Regulating the Optical Properties of Gold Nanoclusters for Biological Applications

Shuxian Zhu, Xiaoyu Wang, Yujie Cong, and Lidong Li*

ABSTRACT: Gold nanoclusters are promising optically functional materials because of their attractive optical properties, such as luminescence, two-photon absorption, photothermal conversion, and photodynamics. Regulating the optical functions of gold nanoclusters and improving their performance have attracted wide interest in biological applications. In this Review, we introduce the principles to manipulate both the intrinsic optical properties and the apparent optical performance of gold nanoclusters. Manipulating the surface ligands and compounding with other nanomaterials are facile and efficient strategies. Based on the regulated optical properties, the gold nanoclusters can be well applied in various biomedical applications from multimodal bioimaging toward theranostics. By correlating structures and optical properties, we expect a better utilization of the optical gold nanoclusters in the biological field.

1. INTRODUCTION
Optical detection has been a convenient method for recent biological research owing to its high sensitivity and high efficiency. Nanostructures with highly controlled optical properties play decisive roles in optical technology. Gold nanoclusters (AuNCs) with ultrasmall size and atomically precise structures attract intense interest due to their unique optical properties. The quantum confinement effect facilitates the discrete electronic structure of nanocluster, which results in a series of molecular-like photophysical and photochemical properties such as strong luminescence, two-photon absorption, molecular chirality, photothermal conversion, and photodynamics. In addition, AuNCs are reported to exhibit superior biocompatibility. Therefore, they hold intriguing promise for applications in biological detection, bioimaging, and phototherapy.

However, in these biological applications, strong ionic strength, variable pH, and abundant biomolecules in complex physiological environment may induce aggregation and even destruction of AuNCs. These problems may hinder the realization of desired optical functions. AuNCs possess unique structures that are composed of metal cores and protected organic ligand shells. Ligands on the surface of nanoclusters significantly influence their structures and change their optical properties. Rapid developments in nanotechnology provide ways to regulate the optical properties of AuNCs by ligand engineering. Exploiting thiolate ligands and biomolecules for water-soluble nanoclusters may facilitate their photostability in physiological environment for targeted imaging of cancer cells. Besides direct ligand modification, modifying the surface ligands of AuNCs with functional groups is also available for regulating the structure-related optical properties. The functional groups can interact with surface ligands through conjugation, noncovalent interaction, ligand exchange, and self-assembly. In particular, the combination of AuNCs with other nanomaterials can remarkably improve their optical properties. Therefore, surface engineering of AuNCs is a promising strategy for achieving enhanced optical properties, such as strong intensity, good photostability, large Stokes shift, adjustable wavelength, and superior stability in a biosystem. These performances are greatly desirable for biological applications.

As mentioned above, AuNCs exhibit highly controllable and tailorable structures. It would be of great importance to focus on regulating the optical properties of AuNCs for biomedical applications. In this Review, we will briefly introduce the surface engineering principles and strategies to manipulate the optical functions of AuNCs. Then, we will summarize recent applications of their optical properties in biological fields from multimodal bioimaging toward theranostics. Finally, we will present our perspectives on regulating the optical properties of AuNCs for further biological applications.

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2. REGULATING THE OPTICAL PROPERTIES OF A GOLD NANocluster

The AuNCs are composed of a few to a hundred gold atoms and the surface organic ligands. Their optical properties are closely related to the precise compositions and structures, and they can be regulated in different ways. As shown in Scheme 1, ligands shape the geometry structures of AuNCs and contribute to the electron and energy transfer between ligands and metal cores. Thus, the ligands can influence the intrinsic optical properties. In another aspect, changing the surface properties through modifying ligands and compounding with other materials is an effective strategy to improve the apparent optical performance in complex environments.

Derived from the quantum confinement effect, AuNCs with ~2 nm metal core can exhibit discrete energy levels. Electronic transitions between the highest occupied molecular orbital and the lowest unoccupied molecular orbital can generate optical absorption and luminescence. Therefore, the geometry structures of metal cores determine the electronic transitions of AuNCs. Suitable organic ligands can efficiently hinder aggregation of excessive gold atoms and isotropic growth of metal cores. The sizes of AuNCs are limited, and the internal structures are determined. Thiolate ligands are the most typical ligands to stabilize AuNCs because the strength of the Au−S bond is similar to that of the Au−Au bond. The Au−Au bonds in metal cores can be modiﬁed by the bond formation between Au cores and thiol groups. The geometry structures of Au cores inevitably alter with different ligands, which results in changes in the core-structure-related optical properties of AuNCs. In this way, Xie et al. reported a mixed-ligand strategy to ﬁne-tune the optical properties of AuNCs. The ligand-induced surface charge anisotropy can lead to the structure distortion of the metal core. Thus, the optical absorptions of Au14 clusters changed with different ligand compositions.

Besides the intraband transition, the ligand—metal charge transfer (LMCT) also contributes to the luminescence of AuNCs. By tuning the electron-donating ability of ligands, the energy levels and optical gaps of AuNCs accordingly change. Using electron-rich ligands can promote the electron transfer between ligands and metal cores, which facilitates the luminescence of AuNCs. Additionally, the vibration and rotation of molecular chains in organic ligands cause energy loss through nonradiative transition. Surface rigidification of AuNCs by introducing counterions, modifying bulky molecules or capping zwitterionic ligands has been demonstrated to significantly enhance the luminescence intensity. Similar to the aggregation induced emission of organic molecules, restricting movement of the organic ligands can also explain the enhanced ﬂuorescence of AuNCs. The ordered assembly of nonluminescence Au(I)-SR complexes reduces the energy dissipation from nonradiative transition and enhances the luminescence from the radiative transition. The more compactly the Au(I)-SR complexes aggregated, the more largely the luminescence enhanced. The longer Au(I)-SR motifs are ﬂexible and possess abundant Au(I), which promotes the aurophilic Au(I)···Au(I) interactions and sustains stronger aggregation induced emission of AuNCs. Therefore, organic ligands not only shape the geometry structures of metal cores but also manipulate the charge and energy transfer for regulating the intrinsic optical properties of AuNCs.

Surface engineering based on ligands is a facile and efﬁcient way to regulate the apparent optical properties of AuNCs. For biological applications, the presence of dissolved oxidizing substances and active biomolecules can oxidize gold cores and cause unstable luminescence. Steric protection through extending ligand chains, modifying bulky functional groups, or introducing interligand interactions is proven to be effective against oxidation in aqueous solution. A wide working pH range is often required for AuNCs as ﬂuorescent probes in biological detection. Water-soluble biomolecules, such as glutathione (GSH) and bovine serum albumin (BSA), can efﬁciently protect AuNCs as ﬂuorescent probe for biological applications. However, the protonation and deprotonation of active groups on biomolecules may inﬂuence dispersion of AuNCs in water over a wide pH range, which typically results in the low AuNCs emission in biological medium. Introducing hydrophilic ligands can solve the problem. We fabricated biligand protected AuNCs with enhanced colloidal stability against acidity, alkalinity and high salt concentrations (Figure 1a). For 11-mercaptoundecanoic acid (MUA) protected AuNCs, the H+ ions in acid solutions interacted with the COO− of MUA and weakened the electrostatic repulsion, which resulted in AuNCs aggregation and a ﬂuorescence decrease. The presence of zwitterionic ligand (ZW) could weaken the protonation of MUA and prevent the aggregation of AuNCs. Compared with MUA protected AuNCs, the ﬂuorescence intensities of biligand protected AuNCs were nearly unchanged over a pH range from 4 to 10 (Figure 1b–e). More importantly, we conducted self-assembly of AuNCs by conjugating MUA with the biotin−streptavidin recognition motif.
motif. During the specific binding process, the LMCT between the ligand and the gold core was not affected. Thus, the radiative transitions of assembled AuNCs were not affected, and fluorescence quenching was avoided. The fluorescence signals were amplified with the number of assembled AuNCs. Therefore, the biligand protected AuNCs could be adopted as stable fluorescent probes.

Apart from direct ligand modification, the combination of AuNCs with other materials is a simple strategy to regulate the optical properties of AuNCs in various physiological environment. Inorganic silica is a promising matrix for the incorporation of nanoclusters. We designed and synthesized fluorescent nanocomposites through in situ reduction of AuNCs in mesoporous silica nanoparticles. For one side, the nanopores of silica regulated the diffusion of ligands and reducing agents, which facilitated the ultrasmall AuNCs formation. On the other hand, a mesoporous framework prevented AuNCs from aggregation in PBS. The aggregation-induced fluorescence attenuation was avoided. The nanocomposites could exhibit stable fluorescence from AuNCs in a solution with low pH value or high ionic strength. The good stability of nanocomposites can benefit cancer cell imaging and detection. The combination of AuNCs with polymers or biomacromolecules is another effective approach to fine-tune the optical properties. We adopt the self-assembly technique to combine organic ligands with polysaccharide and polypeptide, which can form fluorescent nanocomposites with assembly enhanced emission and reactive oxygen species (ROS) generation. As shown in Figure 2a, the GSH ligands on the surface of AuNCs are responsible for the assembly behavior. Through isothermal titration microcalorimetry in Figure 2b and 2c, hydrophobic and electrostatic effects were identified between AuNCs with hyaluronic acid (HA) and protamine (PROT) during the AuNCs-decorated nanocomposites formation. The strong interactions stabilized the Au–S environment around AuNCs, which increased the rigidity and weakened the nonradiative transitions. The fluorescence was enhanced. As the intersystem crossing efficiency is usually associated with the gold cores and maintains constant, the phosphorescence emission also increased, accompanied by enhanced ROS generation. Such AuNC-decorated nano-composites showed great potential as theranostic nanomaterials for target imaging and cancer cells’ killing. In addition, we modified the cyclodextrin on AuNCs and adamanate on polymers, respectively. Based on the host–guest interaction of cyclodextrin and adamanate, AuNCs and polymers could assemble as nanocomposites with enhanced fluorescence and stable optical properties in aqueous solutions. Silver ions can induce AuNCs aggregation and Au(I)/Ag(I)–thiolate motifs formation through Ag(I)–thiolate bonds or metallophilic Ag(I)–Au(I) bonds. The surface-immobilized Ag(I) adjusted the LMCT and ligand-to-metal–metal charge transfer, which resulted in enhanced emission with red-shift. Moreover, we conjugated Au/Ag clusters with gelatin to obtain solid composites. The retained aggregation enhanced emission and ROS generation make it a promising antibacterial solid material.

3. Employing the Optical Properties for Biomedical Applications

3.1. Multimodal Bioimaging. The AuNCs with strong luminescence, good photostability and tunable emission have been widely used for bioimaging techniques. AuNCs with size blow 2 nm can easily enter the cell and adsorb on the biomembranes, which may improve the resolution of intracellular imaging and sensitivity of tissue imaging. By rationally designing ligands and conjugating biomolecules, the intracellular distribution and specific binding of AuNCs can be regulated. Our group developed biligand engineered AuNCs that can assemble on the cell membranes and provide amplified signals for multimodal fluorescent imaging. As shown in Figure 3a, the MUA ligands provide abundant carboxyl for covalent binding of streptavidin and biotin to AuNCs. With the specific recognition between streptavidin and biotin, multilayered AuNCs assembled on biotin modified cell membranes. The zwitterionic ligands could prevent nonspecific adsorption. The multilayered AuNCs overcame aggregation-induced quenching and exhibited amplified fluorescence emissions. Additionally, the engineered AuNCs possessed...
large two-photon absorption cross sections and long fluorescence lifetime. Based on the assembly amplified signals of AuNCs, we performed multimodal imaging of cell membranes through one-photon, two-photon, and fluorescence lifetime imaging technology (Figure 3b). The multimodal analysis could provide detailed information on disease-related biomarkers on cancer cells. By ligands functionalization, the controlled assembly of AuNCs on subcellular structures, such as nucleus, organelles, or cell membranes may achieve. Then, the linear and nonlinear optical properties will permit AuNCs to be applied in multimodal bioimaging.

For in vivo imaging, the combination of different imaging technologies is efficient to provide comprehensive information. For example, zwitterionic ligands protected AuNCs have been developed as multimodal probes for both fluorescence imaging and photoacoustic imaging.32 The high coverage of zwitterionic ligands improves surface rigidity and provides bright near-infrared fluorescence. Meanwhile, the larger gold core enables the AuNCs to adsorb near-infrared (NIR) light and generate photoacoustic signals. In addition, traditional computed tomography and magnetic resonance imaging are also integrated to accurately identify disease sites. A silica-protected Cd3+-AuNCs exhibited significant fluorescence, high X-ray attenuation, and reasonable relaxivity. The AuNCs were then applied for near-infrared fluorescence imaging, computed tomography imaging, and magnetic resonance imaging in tumor-bearing mice.33

3.2. Therapeutic Applications. The AuNCs can be used as therapeutic agents for disease treatment. However, novel AuNCs still need to be developed to improve treatment outcomes and reduce drug resistance. The discrete energy levels and molecule-like optical properties offer great potential for AuNCs to act as photosensitizers. Energy transfer from excited triplet states to oxygen could generate ROS, which facilitated the photodynamic therapy for cancers.10 We prepared therapeutic nanocomposites based on AuNCs with enhanced ROS generation.29 Owing to the specific binding between HA and CD44, the nanocomposites based on AuNCs could serve as efficient photosensitizers to kill MDA-MB-231 cancer cells. Derived from robust ability to adsorb and scatter X-ray, structurally defined gold-levonorgestrel nanoclusters were demonstrated as radiosensitizers for cancer therapy.34 The ROS burst upon irradiation was investigated to cause the cell apoptosis and suppress in vivo tumors’ formation of a mice model. In photothermal therapy, AuNCs with NIR absorptions could implement efficient photothermal conversion for cancer therapy.35 The conjugation of near-infrared dye on AuNCs carriers can also enhance the ICG-mediated photothermal therapy.56

3.3. Toward Theranostics. Multifunctional platforms, which integrate imaging and therapy into a single system, attract significant interest. Biomolecule-protected AuNCs inherit the biological activity of biomaterials and the attractive optical properties of AuNCs. They have been applied for complex and efficient biological diagnosis and treatment. We have developed composites consisting of antibacterial peptides, AuNCs, and conjugated polymer.37 (Figure 4a) The peptide tachyplesin-I was selected as ligand to reduce and stabilize the AuNCs. A photothermal conjugated polymer efficiently converted NIR light energy into heat and facilitated the fluorescent AuNCs formation. With the X-ray photoelectron spectroscopy analysis, we confirmed that the increased temperature promoted Au(1) reduction and accelerated Au(0) collisions to form Au(0)NC@Au(1)AMP core−shell nanostructures. By the NIR light promoted reduction reaction, the more core−shell nanostructures formed and resulted in an enhanced fluorescence as in Figure 4b. Additionally, the antibacterial activity of peptides and the photothermal effect of conjugated polymers were maintained after the reaction (Figure 4c). Hence, these multifunctional composites can be used for treatment of bacterial infection and cancer. The bacteria were initially killed, and the cellular environment was cleared. Then, the cancer cells could be traced with the fluorescent signals from AuNCs. Finally, with the photothermal properties of conjugated polymer, precise killing of cancer cells was triggered by the NIR light. These findings provided an all-in-one therapeutic/diagnostic material for research and treatment of tumors in clinic.

4. CONCLUSIONS AND OUTLOOK

In this Review, we briefly summarized methods and biological applications in regulating the optical properties of AuNCs. Based on the structure−property correlations, varying the ligands is feasible to regulate the intraband transition via shaping the size and internal structure. Rational designing the electronic structure of ligands may manipulate the LMCT process. Directly engineering the ligands may improving structural stability in a physiological environment, which benefits the optical performance of AuNCs. The combination of AuNCs with other materials may restrict the organic ligands’ movement, which will produce aggregation-enhanced emission. On the basis of the above principles and strategies, we can regulate the optical properties of AuNCs. The AuNCs with excellent optical performances are promising materials for multimodal bioimaging and therapeutic applications. Although the structures of AuNCs can be confirmed, there remains a challenge to identify the accurate structures after AuNCs modification. Again, the luminescence of most AuNCs, which locates in the ultraviolet and visible region, is usually blocked by tissue. The lack of penetration depth may limit the in vivo applications of AuNCs. By manipulating the intrinsic optical properties or compounding with other optical materials, AuNCs with NIR response would be achieved. Designing anisotropic surface charged AuNCs may be a promising strategy to realize absorbance and emitting in the shortwave infrared window from 900 to 1700 nm.39 The two-photon absorption of AuNCs will allow excitation in the shortwave infrared region.39,40 With response in the short infrared

Figure 4. (a) Schematic illustration of stepwise killing of bacteria and cancer cells with the composites consisting of antibacterial peptides, AuNCs, and conjugated polymer. (b) Fluorescence emission of AuNCs prepared with NIR light irradiation and control group. (c) Photothermal heating curve and cooling curve of composites under 808 nm NIR irradiation. Reprinted with permission from ref 37. Copyright 2020 American Chemical Society.
window, these AuNCs can be well applied for deep tissue therapy. We expect that the optical properties of AuNCs will be constantly exploited, which will promote biomedical research and applications.

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**Notes**

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Xiaoyu Wang received a Ph.D. in materials science and engineering from the University of Science and Technology Beijing in 2014. After postdoctoral work at Institute of Chemistry, Chinese Academy of Sciences, she was appointed to a lectureship at University of Science and Technology Beijing in 2016. Currently, her research focuses on the preparation and application of composite system based on fluorescent materials.

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