 mixture), rinsed thoroughly with deionized (DI) water and dried. Then the substrates were treated in dichlorodimethylsilane (10% solution in toluene) overnight at room temperature, washed with toluene, acetone, and distilled water, and finally dried in vacuum. To assemble the Con A-dex films, the silylated substrates were immersed in a Con A solution (0.5 mg mL^{-1}, in 0.1 M pH7.4 Tris-HCl buffer containing 1 mM $MnCl_2$ and 1 mM $CaCl_2$) for 30 min to deposit the first layer of Con A [24]. After being rinsed in water for 10 min to remove any weakly adsorbed Con A, the substrates were immersed in a dextran solution (1 mg·mL^{-1} in 0.1 M pH 7.4 Tris-HCl buffer) for 30 min to deposit dextran through the biological affinity between Con A and glucose residues in dextran. The alternate deposition cycle was repeated to fabricate the multilayer films. The resultant film is denoted as "$(Con\ A/Dex)_n$", which means the film is fabricated by repeating the alternate deposition cycle for n times and has a bilayer number of n. Unless otherwise specified, the solution temperature was maintained at 25 °C.

2.3. Swelling properties of the hydrogel films

Reflection spectra of the hydrogel films were measured using an AvaSpec-2048 fiber optic spectrometer. The optical path length (OPL) of the hydrogel films were calculated from the positions of the Fabry-Perot fringes on the reflection spectra according to the following equation: [36,37]

$$\mathrm{OPL} = n_e \cdot \theta = \frac{1}{2(1/\lambda_p - 1/\lambda_{p+1})} \quad (1)$$

where λ_p and λ_{p+1} are two adjacent wavelengths for which the absorbance is maximal, n_e the refractive index, and θ the film thickness.

To determinate the swelling degree (SD) of a film, the OPLs of the film in both dry and swollen states were measured. SD was then calculated using the following equation:

$$SD = \frac{\mathrm{OPL_s} - \mathrm{OPL_d}}{\mathrm{OPL_d}} \quad (2)$$

where $\mathrm{OPL_s}$ and $\mathrm{OPL_d}$ are the OPL of the swollen and dry films, respectively.

To measure the glucose-induced swelling degree of a film, it was immersed in Tris-HCl buffer containing 1 mM $MnCl_2$ and 1 mM $CaCl_2$. A predetermined amount of glucose was then added to the solution. The changes in the swelling degree of the film were followed by its reflection spectra.

3. Results and discussion

3.1. Fabrication of Con A/Dex hydrogel films

The Con A/Dex hydrogel films were fabricated via layer-by-layer assembly of Con A and Dex. For this purpose, silicon slides were dipped into Con A and Dex solution alternately. Before use the substrates were treated with dichlorodimethylsaline to make a hydrophobic surface, as Anzai et al. [24] found that Con A could deposit onto a hydrophobic surface irreversibly. In the following dipping process, Dex and Con A were deposited onto the substrate alternately due to the biospecific lectin-saccharide interaction between Con A and Dex.[8,23–29] In this way, thin films of Con A/Dex were fabricated.

Previously, the growth of Con A-containing LBL films were followed using quartz crystal microbalance [23,24,28,29,38] or UV–vis spectrum [24–26]. Instead, here we used Fabry-Perot fringes on the reflection spectra of the films to study the film growth [36]. As shown in Fig. 1A, the reflection spectra of the Con A/Dex films display oscillations, i.e., Fabry-Perot fringes. These fringes stem from the interferences between beams reflected at the air-film and film-substrate interfaces [36,37,39]. From these fringes, the film thickness θ and/or the optical path length ($\mathrm{OPL} = n_e \cdot \theta$, where n_e is the refractive index) can be easily calculated according to Eq. (1). It is noteworthy that only when the films are thick enough, can Fabry-Perot fringes be observed from their reflection spectra [36]. The previously reported Con A-containing LBL films were too thin to observe these fringes [23,24,27]. In the present case, distinguished Fabry-Perot fringes were observed from films with a bilayer number larger than 20, but not from thinner films (Fig. 1A).

Fig. 1B shows the calculated OPLs as a function of the bilayer number. A linear relationship was found between the calculated OPL and the bilayer number, suggesting equal amount of film materials was deposited onto the substrate in each dipping cycle. A linear growth pattern was previously reported for other LBL films assembled from Con A and polysaccharides, including glycogen [23,25,26] and dextran [38], or glycoproteins [24].

Fig. 2 and Fig. S1 show the effects of various factors on the film growth. Despite of the changes in experimental conditions, a linear growth pattern was observed in all the cases, indicating that the film growth is regular and reproducible from layer to layer under all the experimental conditions. Fig. 2A and Fig. S1A show that the film grows

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