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REVIEW

Progress of Visual Biosensor Based on Gold Nanoparticles

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Abstract: Visual detection method is a means of quantitative analysis by the naked eye through the comparison of color intensity or type of change. Owing to its simplicity, low-cost, rapid operation, and equipment-free, visual detection was widely used in the detection of numerous targets. Gold nanomaterials were widely used in the construction of visual biosensors due to its unique optical properties when compared to other nanomaterials. The local surface plasmon resonance absorption peak would change with the variety in the distance or the morphology. Herein, this paper reviewed the application of gold nanomaterials in the construction of visual biosensors for the detection of target molecules. Meanwhile, we pointed out the main problems of gold nanoparticles based colorimetric methods in the determination of actual samples. The forecast of gold nanoparticles based biosensor was also provided at the end of this article.

Key Words: Gold nanoparticles; Visual biosensor; Detection; Review

1 Introduction

Gold nanoparticles (AuNPs) are widely used in the construction of visual sensing strategies due to their high stability and easy functionalization. Noble nanoparticles with different morphologies or sizes shows unique optical properties, which can be prepared by changing the synthesis conditions simply[1–4]. Unlike traditional dyes-based assays, the AuNPs exhibit extraordinarily high molar extinction coefficient, at least three orders of magnitude higher than that of the traditional methods[5]. On the basis of these advantages, the detection limit of AuNPs-based colorimetric analysis can reach nanomolar level, which is much lower than the traditional colorimetric assay with organic molecules as substrates[6]. In particular, AuNPs display distinct change in local surface plasmon resonance (LSPR) with the morphology, composition, distance or surrounding media, accompanied by an obvious color change[7,8]. The color change can be easily distinguished by naked eye without the aid of any sophisticated instruments. In 1997, Mirkin firstly proposed AuNPs as colorimetric substrate for the visual determination. AuNPs-based colorimetric assays began to have a breakthrough after that, and were widely applied as colorimetric substrate in the detection of nucleic acids, proteins, ions, organic matter and cells, etc[9–12]. In addition, the AuNPs possess intrinsic mimic enzyme activity which can catalyze the oxidation of colorimetric substrate to develop an obvious color change, providing a simple approach to colorimetric detection with the naked eye[13]. Therefore, AuNPs-based colorimetric assay is quite suitable for the on-site rapid detection in resource-limited areas due to the ability to meet the needs of highly sensitive detection and the advantages of simplicity, shortcut, and equipment-free.

2 Distance-dependent AuNPs colorimetric assay

The distance change between AuNPs would cause significant variation in LSPR, resulting in an obvious color difference of the solution, and thus the colorimetric biosensors based on the distance variation can be easily constructed[14].

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Most of these distance-dependent colorimetric assays are based on cross-linking aggregation or non-crosslinking aggregation. Cross-linking aggregation is mainly based on the functionalization of different molecules (such as DNA, antibodies, small molecules, etc.) on the surface of AuNPs, decreasing the distance of AuNPs through the specific recognition between target and the identification molecules (such as DNA hybridization, antigen-antibody recognition, metal-ligand complexation, etc.), resulting a visible color change from red to blue[15–18]. As for non-crosslinking aggregation, it is mainly caused by changing the surface properties of AuNPs, such as pH value, ionic strength, solvent composition, etc[19, 20].

2.1 Crosslinking aggregation

The modification of DNA probe on the surface of AuNPs via Au-S covalent interaction can be used for colorimetric detection of DNA, miRNA or small molecule. Moreover, the specific recognition of target molecule based on the base complementary pairing interaction can also lead to the aggregation of AuNPs. As shown in Fig.1, two different sequences of DNA were modified on the surface of the AuNPs by asymmetric modification, respectively. When the target DNA hybridized with the complementary ssDNA sequences on the surface of AuNPs, Y-type structure was formed according to the strict complementary nature of the base pairs. Thus, AuNPs dimers were formed instead of traditional large aggregation and the solution color change from red to blue, which significant improved detection sensitivity and detection dynamic range[21]. This powerful approach was applied to the colorimetric detection of small molecule by replacing the probe sequence with aptamer that specifically recognizes ochratoxin A (OTA) molecule[22]. Moreover, this technique was successfully employed for the colorimetric detection of miRNA, integrating the merit of asymmetric modification and double-stranded specific nuclease (DSN) cycle amplification strategy with the limit of detection as low as 0.5 fM[23].

AuNPs-based colorimetric biosensors can also be established by modifying functional groups on the surface of AuNPs, and the aggregation event is triggered by the specific recognition between target and reactive group[24,25]. Jiang's group associated the click chemistry-based assays with the visual readout of AuNPs for the detection of Cu^{2+}. The reduction of Cu^{2+} to Cu^{+} by sodium ascorbate cross-linking the alkyne and azide-functionalized AuNPs, resulting in the aggregation of AuNPs with the color change. Therefore, the click chemistry-based AuNPs assay for the determination of Cu^{2+} could be recognized by the naked eye, and the limit of detection was 50 μM[26]. On the basis of this, it was also used for the detection of protein by labeling the copper oxide nanoparticles on the secondary antibody instead of traditional enzyme marker. The antibody-antigen-CuO nanoparticles complex was formed on the plate surface via immune-reaction. The labeled CuO was dissolved to form Cu^{2+} by acid, and then was reduced to Cu^{+} and triggered click chemistry reaction. The red-to-blue color change indicated the aggregation of AuNPs functionalized with azide and alkyne groups, thus indirectly reflecting the concentration of protein. (Fig.2A)[27]. In addition, alkaline phosphatase (ALP) labeled antibody could also be used for the visual detection of antigen. ALP could catalyze the dephosphorylation of ascorbic acid-phosphate (AA-p) to produce ascorbic acid, which would quantitative reduce Cu^{2+} to Cu^{+}. As a consequence, large AuNPs aggregates were formed with the color change from red to blue upon the cross linking by click chemistry reaction (Fig.2B)[28].

The 'naked' AuNPs, not functionalized, can also achieve the purpose of target induced visual detection. Sensitive colorimetric detection of enterovirus 71 (EV71) constructed based on the enzyme-mediated aggregation of unfunction-alized AuNPs[29]. As shown in Fig.3, acetylcholinesterase (AChE) was used as the enzyme marker, which catalyzed the

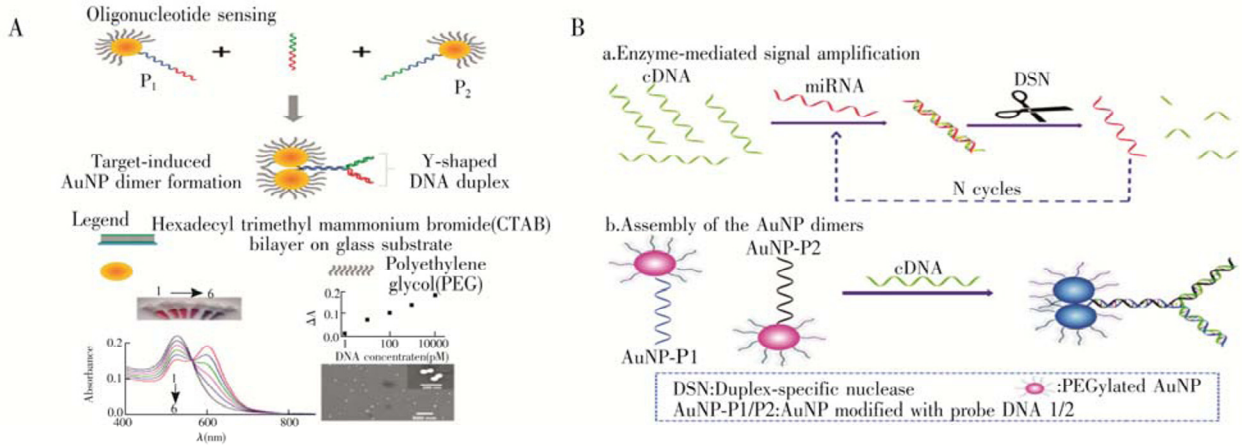

Fig.1 (A) Schematic representation of the colorimetric assay based on asymmetrically functionalized AuNPs[21]. (B) Visual detection of miRNA based on DSN cyclic amplification system[23]