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Responsive principles and applications of smart materials in biosensing

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ABSTRACT

Biosensing is a rising analytical field for detection of biological indicators using transducing systems. Smart materials can response to external stimuli, and translate the stimuli from biological domains into signals that are readable and quantifiable. Smart materials, such as nanomaterials, photonic crystals and hydrogels have been widely used for biosensing purpose. In this review, we illustrate the incorporation of smart materials in biosensing systems, including the design of responsive materials, their responsive mechanism of biosensing, and their applications in detection of four types of common biomolecules (including glucose, nucleic acids, proteins, and enzymes). In the end, we also illustrate the current challenges and prospective of using smart materials in biosensing research fields.

1. Introduction

Biosensing, a rising analytical field for detection of biological indicators using transducing systems [1]. These transduction mechanisms can translate biological variations into optical, thermal, electrical or electrochemical signals that are readable and quantifiable [2]. Biosensing is abundantly applied for detection of various biological targets such as small biomolecules (e.g., uric acid, H2O2, glucose), biomacromolecules (e.g., nucleic acids, peptides, proteins, enzymes), cells, bacteria, and viruses [3–7]. Biosensors with good selectivity, high sensitivity and fast response have broad prospects in clinical testing of biological indices and for the treatment of various diseases [1].

Smart materials are a class of materials that can respond to external stimuli such as pH, temperature, moisture, electric or magnetic fields, light, chemical compounds or bio-stimuli [8]. Smart materials, such as hydrogels, nanomaterials (e.g., gold nanoparticles (AuNPs), quantum dots (QDs), carbon nanotubes (CNTs), graphene) have been widely used for applications in biosensing [8–10]. In addition, photonic crystals (PCs), periodic micro or nanostructures that can control the reflection of light [11,12], provide excellent platform for biosensing with visible readout to report the target analytes [13,14]. Moreover, molecularly imprinting polymers (MIPs), a class of materials with special recognition site to bind with the imprinted molecules [15], have been developed for detection of various biomolecules such as proteins and enzymes [16–18], based on the responsive changes in refractive index and volume of MIPs. The incorporation of smart materials into biosensing platforms is promising for rapid, sensitive, reliable and user-friendly diagnostics [9, 10]. Especially, sensitive materials, such as electrochemical sensors [19, 20], optical sensors [21–23], thermal sensors [24], piezoelectric sensors [25], impedimetric sensors [26] and interferometric biosensors [27], have been widely employed as diagnostic platforms.

In this review, we will discuss the recent incorporation of smart materials in biosensing platforms for detection of four types of common biomolecules, including glucose, nucleic acids, proteins, and enzymes. We highlight the state-of-the-art advances of smart materials-based biosensors, including the design of materials, their responsive principles of sensing, and their applications of target detections. We also illustrate the current limitations and prospective of using smart materials in biosensing research fields.

2. Smart materials for sensing of glucose

Glucose is an indispensable energy source for the metabolism in the body, blood glucose must maintain in certain level to sustain the living of organs and tissues in the body, and abnormal blood glucose levels may cause many diseases such as obesity, diabetes, and cancers [28–30]. Therefore, reliable detection of blood glucose is very important. Glucose detection systems generally use the glucose-sensing elements such as enzymes, glucose binding protein (GBP), or phenylboronic acid (PBA) for signal transduction [31].
Enzyme-based glucose sensing involves enzymes such as glucose dehydrogenase or glucose oxidase (GOx) as glucose-responsive elements [32]. GOx can specifically catalyze glucose in the presence of oxygen, to produce gluconic acid and hydrogen peroxide ($\text{H}_2\text{O}_2$) (equation (1)). The reaction products, including both of gluconic acid and $\text{H}_2\text{O}_2$, can be used to determine the glucose levels.

$$\text{Glucose} + \text{O}_2 + \text{H}_2\text{O} \xrightarrow{\text{GOx}} \text{Gluconic acid} + \text{H}_2\text{O}_2$$  (1)

Benefiting from $\text{H}_2\text{O}_2$ generated in glucose reaction (equation (1)), Zhang and coworkers developed an intelligent zwitterionic hydrogel that can simultaneously monitor pH and glucose levels in diabetic wounds [33]. They encapsulated GOx and horseradish peroxidase (HRP) into zwitterionic poly-carboxybetaine (PCB) hydrogel to achieve high sensitivity to glucose (Fig. 1a). GOx and HRP embedded in the hydrogel catalyzed the glucose oxidation to generate fluorescent product of dichlorofluorescein (DCF) (Fig. 1a). Therefore, the fluorescence intensity
of DCF had a linear relationship with glucose concentrations from 0 to 10 mM (Fig. 1b). This intelligent hydrogel permit the evaluation of glucose levels in wound milieu in mice, and has great applications in wound care.

Benefiting from the acidic microenvironment generated in the glucose reaction (equation (1)), Lei and coworkers developed a smart hydrogel for visualization of glucose both in vitro and in vivo [34]. Gelatin-methacrylamide (GelMA), a hydrogel that can be quickly photo-crosslinked, and carboxymethyl cellulose modified with hydroxyethyl acrylate (CMC-pHEA), a pH-responsive hydrogel, were crosslinked together to obtain the GelMA/CMC-pHEA composite hydrogel. The composite hydrogel showed pH responsive capacity because of the pH responsiveness of CMC-pHEA component (Fig. 2a–b). The pH varied in the GOx-catalyzed glucose reaction (equation (1)), therefore resulted in different swelling ratio of the composite hydrogel (Fig. 2c–d). In high glucose concentrations where low pH value obtained, the hydrogels swelled less, and showed a small shape with strong...
fluorescence intensity (Fig. 2c–d). In normal glucose concentrations where high pH value obtained, the hydrogels swelled more, and exhibited a large shape with weak fluorescence intensity (Fig. 2c–d). This responsive hydrogel permits a rapid visualization of glucose in physiological levels both in vitro and in vivo.

In addition to enzymes, some small molecules which have some affinity to glucose are commonly used for detection of glucose. Among them, PBA and its derivatives are commonly used as the recognition agents for glucose [35–38], taking the advantage that PBA and its derivatives are able to reversibly bind with the adjacent diols of glucose [39, 40]. This property of PBA was widely incorporated into smart hydrogels for biosensing of glucose [35, 36, 41]. For instance, Yetisen and coworkers created a hydrogel optical fiber composed with a core and a cladding [42]. They covalently incorporated 3-acrylamidophenylboronic acid (3-APBA) molecule in the core of the hydrogel fiber (Fig. 3a). After glucose diffused into the fiber, the complexation of glucose with 3-APBA at the core of the hydrogel fiber increased the osmotic pressure of the system (Fig. 3b–c), affecting the refractive index (RI) of light propagating through the hydrogel fiber (Fig. 3b–d). Therefore, the intensity of transmitted light through the hydrogel fibers can reflect the glucose concentrations (Fig. 3a–d). This hydrogel fiber has good biocompatibility, excellent flexibility, and can be easily implanted for monitoring glucose concentrations in real time.

Moreover, the above system containing glucose-responsive principles can be further combined with PCs [43, 44], to construct a structure-color-based sensing system for naked-eye visualization of the analytes [45–47]. Asher and co-workers first integrated PCs within hydrogels to regulate photonic band gaps and to achieve intelligent chemical sensing [48], then many biosensors with PC structures have been reported. For example, Zhao and coworkers developed a novel optical glucose sensor based on inverse opal hydrogels [49]. They used 3-APBA as a functional monomer and ethylene glycol dimethyl acrylate (EGDMA) as a cross-linking agent to prepare the inverse opal hydrogels (Fig. 4a–c). The concentration changes of glucose solutions can be converted to visual signals of the hydrogel from green to red (Fig. 4d). Moreover, the hydrogel sensors could detect glucose with reusability based on the intuitive structural colors (Fig. 4e). This system offers a fast and easy detection of glucose without the use of complex analysis instrument.

Besides the above responsive hydrogel systems for glucose sensing, the burgeoning nanotechnology also offers a great opportunity to develop glucose sensors due to the special properties of nanomaterials. There are many nanomaterial-based optical assays for glucose sensing [50], including QDs [51], AuNPs [52, 53], gold nanorods (AuNRs) [54], multiwalled carbon nanotubes (MWNTs) [55], and molybdenum disulfide (MoS2) nanosheet [56]. For instance, Sun and coworkers integrated sugar-responsive copolymers with AuNPs for their application in colorimetric glucose sensing [52]. They used a sugar-responsive copolymer, 3-(acyryloyl-thiolureido)-phenylboronic acid (PATPBA) copolymerized with N-isopropylacrylamide (PNIPAAm) (PATPBA-co-PNIPAAm), to modify the surface of AuNPs (Fig. 5a). Because PNIPAAm is temperature responsive, the prepared AuNPs aggregated at 37 °C in the solution without glucose (Fig. 5a–b). In the presence of glucose, AuNPs did not aggregate after incubation, and the color of the solution retained the original red (Fig. 5a, c). The dispersion of AuNPs was highly specific to glucose (Fig. 5a–c), and this dispersion-dominated approach of AuNPs effectively improved the accuracy and reduced the false results in complex test environments. In another study, Jiang and coworkers developed AuNRs for highly sensitive and visual approach of glucose detection [54]. The readout of this approach was visible to the naked eyes (Fig. 5d), and a minimum detection limit of 0.07 μM of glucose was achieved by this system (Fig. 5e).
3. Smart materials for sensing of nucleic acids

Nucleic acids are a group of long, linear macromolecules that carry genetic information in living cells and viruses. Specific detection of nucleic acids plays an important role in many clinical diagnosis such as cancer, genetic disorders, and identification of infectious agents [57]. At present, polymerase chain reaction (PCR) is the most commonly used nucleic acid detection method. However, traditional PCR is not suitable for on-site and on-time detection, because it requires the use of thermal amplified instruments, expensive reagents, complicated procedures and long reaction times. Therefore, easy and label-free nucleic acid detection is highly desired. Smart materials-based detection approaches may provide label-free detection, require less detection time and simpler operation [58,59], and are widely used for on-site detection of nucleic acids.

Chen and coworkers have developed a hybrid fluorescent nanoprobe using QDs and AuNPs as Förster resonance energy transfer (FRET) pair for real-time visualization of viral RNA [60]. Due to the proximity of AuNPs to QDs, the assembled construct exhibited high quenching of the QD emission (Fig. 6a). If there was newly synthesized viral RNA, significant increase in fluorescent intensity was detected (Fig. 6b). This work enabled the use of QD-AuNP probe to monitor the replication of viral RNA, which is essential to understand the pathogenesis of viruses. In another work, Huang and coworkers constructed a highly sensitive plasmonic biosensor for DNA detection [61]. They assembled two types of pyramid structures using symmetric DNA frames (Fig. 6c–d). If there was target DNA, these pyramids underwent dynamic reconfiguration or dissociation process, thereby changing the circular dichroism (CD) signals on or off, respectively (Fig. 6c–d). With optimized conditions, target DNA can be detected at attomolar level without the use of amplification process.

In addition to the above examples of nucleic acid detection based on conventional nanomaterials, novel PC-based platforms has attracted extensive attention in nucleic acid detection. Gu and Zhao developed a novel hydrogel suspension array for label-free detection of nucleic acids, taking the advantages of QD-encoded technology, bio-responsive hydrogels and self-reporting photonic beads [62]. The presence of target DNA in the hydrogel grid caused the shrinking of hydrogels, leading to blue shift in the Bragg diffraction peak of the photonic beads [62]. With this approach, a detection limit of nanomolar level of target DNA was achieved [62]. Zhao group further developed a series of works for screening and quantification of microRNA (miRNA) using colloid PC platforms [63–65]. In a recent study, the group fabricated novel MoS2-integrated silica colloidal crystal barcodes (SCCBs) for screening of multiplex tumor miRNA [65]. MoS2 was adsorbed on SCCBs, and hairpin probes was decorated with QDs and then coupled on MoS2 (Fig. 7a, left), where the MoS2 could quench the QDs of the hairpin probes (Fig. 7a, middle). Target miRNA can form a double strand with the probe and thereby keeping QDs away from MoS2 sheets, resulting in the recovery of fluorescence of the QDs (Fig. 7a, right). Since the released QDs were positively correlated with the nucleic acid concentration, therefore, the
target miRNAs can be quantitatively measured by detecting the fluorescence signal of QDs on SCCBs (Fig. 7a). Moreover, by using different MoS2-integrated structural color, quantitative monitoring of multiplex miRNA can be achieved (Fig. 7b). For example, three types of tumor miRNAs were detected with high selectivity and high sensitivity (Fig. 7c–h), with a minimum detection limit of 4.2 ± 0.3 nM. The use of PC structures has the characteristics of low-cost, fast response and high detection capacity, so it offers a promising alternative approach to the traditional PCR technology for nucleic acid detection.

The above examples described the incorporation of smart materials in the sensing of nucleic acid. In turn, nucleic acids themselves can be utilized for sensing of other analytes [66]. For instance, DNA-based hydrogels with stimuli-responsiveness were employed for the sensing of pH [67], temperature [68] and ions [69].

4. Smart materials for sensing of proteins

Proteins are a large class of complex organic compounds that are essential constituents for living cells, and perform a vast array of functions within organisms. The detection of protein is important in clinical diagnosis of diseases, such as cancers, diabetes, neurodegenerative disease, genetic diseases, and pathogens [70,71].

Conventional methods such as immunoassays for detection of protein required many procedures and long reaction time. Smart materials-based sensing may offer a chance to achieve on-site, fast and sensitive detection. In a previous report, Yan and coworkers developed a nanozyme-stripe for rapid and local detection of the glycoprotein of Ebola virus (EBOV) [72], since glycoprotein is the main viral determinant of EBOV pathogenicity [73]. They used Fe3O4 magnetic nanoparticles (MNPs) to prepare the MNP-based immunochromatographic strip (nanozyme-strip) (Fig. 8a–b). Because MNPs possessed intrinsic peroxidase-like activity [74], which can catalyze peroxidase substrates and producing a visible color reaction, therefore, this strip can detect the glycoprotein of EBOV with a minimum detection limit of 1 ng/mL, which was 100 times more sensitive than the standard strip method (Fig. 8c–d). This nanozyme-stripe provide fast and sensitive detection of glycoprotein in EBOV, which holds great promise in the prevention and treatment of infectious diseases such as Ebola, SARS and Covid-19 that seriously affect the lives and health of people worldwide [75].

PC structures also has many applications for the detection of various proteins [76]. Asher group was pioneer in the development of PC-based sensors to detect chemical or biological targets [48,77]. For example, the
group developed a carbohydrate hydrogel containing responsive PC materials for selective and sensitive detection of lectin [78]. They used hydrogels containing lactose, galactose, or mannose to prepare a series of PC sensors that showed selective binding to the respective lectin proteins of ricin, jacalin, and concanavalin A (ConA), respectively (Fig. 9a). Therefore, the formed hydrogel showed specific binding to respective lectin proteins (Fig. 9a). As a consequence, the hydrogels shrunk due to the specific bindings, and leading to a significant shift of the diffraction wavelength of the hydrogels (Fig. 9b–c). The resulting PC sensors can selectively detect the lectin proteins, with a low detection limit of 7.5 x 10^-9 M.
Moreover, Zhao group developed porous hydrogels encapsulated with PCs for multiplex detections of proteins, such as tumor markers [79], cardiovascular biomarkers [80], and skin interstitial fluid (ISF) biomarkers [81]. In a recent study, arranged PC barcodes were embedded inside a microneedle arrays (MNs) for specific detection of ISF biomarkers [81]. When pierced into the skin, the MNs can absorb the analytes in the ISF and enrich the specific biomarkers to the encapsulated PC barcodes (Fig. 10a–b). The corresponding fluorescent probes in the MNs can detect the content of relative biomarkers by their fluorescence intensity of the PC barcodes (Fig. 10b). At the same time, different types of biomarkers can be distinguished by observation of the reflection peaks of the PC barcodes (Fig. 10c–f). This PC barcode-encapsulated MNs showed high efficiency and versatility to capture and detect three inflammatory cytokines of mice, including TNF-α, IL-1β, and IL-6. These

Fig. 10. Encoded MNs with PC barcodes for detection of ISF biomarkers. (a) Preparation of the encoded MNs. (b) Application of the MNs in detection of ISF. (c–f) Optical images of MNs with multiplex barcodes with different structural colors. Blue, green and red barcodes were used for detection of IL-6, IL-1β and TNF-α, respectively. Reprinted with permission from Ref. [81]. Copyright (2019) Wiley.

Fig. 11. Nanomaterials used for detection of protease. (a) QDs and (b) plasmonic AuNPs employed as signal transducers during the detection of protease. Reprinted with permission from Refs. [10]. Copyright (2014) American Association for the Advancement of Science.

$10^{-8}$ M to ricin, $2.3 \times 10^{-7}$ M to jacalin, and $3.8 \times 10^{-8}$ M to Con A, respectively.
encoded MNs possess excellent detection effects with less and simple procedures, and this system is promising for clinical and biomedical detection.

5. Smart materials for sensing of enzymes

Enzymes are a special class of proteins that function as biochemical catalysts in cellular process and metabolic exchanges of living organism. Enzymes become important targets for the development of therapeutic drugs and the treatments of various diseases [82,83]. Biosensors capable of detecting enzymes has been investigated for decades [84]. However, in most cases, these enzyme detection techniques require complicated instruments and long procedures.

Nanomaterials, such as plasmonic AuNPs and QDs, possess unique optical properties, and are widely used in the detection of enzymes as excellent signal transducers [10] (Fig. 11). Mattoussi and coworkers developed a luminescent QD bioconjugates to detect proteolytic activity of different proteases [85]. They used QDs as a FRET donor and a fluophore acceptor linked to the QDs via peptides (Fig. 11a). The designed peptide included a cleavage site that was selectively recognized by the target proteases, and induced a significant reduction in FRET efficiency during cleavage (Fig. 11a) [85]. By changing the peptide sequence, different kinds of enzymes including caspase-1, thrombin, collagenase and chymotrypsin can be selectively detected [85]. Moreover, Stevens and coworkers reported a method for detection of proteases with high sensitivity based on triggered dispersion of AuNP assemblies (Fig. 11b) [10,86].

In addition to the aforementioned nanomaterials-based biosensing system, hydrogels with stimuli-responsive mechanisms were widely used for the sensing of enzymes. Spivak and coworkers developed an aptamer-based hydrogel with responsiveness to the target enzymes for macromolecular signal amplification [87]. This hydrogel exhibited a variable volume and a specific response to the target enzymes, due to the interaction between the crosslinking of protein and aptamer (Fig. 12a). And the volume change of the hydrogel was visible to the naked eyes, with a low detection of femtomolar range of thrombin was achieved this method (Fig. 12a). In practice, this detection method did not require complicated instruments and highly trained personnel, therefore offering an alternative to traditional analytical techniques. In addition, Yao and Wang recently developed a competition-based PC hydrogels (PCHs) for naked-eye detection of enzymes based on antibody-antigen interaction [88]. This PCH biosensors can be employed for naked-eye detection of different biomolecules, regardless of their chemical and physical properties (Fig. 12b). Moreover, this approach was applied to detect kinase-phosphatase activity [88]. These PCH biosensors were capable of visual detection of enzymes with high selectivity, high sensitivity and great reversibility.

Based on the above descriptions, we summarized the key examples of smart materials and their responsive principles in biosensing applications (Table 1). Benefiting from the unique optical properties of nanomaterials, the unique interaction between PCs and light, and the responsiveness of smart hydrogels, various biosensing platforms with high sensitivity, easy manipulation and fast readout have been greatly developed for research as well as clinical applications.

6. Conclusions and outlook

In this review, we have described the recent applications of smart materials in biosensing. We highlighted the design of smart materials, their responsive principles of biosensing, and their applications of target detections including glucose, nucleic acids, proteins and enzymes (Table 1). There are also smart materials that can respond to other biomolecules, which will not repeat here.

Many nanomaterials are rationally selected to develop smart biosensing system, due to their unique optical properties, easy modulation by the target analytes, and their capability to transform the detection events into a readable and quantifiable signal (Table 1). The nanomaterials-based biosensing systems show many advantages, such as high selectivity, high sensitivity, easy and fast for readout, and instrument free. However, the utilization of nanoparticles for in vivo sensing was limited due to the intrinsic toxicological concerns of nanomaterials [89]. In addition, quenching effects and photobleaching from the
Table 1

| Smart Materials | Responsive principles | Applications |
|-----------------|----------------------|--------------|
| AuNPs           | Aggregation/dispersion of AuNPs triggered by analytes resulted in chromogenic changes of solution | Colorimetric testing of glucose [52], enzyme [86] |
| Ag⁺-coated AuNRs | AuNRs served as substrate for the redox reaction between Ag⁺ and glucose | Naked-eye visualization of glucose [54] |
| Fe₃O₄ MNPs      | MNPs catalyzed peroxidase substrates and produced a visible color reaction on the strip | Detection of the glycoprotein [72] |
| QD bioconjugates| The presence of analytes induced a significant reduction in FRET efficiency, leading to the recovery of fluorescence of QDs | Visual detection of RNA [60], enzyme [85] |
| Au/Ag NP pyramids | The presence of target DNA led to the reconfiguration or dissociation of the pyramids, which changed the CD signals of the pyramids | Detection of DNA [61] |
| GO-decorated PC barcodes | Target miRNA bound with probes on PC barcodes which have characteristic reflection peaks, resulting in different photoluminescence intensity at the barcode surface | Multiplex miRNA detection [64] |
| MoS₂-integrated PC barcodes | Target miRNA hybridized with the probes on the barcodes, keeping QDs away from the MoS₂, resulting in fluorescence recovery of QDs | Multiplex miRNA detection [65] |
| Zwitterionic hydrogel | Gox and HRP in the hydrogel catalyzed the glucose oxidation and generated a fluorescent product | Optical monitoring of glucose [33] |
| pH responsive hydrogel | Glucose changed the pH of the solution, resulting in different swelling of the hydrogel | Visual detection of glucose [34] |
| PBA-incorporated Hydrogel | Reaction between glucose and PBA affected the refractive index of light through the hydrogel | Detection of glucose [42] |
| Aptamer-based hydrogel | The interaction between protein and aptamer changed the volume of hydrogel | Detection of thrombin [87] |
| Hydrogel integrated with PCs | The presence of analytes induced the swelling/shrinking of hydrogels, which tuned the diffraction wavelength of encapsulated PCs | Detection of glucose [49], DNA [62], protein [78], and enzyme [88] |
| Hydrogel encapsulated with photonic barcodes | Different types of biomarkers were distinguished by the reflection peaks or the fluorescence of the PC barcodes | Multiplex detection of proteins [79–81] |

Hydrogel biosensors are mainly applied in aqueous environments [92]. Moreover, there is an interference between the solution-induced hydrogel swelling and analyte-induced hydrogel swelling, which may affect the evaluation of the analyte levels [92]. In addition, the response time of large hydrogels is generally too long to meet the requirement of real-time response. These problems may hamper their uses in real-time monitoring of analytes in vivo. Down-scaling the feature size of hydrogels is a possible solution to create structures with enhanced response rate to biological stimuli.

In the future, how to achieve accurate identification of target biomolecules, how to achieve multiplex recognition that respond to different bio-stimuli need to be further investigated. We are confident that next-generation biosensing platforms will emerge with further research on smart materials, and we believe that smart materials-based biosensing is promising in biomedical diagnosis and monitoring.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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