Research Progress of Gold Core-shell Structured Nanoparticles in Tumor Therapy

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Abstract. In previous research, the role of gold nanoparticles in tumor photothermal therapy and radiotherapy has attracted the attention of researchers. However, its limited photothermal conversion efficiency and inevitable biological toxicity restrict its further application. With the development of the field of nanomaterials, researchers have discovered that combining gold into core-shell structured nanomaterials can exhibit many surprising properties and has great potential in the field of tumor therapy. This article systematically reviews the progress of gold core-shell structured nanomaterials in the field of tumor therapy in recent years. In this paper, the progress of gold-core-shell nanomaterials in the field of cancer treatment in recent years is reviewed systematically, and the characteristics, preparation methods and deficiencies of gold core-shell nanoparticles are introduced respectively. Although gold core-shell nanoparticles have a good application prospect due to their low toxicity and good biocompatibility, a lot of research work is still needed to solve the problems such as aggregation, photothermal conversion efficiency and large-scale production.

1. Introduction
Cancer is a common malignant tumor pathology in clinical practice. This disease is caused by abnormal cell growth and proliferation mechanisms. In addition to the uncontrolled growth of cancer cells, they can also locally invade surrounding normal tissues and even metastasize to other parts of the body via the circulatory system or lymphatic system. Cancer has always been one of the important diseases threatening human health. In recent years, cancer has even replaced cardiovascular disease as the leading cause of death in the world, and tumor diagnosis and treatment are the key to curing cancer [1]. However, the effective diagnosis and treatment of tumors is still a serious challenge facing modern medicine.

In the past few decades, materials science has been thinking about the direction of interdisciplinary development. Its research is no longer limited to traditional compounds, but has turned to the hybridization of organic, inorganic, polymer and biological materials. Among the hybrid materials, core-shell nanocomposites have special optoelectronic and chemical properties due to their different composition sizes and structural arrangements. In recent years, they have received widespread attention from scientists [2]. The development of core-shell structured nanomaterials in the medical field provides a new opportunity for the establishment of effective tumor diagnosis and treatment technologies. Among them, gold core-shell structured nanoparticles have been favored by scientists, and much progress has been made recently. This article will review the latest advances in the field of
gold core-shell structured nanoparticles at home and abroad in these years. Through reading the relevant literature at home and abroad, the characteristics and preparation of gold core and gold-shell core-shell structured nanoparticles will be introduced, and its application prospects are also prospected, so that researchers who are new to this field can quickly have a basic understanding of the research progress of gold core-shell structured nanoparticles.

2. Overview of Core-shell Structured Nanoparticles
Core-shell structured nanocomposites (CSNC) are generally composed of a central core and a shell covering the outside. The core and shell in CSNC are connected to each other through physical and chemical interactions [3]. The broad core-shell structure includes not only nanocomposite materials with core-shell structure composed of different substances, but also nanocomposite materials such as hollow microspheres and microcapsules. The core-shell nanomaterials can have different properties by changing and increasing the composition of the shell material. Core-shell composite nanoparticles not only have the function of coating, but also can give their core particles specific catalytic activity, electrical, optical, and magnetic properties through a special gradient structure.

Due to the synergistic effect between the different components, the shell material and the core material have the greatest advantages. Compared with single-component nanomaterials, core-shell composite materials prepared from different materials have various properties and advantages. First, the shell can prevent the agglomeration of internal nano-core particles, protect the core, and make the core more stable. Second, combining two different materials, the composite nanomaterials formed have different properties of the two materials at the same time. Third, the electronic structure of the core-shell structure can be hybridized, which can optimize the core-shell performance. Fourth, the core-shell structure is one uniform and symmetrical structural system with balanced and isotropic chemical properties.

Core-shell nanomaterials, according to the composition and composition of the core-shell materials, usually have the properties of the core and the shell and new properties that the single core-shell component does not have. Core-shell materials generally include inorganic/organic, inorganic/inorganic, organic/organic, hollow spheres, and microcapsules. The usual preparation methods include sol gel, seed method, interfacial growth method and so on.

![Figure 1. Schematic illustration of the core-shell composition microspheres: (a) classic core-shell; (b) hollow microsphere; (c) urchin-like; (d) capsule [3]](image)

3. Analysis and Discussion of Gold Core-shell Structured Nanoparticles
Radiotherapy is currently one of the main methods of clinical treatment of cancer. Its essence is to use radioactive rays to kill cancer cells, so as to achieve the purpose of curing tumors. However, radiotherapy can not only be effective on tumors, but also causes inevitable damage to normal cells and tissues. In addition, repeated radiotherapy may cause cancer cells to tolerate the radiation, making the treatment effect unsatisfactory, so specific tumor radiosensitizers are very necessary. Therefore, researchers turned their attention to functional nanomaterials with unique physical and chemical properties, and discovered their great prospects in the field of tumor diagnosis and treatment. Among many functional nanomaterials, the localized surface plasmon resonance (LSPR) of gold nanoparticles has attracted the attention of researchers. LSPR enables gold nanoparticles to concentrate the light in its own space on the adjacent sub-wavelengths of its surface under resonance excitation. This ability can achieve a great electric field around the nano-gold, and generate a variety of interactions between light matter and new mechanisms. Among them, the characteristics of photothermal conversion and...
radiosensitization have made scholars begin to study the photothermal treatment and radiation therapy of nano-gold in tumors [2].

![Figure 2. Different shapes of Au nanoparticles [2] a. spherical; b. flower-shaped; c. disc-shaped; d. cage-shaped; e. star-shaped; f. rod-shaped](image)

In 2003, L. R. Hirsch et al. [4] used gold nanoparticles for the photothermal treatment of tumors for the first time. They demonstrated that gold nanoparticles caused tumor cell death and tumor ablation under the excitation of near-infrared light, which bring nano gold into the field of tumor treatment. With the deepening of research on gold nanomaterials, researchers have gradually discovered the limitations and deficiencies of single gold nanomaterials for tumor treatment, which means that, its limited photothermal conversion efficiency is still at a relatively low stage compared with some organic photothermal materials. And its stubborn surfactants can bring cytotoxicity, so people have turned their attention to core-shell structured nanoparticles with special properties.

The core-shell structured nanoparticles have many advantages that a single nanoparticle does not possess. For example, when two different materials are re-cored, the core-shell structured nanoparticles will have the properties of the two materials; at the same time with a large-area core layer inside it. The structure can be doped with other nanomaterials, and the shell structure can be modified. These unique characteristics make the gold core-shell structured nanoparticles attract the attention of scholars [5]. In this section, the author will review the recent research on gold core-shell structured nanoparticles in the field of tumor diagnosis and treatment.

### 3.1. Gold shell nanoparticles

Magnetic nanoparticles are used in biomedical fields such as targeted drug delivery, early diagnosis of tumors, and selective destruction of tumor cells due to their high magnetization and appropriate coercivity. However, due to its shortcomings such as easy agglomeration, easy biodegradation, and instability in a magnetic field, it is often difficult to directly apply. Gold nanoparticles have good biocompatibility. When they are covered as a shell layer, the excellent magnetic properties of the inner magnetic nanoparticles are not affected, and they are difficult to agglomerate under the action of a magnetic field and are not easily biodegraded. In addition, this magnetic core-gold shell nanomaterial also integrates the unique properties of gold nanoparticles.

Generally, there are two ways to synthesize multifunctional nanocomposites composed of magnetic cores and gold nanoshells. The first method is to directly coat the gold nanoshells on the iron oxide nanoparticles. Although this method is a simple and economical strategy, agglomerations are often formed during the coating process, resulting in the saturation magnetization of the magnetic nanoparticles, which decrease and lose the potential application in the near infrared resonance (NIR) optical absorption performance of the gold nanoshell. Another method is to use a silicon or polymer
intermediate layer as a bridge between the magnetic core and the outer gold nanoshell. In recent reports, polymers used as intermediate layers have also been developed. Hsiao's research team prepared magnetic nanoparticles using hydrothermal methods, and then polymerized styrene and methyl methacrylate onto Fe3O4 and self-reducing gold on the outer layer of the particles. However, it is difficult to obtain continuous gold nanoshells on the polymer surface by self-reduction method, which will affect the near-infrared light absorption in hyperthermia.

In order to overcome the above problems, Wang Xuandong et al. reported a new method with Fe3O4 as the core in the carboxylated polystyrene sphere based on the coating of gold nanoshells on the surface of carboxylated polystyrene spheres: Polysaccharides (CHI) modify the surface of the polymer ball to further combine with the gold colloid to form Fe3O4@P(St/MAA)@Chitosan@Au. As an excellent modified molecule, chitosan is widely used because of its good biocompatibility, biodegradability and biological activity. This polymer can prevent direct contact between the gold nanoshell and the magnetic particles, and at the same time will not reduce the magnetic field strength as quickly as other reports. Besides, the polymer layer can reduce agglomeration during the coating process. In addition, the Fe3O4 core of the nanoparticles helps magnetic field guide movement and MRI imaging. Gold nanoshells can also be used as DFI contrast agents and for photothermal treatment of tumor cells. These combined functions have great potential in biomedical applications and provide a powerful way for personalized treatment of diseases.

In addition to the magnetic core gold shell nanoparticles, Zhou Jialin added doxorubicin hydrochloride and cobalt nanoparticles to react on the basis of the synthesis of hollow gold nanoparticles, so that the doxorubicin hydrochloride lost the hydrochloric acid root and precipitated in the gold shell. In the inner core, doxorubicin-gold core-shell nanoparticles (DAuNS) were synthesized. The nanoparticles have dual anti-tumor effects-hyperthermia and chemotherapy mediated by near-infrared light. Its gold shell has excellent photothermal conversion efficiency. At the same time, it can trigger the release of doxorubicin under the mediation of near-infrared light to realize the timing and positioning of the drug release. In ovarian cancer SKOV3 cells, DAuNS showed a good chemotherapy effect and a combination of chemotherapy and hyperthermia, and experiments showed that DAuNS has good biological safety.

### 3.2. Gold core nanoparticles

Ma Kun used gold seed-mediated method to prepare and synthesize GNR, and synthesized the nano core-shell structure composite material GNR@LDH of GNR and LDH by the one-pot method of heterogeneous nucleation, and its synthesis path is shown in figure 4.
The photothermal conversion performance of GNR@LDH is applied to in vitro tumor suppression, bio-in vivo tumor imaging and photothermal therapy experiments. Due to its high photothermal conversion efficiency, GNR@LDH exhibits under near-infrared light and appropriate concentration conditions and it has obvious effect of light and heat to kill cancer cells, and has low toxicity. In animal tumor experiments, GNR@LDH is enriched at the tumor site due to enhanced penetration and retention effects, while GNE has PA imaging and CT imaging capabilities, making it tumor-oriented imaging capabilities. Under near-infrared light, the tumor ablated and the whole process did not cause other damages to the mice. In this study, GNR@LDH is expected to be a new and safe photothermal treatment reagent.

Chen Jie [1] prepared core-shell Au@FeS particles by high-temperature oil phase reaction and used the layer-by-layer coating method to modify their surface appropriately to make them have good stability and biocompatibility. Experiments in mice found that the nanoparticles were basically non-toxic at low concentrations, and were less toxic even at high concentrations. At the same time, under near-infrared illumination, it was found that Au@FeS-PEG particles have ideal photothermal conversion efficiency, and the heat generation effect can be controlled by adjusting the concentration and has good photothermal stability. The hypoxic area of solid tumor tissues causes tumors to be resistant to radiotherapy and chemotherapy. Therefore, improving the hypoxic state in the tumor microenvironment is of great help in improving the efficacy of tumor radiotherapy. Experiments have found that the moderate hyperthermia produced by Au@FeS-PEG nanoparticles under near-infrared light improves the hypoxia of tumor tissues, which greatly improves the sensitivity of tumor radiotherapy. Au@FeS-PEG nanoparticles not only kill tumors through photothermal therapy, but also use the radiation sensitization properties of precious metal nanomaterials to make them have radiosensitization effects. Further research found that Au@FeS-PEG nanoparticles have a good photoacoustic imaging effect, which can accurately and real-time monitor the temperature of the tissue during hyperthermia, and prevent light energy deposition from damaging normal tissues. It also has an enhanced MRI T2 display.

To sum up, Au@FeS-PEG is a kind of multifunctional nanomaterials that integrates treatment and imaging, and its further application has great potential in clinic.
Au@pda-mtx/LDH platform for the administration of anti-tumor drugs and vascular treatment. They used diallyldimethylammonium chloride (PDDA) and MTX molecular Laver by-Laver (LbL) technology to obtain the core-shell structures (Au@pda-MTX) directly on the MTX/LDH hybrid surface through electrostatic attraction to obtain Au@PDDA MTX/ LDH NPs. MTX is used as both a surface modifier and an antitumor drug in chemotherapy. Au@pda-mtx/LDH nanoparticles not only have high drug loading capacity, but also have good colloidal stability and interesting pH response release spectrum. In vitro drug release, studies have shown that the release of Au@pda-MTX/LDH is relatively slow at normal physiological pH, but is significantly enhanced at weakly acidic pH. What is more, the use of au@pda-mtx/LDH combined with hyperthermia ablation and chemotherapy to treat cancer has been shown to have a higher therapeutic effect than single treatment alone, highlighting the huge potential of this platform in cancer treatment.

4. Conclusion
Gold core-shell structured nanomaterials have good application prospects in biology, medicine, chemistry, physics, and radiology. This article reviews the research of gold core-shell nanomaterials in the field of tumor therapy. They have good application potential in tumor photothermal therapy, radiosensitization, diagnosis, drug delivery and release.

The gold core-shell structured nanomaterials have relatively low toxicity and good biocompatibility. However, to further apply gold core-shell structured nanomaterials to clinics, it is necessary to do more research work. If the problems of agglomeration, photothermal conversion efficiency, biological toxicity, and large-scale production and preparation of gold core-shell nanomaterials can be better solved, and a more in-depth study of the behavior of gold core-shell nanomaterials in the complex biological environment can be carried out at the same time, this material will have better application prospects in the field of biomedicine.

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