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Gold Nanomaterials in Biosensing Applications

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Abstract. This paper provides an overview of the preparation and application of gold nanomaterials in biosensing, including four aspects: biomolecular detection, medical bioimaging, pathogen detection, and immunoassay. Firstly, the preparation methods of gold nanomaterials are introduced, including chemical reduction, laser radiation, and vacuum evaporation. Secondly, the applications of gold nanomaterials biosensors in various fields are outlined. One such field is biomolecule detection. gold nanomaterials has good optoelectronic properties, which can quantitatively detect biomolecules through fluorescence signals. Another field is medical bio-imaging. gold nanomaterials exhibits high X-ray absorption coefficients, rendering it a suitable contrast agent for medical imaging. Additionally, gold nanomaterials displays a high antigen-antibody reaction activity, making it an effective tool for rapid pathogen detection. Finally, the prospective development trend of gold nanomaterials biosensors is presented.

Keywords: Gold nanomaterials; Biomolecular Detection; Medical Bioimaging; Pathogen detection; Immunoassay.

1. Introduction

Gold nanomaterials exhibit a multitude of exceptional physicochemical properties, which are closely related to their morphology. The most prevalent morphology of gold nanomaterials is that of gold nanorods, gold nanospheres, gold nanocages, and gold nanoparticles[1-2].Gold nanorods are gold nanoparticles with a high aspect ratio, which are shaped like slender gold rods. The optical properties of gold nanorods are intimately connected to their aspect ratios. As the aspect ratio of the nanorods increases, the surface plasmon resonance effect becomes more pronounced, resulting in enhanced UV-visible light absorption and scattering capabilities. Gold nanospheres are spherical gold nanoparticles with a diameter typically between 1 and 100 nanometers. Gold nanospheres are biocompatible and can be employed in a variety of applications, including bioimaging, drug delivery, and biosensors. A gold nanocage is a cage-like polyhedral structure comprising gold nanoparticles. Gold nanocages, with their high specific surface area and cavity structure, are capable of effectively loading biomolecules and drug molecules, thereby enhancing the efficiency and selectivity of drug delivery. Gold nanoparticles are amorphous nanoparticles composed of gold of varying shapes and sizes. Gold nanoparticles exhibit excellent biocompatibility, catalytic activity, and optical properties, rendering them suitable for a multitude of applications in bioimaging, catalysis, optics, and electronics. Moreover, gold nanoparticles exhibit distinctive optical characteristics. In addition to the photothermal effect, the aggregation of gold nanoparticles will result in a change in the color of the solution from red to blue. The color change will be reversed when the aggregated gold nanoparticles are dispersed again. This phenomenon is attributed to the surface plasmon resonance effect. When the distance between two gold nanoparticles is equal to or less than their binding radius, the oscillatory coupling of neighboring gold nanoparticles reduces the vibrational frequency, which manifests as a shift in the spectral absorption bands. This color change characteristic caused by agglomeration and dispersion can be utilized to construct a biological real-time detection method based on the induced aggregation of gold nanoparticles.

Gold nanomaterials materials are known to exhibit good biocompatibility, which is defined as the ability of a material to interact with biological systems in a manner that does not cause an adverse reaction. gold nanomaterials are typically observed to exhibit a spherical morphology and a size that is smaller than that of cells or tissues. This allows it to readily traverse cellular barriers, thereby enabling nanoparticles to penetrate blood vessels and tissues as probes into the body. gold nanomaterials are absorbed by the kidneys and liver at a much slower rate than other molecules, allowing it to remain in the body for a longer period of time. This property is advantageous for reaching the intended target site. Furthermore, due to its electrical conductivity and surface plasmon resonance effect [1-2], it can be employed as a material for signal conversion and amplification in biosensors. The exploitation of these characteristics of gold nanomaterials allows the design of a range of biosensors with high sensitivity, high selectivity, and a rapid response time.

The ongoing advancement of gold nanoparticle preparation technology and the enhancement of surface functionalization will facilitate the broader deployment of gold nanosensors in biomedical applications in the future. Over the past decade, as the utilization of gold nanoparticles in biosensors has become increasingly prevalent, researchers have commenced investigations into their applications in other domains, including bioimaging [3], tumor therapy [4], and drug delivery [5]. The functionalization of gold nanoparticles (AuNPs) has the potential to enhance the sensitivity, selectivity, and rapid response time of biosensors [6].

2. Preparation of gold nanomaterials biosensors

2.1. Preparation of gold nanoparticles

At present, the preparation methods of gold nanoparticles can be roughly categorized into two types: physical and chemical methods [7-9]. Physical methods encompass mechanical grinding, laser ablation, and radiation techniques, among others. These methods have the advantage of higher product purity, but they consume more energy, require higher-grade equipment, and the particle size is difficult to control. Consequently, they are more suitable for industrial applications that do not necessitate a high degree of shape and size precision [10]. The chemical reduction method entails the reduction of metal ions into metal nanoparticles through the use of a reducing agent. This method offers several advantages, including the ability to control the particle size, a low production cost, a high yield, and an ease of operation. The nanoparticles produced by this method have a range of potential applications, including in fields such as optics, biomedicine, and electrochemistry, which require high performance [10-11].

Mechanical milling method: The mechanical milling method is a physical method that achieves nanosizing of metal particles by milling the metal powder in a ball mill for an extended period of time. This method is relatively straightforward to operate and also produces gold nanoparticles with higher purity and a smaller particle size.

Plasma method: The plasma method is a process that employs gas-phase plasma to prepare gold nanoparticles. By regulating the parameters of the gas-phase plasma, this method facilitates the chemical reaction of gold atoms in the gas-phase state, which subsequently results in the formation of gold nanoparticles.

Chemical reduction method: chemical reduction method is one of the most commonly used methods for producing gold nanoparticles, usually gold salts (e.g., chloroauric acid, gold borohydride, etc.) are dissolved in water to make a certain concentration of solution and mixed with reducing agents (e.g., sodium citrate, vitamin C, etc.), and then by adjusting the pH of the solution, the temperature and the reaction time, etc., the gold ions are reduced into gold nanoparticles. After the reaction is completed, the gold nanoparticles need to be separated from the reaction solution by centrifugation or filtration. During the preparation of gold nanoparticles by chemical methods, it is often necessary to add dispersants to take advantage of their electrostatic or potential resistance effects in the system, and these dispersants help to regulate the particle size and morphology of gold nanoparticles [12-14].

2.2. Functionalization of gold nanomaterials

In order to expand the range of applications of gold nanomaterials, it needs to be modified by functionalization. The purpose of functionalization is to introduce special functional groups to give the gold nanomaterials surface a specific chemical activity or bioaffinity. Below are some common methods of functionalizing gold nanomaterials:

Chemical Binding: Functionalization of gold nanoparticles is achieved by attaching molecules or groups with specific functions to the gold nanoparticle surface through chemical reactions. This method is very flexible and allows the introduction of a variety of molecules or groups with different properties, for example, reverse thermogel is a hydrogel material with excellent thermal responsiveness, and by introducing gold nanoparticles into it, the electrical conductivity of the gel can be improved, Brisa Peña et al. chemically bound gold nanoparticles (AuNPs) to a highly functionalized biomimetic reverse thermogel (RTG) framework, thus realizing the need for temperature sensing and conductive applications[15].

Coordination Chemistry: Uses the free electrons on the surface of gold nanoparticles to coordinate with molecules or ions containing lone pairs of electrons, thereby modifying the surface properties of gold nanoparticles.

The surface properties of gold nanoparticles can be modified by ligand binding to molecules or ions containing lone pairs of electrons. Through coordination chemistry complexation, gold nanoparticles can be encapsulated in polymer ligands, which can not only improve the stability and dispersion of gold nanoparticles, but also improve their water solubility and biocompatibility [16-18].

Adsorption: Molecules or groups with specific functions are loaded onto the gold nanomaterials surface by adsorption methods. Taking biological imaging as an example, researchers can load fluorescent dyes onto the surface of gold nanoparticles by adsorption to prepare fluorescent gold nanoparticles. These fluorescent gold nanoparticles can be targeted and bound to the cell surface, enabling cell imaging and tracking through changes in fluorescence signals. By utilizing the abundant functional groups such as hydroxyl and amino groups on the gold nanomaterials surface, small molecules or biomolecules are adsorbed onto the gold nanomaterials surface through non-covalent interactions such as π-π interactions and hydrogen bonding. In addition, by tuning the functional groups on the gold nanomaterials surface and the nature of the adsorbed molecules, specific binding of gold nanomaterials particles to biomolecules can be achieved, improving the accuracy and sensitivity of imaging.

2.3. Preparation of gold nanomaterials biosensors

Gold nanomaterials biosensors are usually prepared by immobilizing biorecognition units (e.g., antibodies, enzymes, nucleic acids, etc.) on the surface of the gold nanomaterials material and utilizing the biorecognition units (e.g., antibodies, enzymes, nucleic acids, etc.) to specifically recognize and bind to the target analyte, resulting in a change in the sensor signal. Due to the high specificity and affinity of the biorecognition units, the selectivity and sensitivity of gold nanomaterials biosensors can be greatly improved.For example, Ning[19] et al. developed a gold nanoparticle probe that can directly detect Classical Swine Fever Virus (CSFV) by generating a fluorescent signal through nucleic acid hybridization. The probe consists of a capture probe and a reporter probe specifically designed to bind complementarily to the CSFV genomic sequence. The reporter probe is modified with a fluorescent moiety at one end and a nucleic acid sequence at the other end that can hybridize to the complementary sequence on the capture probe. When the presence of CSFV causes the capture probe to bind to the viral genome, the reporter probe further hybridizes to the complementary sequence on the capture probe to form a nucleic acid hybrid molecule. And since the nanoscale gaps between the gold nanoparticles can effectively limit the non-radiative energy transfer between the fluorescent groups, the fluorescent groups on the reporter probe produce fluorescent signals, and the quantitative detection of CSFV can be realized by measuring the intensity of the fluorescent signals. Khlebtsov et al[20] used the gold nano-island membrane as a reusable surface-enhanced Raman scattering (SERS) substrate, the structure of the gold nanomaterials island membrane makes it form a large number of localized surface plasmon resonance hotspots on the surface, and these hotspots can effectively enhance the Raman scattering signals of the nearby molecules, and its use for the detection of the fungicide content on the surface of apples can demonstrate the high sensitivity of the detection ability of the gold nanomaterials material.

Yang [21] et al. achieved highly sensitive detection and quantitative analysis of bacteria using Au@Ag@SiO2 core-shell nanostructures as SERS substrates. In bacterial detection experiments, they modified the nanospheres into microbial sample tubes, and when the bacteria came into contact with the nanospheres, the components on the bacterial surface interacted with the nanospheres, resulting in changes in the Raman signals on the nanospheres.For tumor marker detection, they used Au@Ag@SiO2 nanospheres for alpha-fetoprotein (AFP), and due to the AFP-nanospheres interaction, the Raman signal of the AFP molecule was significantly enhanced. Analysis of these altered Raman signals enabled the detection and quantification of bacteria and the sensitive detection of AFP. In a study by Vincent's group [22], they designed a biosensor for the detection of bacteria using gold nanospheres as the material for signal conversion and amplification. They modified the gold nanospheres with β-galactosidase, and when the β-galactosidase produced by bacteria binds to the gold nanospheres, a plasma resonance effect occurs, resulting in a color change of the gold nanospheres, and by detecting this color change, highly sensitive detection of bacteria can be achieved. Jia Licong et al [23] constructed a novel electrochemical biosensor for 17β-estradiol using PDA-GO composite and gold nanomaterials modified electrode with ligand as the recognition unit and methylene blue as the signaling unit, which is a sensor in which the presence of the target analyte leads to a change in the current or voltage signal during the electrochemical reaction to achieve the detection of the analyte.

3. Applications of gold nanomaterials biosensors

Gold nanomaterials has become the focus of scientific attention due to its unique optical and electromagnetic properties, and biomolecular detection, bioimaging and pathogen detection are the main application scenarios for gold nanomaterials biosensors.

3.1. Biomolecular detection

Gold nanomaterials biomolecule detection is a technique that utilizes gold nanomaterials materials to improve the sensitivity, selectivity and specificity of biomolecule detection. The surface of gold nanoparticles is biocompatible and can bind to biomolecules (e.g. proteins, DNA, RNA, etc.) to form stable complexes. When gold nanomaterials bind to biomolecules, their optical, electrical, or thermal properties change, enabling highly sensitive detection of biomolecules.

He Lei [24] et al. developed a porous silicon biosensor material with high fluorescence signal and biocompatibility by utilizing the plasma effect to enhance the fluorescence signal of fluorescent markers in porous silicon, and they modified gold nanomaterials on the surface of porous silicon to prepare a biosensor material with high fluorescence signal and biocompatibility. By attaching a biofluorescent probe to a DNA molecule, the researchers can achieve highly sensitive detection of DNA concentration. When the DNA molecule binds to the biofluorescent probe, the intensity of the fluorescence signal changes, enabling the detection of DNA concentration with a detection limit of 121 nM.

RodrigoD group [25] proposed a multi-periodic gold nanowire array that can realize multiple resonances for NIR-MIR biomolecule detection. This array structure makes full use of the optical properties of the gold nanomaterials wires, enabling them to generate multiple resonance peaks in the NIR to mid-infrared wavelength range.This resonance effect can effectively enhance the optical signal response of the array to the biomolecules.By adjusting the period and shape of the nanowires, the absorption and scattering characteristics of the array can be optimized, thus improving its detection sensitivity and specificity. Chen et al [26] improved the detection sensitivity and specificity of the gold nanomaterials wires by synthesizing gold nanoparticles (AuNP@AuNCs) protected by AuNCs by wrapping gold nanoparticles (AuNP) with gold nanoclusters (AuNC), which possessed both fluorescence and glucose oxidase mimetic activities. By catalyzing the oxidation of glucose to produce H2O2, the AuNP@AuNCs were able to induce fluorescence burst, thus enabling one-step, external indicator-free glucose detection.

3.2. Bioimaging

In gold nanoparticle biosensors, gold nanoparticles are usually used as a medium for signal amplification and transmission. By utilizing the good optical properties of gold nanoparticles (e.g., surface plasmon resonance), signal changes can be generated during the interaction of biomolecules with gold nanoparticles, which can lead to the detection and imaging of biomolecules. Wenshi Zhang et al [27] designed a novel multifunctional peptide that can induce in situ reduction and self-assembly of gold nanoclusters in a one-step method to synthesize a peptide-gold nanocluster hybrid fiber (PNF-AuNCs) with red fluorescence. The fluorescence intensity of the gold nanoclusters was significantly enhanced by self-assembly, and using this fluorescence enhancement effect, Zhang Wenshi et al. applied the PNF-AuNCs nanohybrid fibers to the field of temperature sensing, and meanwhile successfully realized cellular imaging applications by combining the cellular recognition sequences on the surface of the peptide nanofibers. Honghao Zhang et al [28] found that the incorporation of gold nanoclusters and glycerol could improve the β-folding and crystallinity of gold nanocluster composite filament films, thus enhancing their fracture strength, and the gold nanocluster composite filament films prepared under alkaline conditions exhibited strong fluorescence emission at 680 nm, and real-time non-destructive bioimaging was achieved by utilizing this red fluorescence with high transmittance. Due to the surface plasmon resonance effect of gold nanoparticles, molecular electromagnetic field signals are enhanced when they are on the surface of gold nanomaterials or within no more than 10 nm of the surface of gold nanomaterials, and this effect can be applied to bioimaging techniques to realize the detection and imaging of biomolecules by extracting these enhanced electromagnetic field signals [29].

3.3. Pathogen Detection

Gold nanomaterials biosensors play an important role in pathogen detection. By combining gold nanomaterials particles with biosensor technology, highly sensitive and specific pathogen detection can be realized. Surface plasmon resonance (SPR) sensor: The SPR sensor is a biosensor based on the principle of photorefraction. The modification of gold nanoparticles on the surface of the SPR sensor can increase the binding affinity of the sensor to pathogen molecules and signal amplification. When pathogen molecules are bound to the surface of the gold nanoparticle-modified SPR sensor, the refractive index can be changed, and pathogen detection can be realized by detecting the change in refractive index. The rod-shaped gold nanomaterials has a strong photothermal conversion effect[30], in Qu Xiaogang's group, they developed a photothermal-responsive hydrophobic drug delivery system, prepared gold nanomaterials rods with a silicon layer coated on the surface, and loaded anticancer drugs into the rod structure, and used the aptamer DNA to block the pores in the rod structure in the way of controlled drug release using the photothermal effect in mice, and at the same time, effectively kill cancer cells[31]. In addition, the group demonstrated that functionalized gold nanomaterials could not only cross the blood-brain barrier and effectively alleviate the symptoms of Alzheimer's disease in mice, but also serve as a bioprobe for the detection of the abnormal protein β-amyloid [32] which is potentially clinically applicable. The results of the research group of ElSayed [33] showed that colloidal gold nanomaterials particles were non-specific in both normal and malignant epithelial cells, colloidal gold nanomaterials particles could not distinguish between normal and malignant cells. However, after conjugation of monoclonal anti-epidermal growth factor receptor antibodies to gold nanoparticles, it was observed that the particles specifically and uniformly bound to the surface of cancer cells, which had a relatively clearer redshift maximum compared to the SPR uptake bands formed by non-cancerous cells. By tuning the size, shape and composition of the gold nanoparticles, their ability to specifically recognize specific cell surface antigens was improved. The gold nanoparticles serve as a biosensor for the non-invasive and highly selective detection of cancer cells.

3.4. Immunoassay

Yuan Zhang [34] explored the application of magnetic immunoassay strategy in the isolation and enrichment of cancer cells and established a new immunoassay method combining the technique of cellular magnetic immunoassay sample pretreatment with gold nanomaterials labeling ICP-MS detection.He used gold nanomaterials(AuNPs) as labels, which were labeled on the surface of Jurkat T cells by combining them with anti-CD2 antibody. After acid desorption, the labeled cells were introduced into an ICP-MS (Inductively Coupled Plasma Mass Spectrometer) for subsequent measurements, and cellular information was obtained by detecting the Au signal.

Currently, antibodies are usually covalently conjugated to AuNPs to form stable biosensors, and in these antibody-based gold nanomaterials biosensors, AuNPs serve not only as substrates for antibody immobilization, but also as signaling molecules and signal amplification elements. The group of Riccardo Farrador[35] used the LSPR signals of AuNPs to detect biotin, based on the highly specific interactions between biotin and affinin or streptavidin. Binding of biotin to affinomycin or streptavidin leads to a change in the refractive index of the binding region, which causes a change in the LSPR signal of AuNPs. The number and concentration of biotin molecules can be inferred by detecting the intensity or wavelength shift of the LSPR signal.

Zhang et al [36]. discovered an immunoassay method for quantitative analysis of proteins combining gold nanomaterials-labeled antibody with ICP-MS detection, which was achieved by using gold nanomaterials as a labeled probe and combining ICP-MS detection technique with immunoassay method for rabbit anti-human serum albumin IgG antibody with a detection limit of 0. 4 fg/L-1. It utilizes the surface plasma resonance effect and good biocompatibility of gold nanomaterials and applies it as a biomarker in the field of immunoassay.

4. Conclusion

Despite the remarkable progress of gold nanomaterials biosensors in various fields, gold nanomaterials biosensors still face some challenges in clinical applications.gold nanomaterials particles may cause adverse reactions in biological systems, such as oxidative stress, cytotoxicity, and inflammatory responses, therefore, the biocompatibility of gold nanomaterials materials needs to be studied and optimized. In vivo stability is another important challenge for the clinical application of gold nanomaterials biosensors. In living organisms, gold nanoparticles may be affected by adsorption, aggregation, and degradation of biomolecules, which can lead to a decrease in sensor performance. Therefore, there is a need to design stabilized gold nanoparticles to improve their stability in organisms.

In future research, by optimizing the properties of gold nanomaterials materials, developing novel biorecognition units and improving the integration of gold nanomaterials biosensors, it is expected to provide more efficient and accurate tools for disease diagnosis, biological research and other fields. Meanwhile, strengthening the clinical translational research and bioethical research of gold nanomaterials biosensors is of great significance to promote the wide application of gold nanomaterials biosensors.

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