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REVIEW PAPER

Colorimetric gold nanoparticles-based aptasensors

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ABSTRACT

Recognition of different agents including chemical and biological plays important role in forensic, biomedical and environmentalfield.In recent decades, nanotechnology and nano materials had a high impact on development of sensors. Using nanomaterials in construction of biosensors can effectively improve the Sensitivity and other features of biosensors. Different type of nanostructures including nanotubes, nanodiamonds, thin films ,nanorods, nanoparticles(NP), nanofibers andvarious clusters have been explored and applied in construction of biosensors. Among nanomaterials mentioned above, gold nanoparticle (GNP)as a new class of unique fluorescence quenchers, is receiving significant attention in developing of optical biosensors because of their unique physical, chemical and biological properties. In this mini review, we discussed the use of GNPs in construction of colorimetric aptasensorsas a class of optical sensors for detection of antibiotics, toxins and infection diseases.

Keywords: *Antibiotics, Colorimetric aptasensor, Gold nanoparticles, Toxins*

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INTRODUCTION

Nanotechnology is a rapidly growing science which involves in the study, manipulation and production of materials, systems and devices usually with dimensions smaller than 100 nm. Nanotechnology is playing a significant role in the development and improvement of biosensors [1, 2]. Biosensors are devices composed oftwo of the recognition element and the analyte. Aptasensors, aptamer-based biosensors, have been widely used for recognition of different targets [3]. Aptamers also known as chemical antibodies are single-stranded oligonucleotides that bind strongly to a wide variety of targets with high specificity and affinity.Aptamers are generated by an *in vitro* selection process, termed Systematic Evolution of Ligands by EXponential enrichment (SELEX). They have great potential as targeting agents in different fields, such as analytical methods, diagnostic and therapeutic applications. In aptasensors, aptamers are used as recognition elements [4]. Aptamers have considerable advantages compared to antibodies, Including simple modification and synthesis, low cost and thermal stability [5, 6].

Sensitivity, simplicity and accurate detection of biosensors can be improved using nanomaterials.

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Among nanomaterials, Gold nanoparticles (GNPs) have attracted great attention, due to their strong optical absorption, scattering properties, universal fluorescence quenching, unique electronic, chemical and biological properties and low or no toxicity [7, 8]. Among different biosensing assays, colorimetric method has been used extensively, owing to its low cost, simplicity, practicality and observation of the color change by the naked eyes. In this mini review, we summarized colorimetric gold nanoparticles-based aptasensors and focused on detection of antibiotics, toxins and infection diseases through this type of aptasensor, in order to provide readers with a complete understanding of colorimetric gold nanoparticles-based aptasensors improvement and progress.

Colorimetric gold nanoparticles based aptasensors for detection of antibiotics

Antibiotics have been broadly applied for treating diseases in human and veterinary. Antibiotics can be found in foodstuffs, such as meat, milk, fish and eggs and considered as a serious risk for human health due to their side effects and increase of antimicrobial resistance [9]. Antibiotics are classified into seven families including tetracyclines, macrolide antibiotics, aminoglycosides, peptide antibiotics, lincosamides, streptogramins, and β-lactam antibiotics[10].To protect the health of consumers and reduce the risk of anti-bacterial resistance , various sensitive and selective biosensors have been developed for detection and quantification of antibiotics in food products. The combination of gold nanoparticles and aptamers have been broadly used to fabricate colorimetric aptasensors for optical detection of Antibiotics [11].

Song and colleagues designed a DNA aptamer-based detection assay with high sensitivity for detection kanamycin [detection limit of 25 nM). They applied ssDNA aptamer, with high specificity for kanamycin that was adsorbed onto the surface of GNPs through electrostatic interaction. In the presence of kanamycin, aptamer attached to kanamycin and left the GNPs surface. So addition of salt (NaCl) led to aggregation of GNPs through shielding the negative charge of GNPs and the color of sample changed from red to blue [12].

In another work, amixture of three ssDNA aptamers (1:1:1ratio) and unmodified GNPs were used for homogeneous recognition of sulfadimethoxine, kanamycin and adenosine. Three Aptamers were adsorbed onto the surface of GNPsby electrostatic interaction. Addition of all three targets resulted in the release of aptamers from GNPs. Then, GNPs were aggregated by addition of NaCl, leading to the color change from red to purple/blue and multiple target detection was realized. The limit of detections (LODs) was 500 $ng.mL^{-1}$, 500 $ng.mL^{-1}$ and 100 $ng.mL^{-1}$ for adenosine, sulfadimethoxine and kanamycin, respectively. Also, the sensitivity of this multiple aptasensorwas comparable witha single-target aptasensor for each target individually[13].

Another multiplex aptasensor for aminoglycoside detection was fabricated using GNPs and functionalized RNA aptamer. The colorimetric aptasensor showed high sensitivity for kanamycin. The linear range was in the range of 1-100 nM [14].Our team for the first time, developed a colorimetric aptasensor for streptomycin detection in blood serum and milk based on GNPs and double-stranded DNA. In the absence of streptomycin, dsDNA remained intact and could not protect GNPs against salt-induced aggregation, because of its rigid structure. So, NaCl addition resulted in the aggregation of GNPs and the color of the sample obviously changes from red to blue. It has been proved that aptamer interacts with its target with a better binding affinity relative to its complementary strand. Thus, upon the addition of target, the complementary strand left the aptamer and aptamer/target complex forms. The isolated complementary strand was adsorbed on the surface of GNPs and protected the nanoparticles against salt-induced aggregation.(Aptamer/Complementary strand) The aptasensor indicated LOD as low as 73.1 nM [15].

Gu et al. employed a highly specific aptasensor for oxytetracycline using ssDNA aptamer and unmodified GNPs to distinguish oxytetracycline from other tetracyclines, such as doxycycline and tetracycline. After the addition of NaCl, the color change of GNPs in the presence of target was easily observed by the naked eye and measured by UV/vis spectrometer. The detection limit of OTC was 25 nM [16]. Fluoroquinolones (FQs) area kind of antibiotics used for human and veterinary diseases and in comparison with other antibiotics possess lower solubility, bioavailability, and more gather in sediment. So, screening of FQs at trace levels in samples is urgent [17].

Using reduction-catalyzing activity of GNPs, a

sensitive colorimetric aptasensor was introduced by our group for FQs detection with a detection limit of 1.2 nM. In this sensor in the present of target, aptamer attached to FQs and left the surface of GNPs.

Consequently, colorimetric probe (4-nitrophenol, yellow color) had access to the surface of GNPs and was reduced to 4-aminophenol (colorless) by the catalytic activity of the surface of GNPs. This colorimetric aptasensor indicated a wide range of linear response from 4 nM to500 nM toward FQs[18]. (Table 1)

Colorimetric gold nanoparticles-based aptasensors for detection of toxins

OchratoxinA (OTA) is a toxinand secondary metabolite of fungi which produced by Aspergillus and Penicillium strains. OTA is commonly found in foodstuffs [19]. Luan group designed a colorimetric detection system using GNPs functionalized with a label-free aptamer to detect OTA. In the presence of OTA, the OTA aptamer changed its random coil structure to bind to the analyte. So, addition of PDDA (polymer poly diallyldimethyl ammonium chloride) as a cationic polymer triggered the aggregation of GNPs, leading to a change in the color system from wine-red to blue. LOD of this sensing plat form was determined as low as 0.009 ng/mL[20].Xiao and coworkers in another work introduced a colorimetric aptasensor for detection of OTA using GNPs. GNPs were functionalized with poly (ethylene glycol) 2-thioethyl ether acetic acid (PEG), and conjugated to DNA probes. In the absence of OTA, the probes were linked together by partial hybridization with aptamer, leading to assembly of GNPs dimers and blue color because of the aggregation of GNPs. When OTA is presented, it could potentially compete with probes for binding to aptamer and disassembly of GNPs dimers, leading to change color from blue to red. The LOD in this method was measured to be 0.05 nM [21]. (Table 2)

Table 1. Colorimetric gold nanoparticles-based aptasensors for detection of antibiotics

Name of antibiotics	Limit of detection	References
Kanamycin	25 nM	[12]
adenosine sulfadimethoxine kanamycin	500 ng.mL–1, 500 ng.mL–1 100 ng.mL–1	[13]
Kanamycin		[14]
streptomycin	73.1 nM	[15]
oxytetracycline	25 nM	[16]
Fluoroquinolones	1.2 nM	[18]

Colorimetric gold nanoparticles-based aptasensors for detection of bacteria

A high sensitive and specific colorimetric aptasensor was developed for detection of Staphylococcus aureus(S. aureus) via tyramine signal amplification . Streptavidin as a crosslinker was immobilized onto the microtiter plate. Then, biotinylated aptamer conjugated by streptavidin-HRP, the bacteria (S. aureus), hydrogen peroxide, avidin–catalase and biotinylated tyramine were captured into the walls of plate. In the present of target, catalase consumed H2O2 and resulted in the aggregation of nanoparticles. Change in aggregation was measured by molecular devices spectraMax M5 plate reader. LOD of this model was determined as 9 cfu.mL-1 [22]. Wu et al. demonstrated a colorimetric sensorbased on gold nanoparticles and label-free aptamers for detection of Salmonella typhimurium and Escherichia coli (E. coli). The bacteria binding aptamers were adsorbed on the surface of GNPsand prevent the salt-induced aggregation of nanoparticle. Interestingly, the addition of target bacteria could change the conformation of aptamers and led to release of aptamers from the GNPs surface. The color changed from red to purple due to the reduction in capability of protecting GNPs against salt-induced aggregation [23]. (Table 3)

Colorimetric gold nanoparticles-based aptasensor for detection of parasite

Malariaisanimportantparasiticinfectioncaused by protozoan parasites the genus Plasmodium [24]. This parasite causes major morbidity and

Table 2. Colorimetric gold nanoparticles-based aptasensors for detection of toxins

Name of Toxin	Limit of detection	References
OchratoxinA	0.009 ng/mL	[20]
OchratoxinA	0.05 nM	[21]

Table 3. Colorimetric gold nanoparticles-based aptasensors for detection of bacteria

Name of bacteria	Limit of detection	References
Staphylococcus aureus	9 cfu.mL-1	[22]
Salmonella typhimurium	10^5colony-forming units (CFU)/ml	[23]
Escherichia coli	10^5colony-forming units (CFU)/ml	[23]

Table 4. Colorimetric gold nanoparticles-based aptasensors for detection of parasite

Name of parasite	Limit of detection	References
Plasmodium falciparum	92-97 parasites/µL	[26]
Plasmodium vivax	74-80 parasites/µL	[26]

mortality. Thus, methods for malaria diagnosis and treatment should be developed for saving human life [25].In one study; a colorimetric aptasensor for sensitive and specific detection of Plasmodium lactate dehydrogenase (pLDH) in malaria was designed by Jeon et al. Their sensing platform was based on the interaction of pLDH with ssDNA PL1 aptamer (Plasmodium falciparum lactate dehydrogenase (PfLDH) and Plasmodium vivax lactate dehydrogenase (PvLDH). In the absence of target, pLDH aptamer attached to cationic polymers such as poly diallyldimethylammonium chloride (PDDA) and poly allylamine hydrochloride (PAH) and could inhibit the aggregation of GNPs by cationic polymers, resulting in a red color in the sample. When pLDH was present, aptamer interacted with pLDH, leading to aggregation of GNPs by cationic polymer. In this system, the LOD for P.vivax was determined 80 parasites/µL for PDDA and 74 parasites/µL for PAH. Moreover, the LOD of 92 parasites/µL for PDDA and 97 parasites/µL for PAH were calculated for P. falciparum [26]. (Table 4)

CONCLUSION

Gold nanoparticles have obtained great attention as colorimetric reporters, due to their high extinction coefficients, ease of synthesis, and strongly distance-dependent optical characteristics. Colorimetric gold nanoparticles-aptasensors have gained considerable attention for detection of different targets because the molecular recognition events can be easily detected by the naked eyes without the need for any sophisticated equipment. So, colorimetric gold nanoparticles-aptasensors have great potential as commercial diagnostic tools.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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