Gold Nanoparticles for Cancer Photothermal Therapy

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Abstract: In recent years, there has been a great deal of interest in the new therapy of cancer treatment. Photothermal therapy is one of the new ways to inhibit tumor formation. Many studies have confirmed gold nanoparticles can absorb light at specific wavelengths, especially near-infrared light, through their unique optical properties called localized surface plasmon resonance (LSPR) to achieve photothermal treatment of tumor cells. Moreover, a large number of experiments have shown that gold nanoparticles with different structures have different absorption spectra and LSPR peak position, which make them have different photothermal efficiencies. In addition, gold nanoparticles modified by different functionalized compounds have better biocompatibility and targeting ability, which greatly broadens the scope of its application in tumor photothermal therapy and improves the therapeutic effect. In this paper, we conclude recent progress in gold nanoparticles for cancer photothermal therapy. First, we introduce the optical properties of gold nanoparticles and the principle of photothermal conversion. Then, the influence of different nanostructures and functional modifications on the effect of photothermal treatment is discussed. Finally, we briefly describe several common types of multifunctional gold nanoparticles, and introduce their basic principles and functions. Due to the large amount of experimental data in relevant aspects, this paper mainly discusses the research progress of gold nanoparticles in the field of photothermal therapy after 2015.

1 INTRODUCTION

Many studies have confirmed that gold nanoparticles have unique optical properties. One of the most vital optical properties of gold nanoparticles is the collective coherent oscillation of their free conduction band electrons, or the localized surface plasmon resonance (LSPR) (Austin 2014). LSPR is the coherent oscillation of the nanostructure’s conduction band free electrons in resonance with the incident electromagnetic field. Since the incident light causes a high degree of polarization of the free conduction band electrons, when gold nanoparticles are placed in an external field, a displacement of negative and positive charges will occur, that is, a net charge difference is generated at the boundaries of the nanoparticles (Ghosh 2007). Gold nanoparticles can absorb/scatter incident light, and photon confinement causes strong electromagnetic fields and various optical phenomena on the metal surface (Abadeer, 2016). This interaction strongly depends on the composition, size, geometry, dielectric environment and particle-particle separation distance of nanoparticles (Petryayeva, 2011). So, the LSPR peak of the gold nanoparticles can be changed by preparing nanoparticles with different structures.

It is precisely because of the characteristics of LSPR that gold nanoparticles can absorb light at a specific resonance frequency, and the energy absorbed can also be attenuated in the form of radiation (such as optical scattering) and non-radiation. Photothermal therapy uses the non-radiative attenuation of energy, and uses the LSPR effect to cause coherent oscillations of electrons in the crystal lattice. In a very short time (femtosecond scale), the electron pulses collide with the gold crystal lattice, causing the electrons to generate extremely high temperatures. Then, heat is transferred to the outer surface of the gold nanoparticle through the interaction between the electron and the electron, the electron and the phonon, and the phonon and the phonon, so that the gold nanoparticle can heat the surrounding medium (Austin, 2014).

Since tumors are more sensitive to temperature, a short period of high temperature can effectively kill
cancer cells around the gold nanoparticles and induce their apoptosis. Also, by changing the structure of gold nanoparticles, the LSPR can be excited at near-infrared light, and near-infrared light has a stronger penetration of physiological structures, which can better activate the nanoparticles in the body.

Gold nanoparticles can also be functionalized with surface modification to improve their targeting ability and specificity, so that they can be better enriched at the tumor site, thereby improving the effect of photothermal treatment.

Therefore, this review focuses on the impact of the structure and functionalization of gold nanoparticles on the effect of photothermal therapy. By summarizing the photothermal conversion efficiency of gold nanoparticles of various structures, we try to find the most advantageous structure, hoping to provide structural suggestions for the future research of gold nanoparticle photothermal therapy.

2 CHARACTERIZATION OF GOLD NANOPARTICLE

A large number of studies have shown that in addition to increasing the heat output by changing the incident light power, the shape, size and surface characteristics of the gold nanoparticles can also be optimized to adjust the LSPR peak and photothermal conversion efficiency (Singh, 2018). Considering the penetration depth and safety of light in physiological tissues, the LSPR peak of gold nanoparticles used in most photothermal treatments is in the first (650-850 nm) or second (950-1350 nm) near-infrared window (Riley, 2017). Therefore, the structure of the nanoparticles needs to be adjusted to maximize the absorption of laser light in this window.

Studies have shown that small size (<8nm) gold nanoparticle is little cytotoxicity, which can be filtered in the kidneys, whereas larger nanoparticles size (> 10nm) likely to remain in the body cannot be discharged, which aggregates in the liver and kidneys, causing damage to cells (Vines, 2019). However, small-sized gold nanoparticles are easily excreted and are not easy to aggregate in tumor cells, and oversized nanoparticles are not easy to pass through the blood vessel wall into tumor cells. Both of these will affect the killing effect of photothermal therapy on tumor cells. Therefore, it is necessary to control the size of gold nanoparticles to find the best effect.

At present, common gold nanoparticle shapes include gold nanospheres, gold nanorods, gold nanoshells, gold nanostars, and gold nanocages. These shapes have different light absorption cross-section and LSPR peaks, so as to have a different wavelength of light absorption and photothermal conversion efficiency. In addition, the different shapes mean that the surface properties of these gold nanoparticles are different, which affects their ability to adsorb to tumor cells or the difficulty of being swallowed by them. These can be changed by improving the structure of nanoparticles, thereby ultimately increasing their enrichment at the tumor site, reducing damage to the surrounding normal tissues, and effectively improving the efficiency of photothermal conversion (Guo, 2017).

<table>
<thead>
<tr>
<th>Gold nanoparticle shape</th>
<th>Size(nm)</th>
<th>LSPR peak position(nm)</th>
<th>Laser</th>
<th>Photothermal conversion efficiency</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>nanorods</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Au-TEMPO NRs</td>
<td>39.2(aspect ratio 3.85)</td>
<td>785</td>
<td>808nm, 1.13 W/cm2</td>
<td>-</td>
<td>(Xia 2018)</td>
</tr>
<tr>
<td>AuNR-MEND</td>
<td>68±18.3</td>
<td>788</td>
<td>750–900nm, 1.0W/cm2</td>
<td>-</td>
<td>(Paraiso 2017)</td>
</tr>
<tr>
<td>Bi2S3-Au NRs</td>
<td>271±19.5</td>
<td>-</td>
<td>808nm, 0.75W/cm2</td>
<td>51.06%</td>
<td>(Cheng 2018)</td>
</tr>
<tr>
<td>AuNR-Glu</td>
<td>134.4(±6.2)×23.9(±1.8)</td>
<td>1070</td>
<td>1064nm, 1.0W/cm2</td>
<td>43.12%</td>
<td>(Li 2018)</td>
</tr>
<tr>
<td>GNRS-HA-FA-DOX</td>
<td>70.9±1.4</td>
<td>779</td>
<td>808nm, 2.0W/cm2</td>
<td>-</td>
<td>(Xu 2017)</td>
</tr>
<tr>
<td>GNR-HA-ALA/Cy7.5-HER2</td>
<td>55.1(±1.7)×14.1(±1.1)</td>
<td>800</td>
<td>808nm, 2.0W/cm2</td>
<td>-</td>
<td>(Xu 2019)</td>
</tr>
<tr>
<td>nanoshells</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tf-GNRS</td>
<td>205.8(±13.1)×112.0(±4.8)</td>
<td>808</td>
<td>808nm, 8.0W/cm2</td>
<td>17.70%</td>
<td>(Zhao 2017)</td>
</tr>
</tbody>
</table>
There have been many studies on the influence of the structure and size of gold nanoparticles on the efficiency of photothermal conversion. The structure and photothermal conversion efficiency of them are shown in the table, and there is a big difference between them. (Table 1) It is noted that the LSPR peak positions of the gold nanoparticles with the same shape are almost the same. Most of them will have a certain blue shift or red shift due to the difference in functional modification and size. However, a few of them have different structures due to special synthesis or processing methods, which makes them have a big difference in optical properties from other nanoparticles of the same type of structure. The positions of the LSPR peaks of the gold nanoparticles prepared into different shapes are quite different, since the different surface characteristics caused by their shapes leads to the differences of the electromagnetic wave wavelengths which cause surface ion resonance. However, the photothermal conversion efficiency is not necessarily related to the difference in these structures or surface modifications. Since these efficiencies are not measured in a physiological environment, the photothermal conversion efficiency of gold nanoparticles in vivo may be affected by many factors and changes. It is noted that many reports indicate that gold nanoparticles may aggregate in a physiological environment, and changing the intensity of laser irradiation and the concentration of the gold nanoparticle solution will also affect the photothermal conversion, which makes it impossible to compare the efficiencies measured in different experiments. In addition, some materials used for functionalization or surface modification of gold nanoparticles will also affect their light/heat conductivity, thereby affecting the efficiency of photothermal conversion. For example, gold nanorods functionalized based on hyaluronic acid are modified differently to have different photothermal treatment effects. Xu, W et al (Xu, 2017). In vitro experiments, the total apoptotic rate of MCF-7 cells treated with hyaluronic acid functionalized gold nanorods modified by folic acid (GNRS-HA-FA-DOX, 66.00%) was much higher than that of those that were not modified by folic acid (GNRS-HA-DOX, 37.17%). Therefore, it is impossible to conclude which shape or functionalization of gold nanoparticles has the best photothermal conversion efficiency. In view of this, it is considered that it is useful to calculate the photothermal conversion efficiency when improving the photothermal treatment effect of a certain gold nanoparticle, which can reflect its heating efficiency in the body and its killing effect on cancer cells to a certain extent.

Although the properties of gold nanoparticles with the same structure will be very different, they also have many commonalities. For example, due to its unique shape, gold nanorods have been a popular structural research direction since they were first synthesized. As a slender anisotropic shape, it has two LSPR peak positions, including transverse plasmon resonance (TSPR) on the short axis (mostly
in the visible region) and longitudinal plasmon resonance (LSPR) on the long axis (mostly in the near-infrared region) (Elahi 2018). In addition, the longitudinal absorption peak is affected by the aspect ratio, which shows that the peak position redshifts as the aspect ratio increases (Brolossy 2008). Thus, because of its unique optical and physicochemical properties, the gold nanorods are widely used in photothermal therapy. As one of the first studied structures, gold nanospheres have gained popularity due to their small size and ease of synthesis. The position of the LSPR peak of gold nanospheres is mainly affected by its size. The size increases from 1 to 100 nm, and the relative absorption peak of the size is 500 to 550 nm (Elahi 2018). Due to its small size, it can be coupled or modified with many ligands, effectively improving its photothermal performance.

3 MULTIFUNCTIONAL GOLD NANOPARTICLES

In many studies, gold nanoparticles for photothermal therapy are not single functional. Many of them will be combined with other popular anti-cancer detection methods or treatment methods, including photodynamic therapy, tumor imaging, biosensing and drug delivery.

The common multifunctional combination of gold nanoparticles is photodynamic therapy and photothermal therapy, both of which use light absorption to kill tumor cells. Effective fluorescence quenching and local surface plasmon resonance (LSPR) absorption, easy to combine with mercaptans, disulfides and amines, gold binding facilitates intracellular penetration is also the reason why gold nanoparticles can be used for photodynamic therapy. The difference is that photodynamic therapy is a biochemical action induced by a photochemical reaction, which uses light, photosensitizers, and oxygen from tissues. During the process, the photosensitizer needs to be injected into the tumor site. Because the half-life of the photosensitizer administered systemically or locally is different in each tissue, the concentration of the photosensitizer in the tumor tissue is significantly higher than that in the normal tissue after a period of time. Selective retention, under the action of excitation light of a specific wavelength, and in the presence of molecular oxygen, singlet oxygen and other reactive oxygen species (ROS) are produced, leading to tumor cell necrosis and apoptosis. Secondly, PDT can also destroy the capillaries in tumor tissues, causing ischemia and hypoxia, leading to cell death. Finally, PDT can induce a variety of immune cells to rapidly infiltrate the tumor, activate the complement system, and promote the production and release of a variety of cytokines/chemical factors, and finally initiate the body's immune response to kill the tumor (Singh, 2018, Elahi, 2018). Unlike PTT, which does not rely on oxygen, PDT is completely dependent on the availability of tissue oxygen. Therefore, photodynamic therapy does not affect the photothermal treatment effect of gold nanoparticles itself. For example, based on the new photosensitizer BPS, combined with the plasma photothermal agent Au nanoparticles and the targeting agent Fe3O4 nanoparticles, the multifunctional BPS@Au@Fe3O4 was successfully prepared through a simple, gentle and reproducible method. The final prepared composite material has a wide light absorption band and photodegradable properties. Yang, D et al (Yang, 2017). Experimental results show that BPS@Au@Fe3O4 nanoparticles have a high degree of biocompatibility, and low-power near-infrared laser-mediated synergistic photothermal and photodynamic therapy shows excellent tumor suppression effects. At the same time, the combination of photodynamic effect, photothermal effect and magnetic resonance imaging is helpful for comprehensive and integrated treatment of tumor sites and improve the effect of cancer treatment.

The most common combination is to use gold nanoparticles as a carrier, not only for photothermal therapy, but also as a carrier for other drugs or ingredients, to play a role in drug delivery. The coupling of gold nanoparticles and drug molecules plays an important role in the treatment of intracellular diseases. Their unique physiologic properties can promote the delivery of drugs into cells, thereby improving the efficacy of drugs. Antibiotics or other drug molecules can be directly coupled to gold nanoparticles through ionic or covalent bonds or physical absorption. At the same time, because AuNPs have unique optical, physical and chemical properties, biocompatibility, functional flexibility, adjustable monomolecular membrane, controllable dispersibility, high drug loading density surface area, stability and non-toxicity, etc. Make it an effective nanocarrier in the drug delivery system (DDSS). These effective nanocarriers can transfer various drugs, such as peptides, proteins, plasmid DNA (PDNAs), small interfering RNAs (SiRNAs) and chemotherapeutic drugs. Gold nanoparticle
carriers can be used to control drug delivery and release methods, such as the use of external stimuli (such as light) or internal stimuli. Therefore, it can effectively combine chemotherapy and photothermal therapy, while using physical and biochemical methods to kill tumors (Elahi, 2018, Kong, 2017). For example, the gold nanocage wrapped in red blood cell membrane is used as a carrier to load the anti-tumor drug paclitaxel (PTX) for targeted photothermal and chemotherapy for cancer. Zhu, D et al (Zhu, 2018). The results show that EpCam-RPAuNs nanoparticles have better targeting ability to 4T1 cells than unmodified nanoparticles. The high temperature generated by AUNS under 808 nm near-infrared radiation has a dual effect. First, the increase in temperature promotes the release of PTX by destroying red blood cell vesicles. Second, as a photothermal treatment method, it directly uses hyperthermia to kill cancer cells. In addition, overheated AuNs will cause a large number of cancer cell deaths, which will greatly reduce the viability of 4T1 cells. The combination of the two results in better tumor treatment efficiency. For another example, a cancer cell-erythrocyte hybrid coated doxorubicin (DOX) gold-loaded nanocage (CM-EM-GNCs@DOX) is used for the combined treatment of breast cancer with photothermal/radiotherapy/chemotherapy. Sun, M et al (Sun 2020). CM-EM-GNCs@DOX has high photothermal conversion effect and near-infrared response drug release behavior. Compared with naked GNCs, CM-EM-GNCs@DOX has high homology targeting to MCF-7 cells, and because it retains the characteristics of cancer cell membranes and red blood cell membranes, it has a good immune escape ability. Under near-infrared irradiation, CM-EM-GNCs@DOX exhibits a high photothermal effect, which not only breaks CM-EM-GNCs@DOX, releases DOX for precise and controllable chemotherapy, and is enhanced by photothermal therapy Received chemotherapy/radiotherapy.

In addition to the above two common multifunctional gold nanoparticles combined with photothermal therapy, some gold nanoparticles are designed with both sensing and imaging in mind, integrating tumor inspection and treatment, thereby improving cancer treatment efficiency. Due to the LSPR effect, gold nanoparticles show strongly enhanced radiation properties (ie, light absorption, scattering, and fluorescence), making them a potential multi-modal imaging agent. The currently commonly used iodinated aromatic compound contrast agents have high water solubility and low toxicity, but the blood circulation time is very short, and they will be excreted through the kidneys soon. Compared with ordinary reagents, gold nanoparticles can stay in the blood vessel for a longer period of time while taking into account the non-toxic and harmless safety. Therefore, it can be used as a contrast agent for tumor imaging at the same time as photothermal therapy (Elahi, 2018, Dreaden, 2012). The rich chemical and physical properties of gold nanoparticles make them also useful for biosensing. Sensors for different purposes take advantage of the different characteristics of AuNPs. For example, fluorescence-based sensors utilize the fluorescence quenching properties of AuNPs, surface plasmon resonance sensors based on the optical properties of AuNPs, and biological barcode analysis based on strong binding affinity to thiols and visible color changes due to aggregation of gold nanoparticles (Elahi, 2018). These sensors that use the properties of gold nanoparticles can be combined with photothermal therapy to perform treatment while detecting.

4 CONCLUSION AND PERSPECTIVES

In conclusion, we summarized the basic principles of the photothermal properties of gold nanoparticles, and analyzed the latest research on nanoparticles of various structures to find out how the structure and functionalization affect the photothermal conversion efficiency, such as changing the effective light absorption area, aspect ratio or size. Besides, we have confirmed the commonalities of nanoparticles with the same structure, which allows us to use the advantages of gold nanoparticles with different structures to solve different photothermal treatment needs.

In recent years, the technology of synthesis and functional modification of gold nanoparticles has developed rapidly, leading to the production of many gold nanoparticles with unique properties and different structures. And because of the antibacterial, anti-oxidant and easy modification properties of gold itself, taking advantage of these characteristics and functionalizing nanoparticles can make it more widely used in the field of photothermal therapy. In future research work, more attention should be paid to the targeting properties of gold nanoparticles so that they can be more actively targeted to specific sites. Moreover, it is necessary to continue to improve the structure or surface modification to reduce its cytotoxicity and avoid its excessive
discharge from the body or long-term retention in the body. Last but not least, it is also vital to study gold nanoparticles that combine photothermal therapy with other tumor treatment methods, such as drug delivery or optical imaging, so as to achieve a comprehensive cancer treatment that integrates diagnosis and treatment.

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