Structure, Synthesis, and Modification of AuNPs in PTT Application

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Abstract. In the 21st century, cancer has caused serious harm to society, and traditional cancer therapies have non-negligible shortcomings. Emerging photothermal therapy (PTT), with advantages of targeting, high efficiency, and low toxicity, is expected to make up for the shortcomings of previous cancer treatments, and gold nanoparticles (AuNPs), due to their localized surface plasmon resonance (LSPR), are the principal photothermal agents for PTT. This paper reviews relevant review articles and research papers from roughly the past decade on AuNPs applied to PTT, extracts the main structures, synthesis methods, and surface modifications of AuNPs, and provides a summary and analysis. At present, the structures adopted for AuNPs mainly include four types: rods, shells, cages, and stars; the main synthesis methods include sodium citrate reduction, the biphasic method, seed-mediated growth, and seedless growth; and surface modifications can be categorized into four types: surface anchoring, hydrophilic coating, functionalization, and biological ligands. For AuNPs to further promote the clinical development of PTT, it remains necessary to study more diversified structures, more scalable synthesis methods, and surface modifications that can reduce their toxicity while providing additional functions.

Keywords: PTT; AuNPs structure; AuNPs synthesis methods; AuNPs surface modification.

1. Introduction

In the 21st century, a major public health problem is cancer, which accounts for about one sixth of deaths caused by noncommunicable diseases and is also one of the three leading causes of premature death in 177 countries [1]. It is estimated that this disease will occur at least once in the lifetime of one in five people, bringing huge negative impacts to society and the economy [2]. However, although there are currently therapies for cancer such as chemotherapy, radiotherapy, and surgery, each still has certain defects. For example, because heterogeneous tumors are difficult to be targeted selectively, chemotherapy may cause systemic toxicity; because the immune system and blood are damaged by radiotherapy, cancer cells may take the opportunity to spread rapidly, etc., and these are pain points in clinical practice [3]. Recently, the emergence of PTT, which uses materials with high photothermal conversion efficiency (photothermal agents) to convert absorbed light into heat to ablate cancer cells, has brought new hope, because while having high precision and low invasiveness it strives to achieve the goal of protecting healthy tissues. PTT is a therapy in which photothermal agents are first injected into the patient’s body, the photothermal agents accumulate at the tumor site, and then near-infrared light is irradiated onto the photothermal agents to generate a large amount of heat to kill cancer cells to treat cancer [3]. Among various photothermal agents, the most popular at present is AuNPs, whose most prominent characteristic is LSPR. LSPR means that when gold nanoparticles are irradiated with incident light of a specific frequency, their free electrons will resonate on the metal surface; this resonance releases heat through nonradiative relaxation, endowing AuNPs with excellent photothermal conversion efficiency [3] and enabling them to provide excellent effects for PTT. The structure of AuNPs is related to their photothermal conversion efficiency and their role in clinical treatment; the synthesis methods of AuNPs are related to the feasibility of large-scale production and application; and the surface modifications of AuNPs are related to their transition from theory to practice and to additional functions. At present, AuNPs have a variety of different structures, synthesis methods, and surface modifications, each providing its own unique properties, enabling them to exert greater potential in the practice of PTT [4]. Therefore, this paper puts forward some suggestions on structural applications, choices of synthesis methods and surface modifications, and makes some prospects for AuNPs in PTT. It is believed that the development of AuNPs will become increasingly mature, and PTT will be applied more and more widely in the clinical treatment of cancer, thereby truly compensating for the shortcomings of traditional cancer therapies in a practical sense.

2. Different Structures of AuNPs

AuNPs can have different unique optical properties according to their different morphologies; in PTT applications they each have their own advantages and characteristics, but at the same time each has certain shortcomings. At present, the gold nanostructures mainly mentioned include the classic gold nanorods and gold nanoshells, while the more novel gold nanocages and gold nanostars also present some features favorable to cancer therapy [4]. Below, this paper will describe the structures of these four types of AuNPs: gold nanorods, gold nanoshells, gold nanocages, and gold nanostars in Table 1.

Table 1. Four main structures of AuNPs and their advantages and disadvantages.

AuNPs structure	Advantages	Drawbacks
Gold nanorods	Produce strong absorption and scattering to near-infrared light[5]	High toxicity and high production cost[9]
Gold nanoshells	Outstanding plasmonic tunability[6]	Synthesis reproducibility remains to be developed[10]
Gold nanocages	Unique potential to carry antitumor drugs[7]	Relatively poor photostability[11]
Gold nanostars	Can serve as contrast agents for photoacoustic imaging[8]	Pharmacokinetics and biodistribution are easily affected[8]

2.1. Gold nanorods

As shown in figure 1(a), gold nanorods are a rod-shaped AuNPs structure with an appropriate aspect ratio. Unlike gold nanospheres, which have only one visible absorption band (around 520 nm), gold nanorods can produce an additional strong long-wavelength band under light irradiation. This indicates that gold nanorods exhibit strong absorption and scattering of light, especially near-infrared light, making them an excellent photothermal agent for PTT [5].

2.2. Gold nanoshells

As shown in figure 1(b), gold nanoshells are a shell-like AuNPs structure with a spherical dielectric core nanoparticle (such as silica) at the center and a very thin gold layer as the outer shell; their advantage lies in outstanding plasmonic tunability [6]. This property allows adjustment of the relative thicknesses of the nanoparticle core and the thin gold shell, thereby tuning the optical absorption of AuNPs, including in the near-infrared region, further improving the targeting of PTT for ablating cancer cells, making gold nanoshells an excellent nanomaterial for PTT [6].

2.3. Gold nanocages

As shown in figure 1(c), gold nanocages are a porous, cage-like AuNPs structure with a unique hollow interior; while possessing tunable localized surface plasmon resonance peaks, they have a unique potential to carry anticancer drugs. In chemotherapy, gold nanocages can serve as platforms to deliver drugs; in PTT, gold nanocages can efficiently convert light into heat, which makes them highly promising for PTT combined with chemotherapy [7].

2.4. Gold nanostars

As shown in figure 1(d), nanostars are a star-shaped AuNPs structure resembling a pentagram with multiple antennae; as AuNPs that can also efficiently absorb light, they have a more unique characteristic—serving as contrast agents for photoacoustic imaging. In addition, the structure of gold nanostars also improves their biocompatibility and reduces their toxicity; compared with other AuNPs structures, the advantages of gold nanostars as photoacoustic probes are incomparable [8].

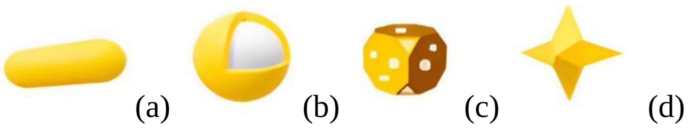

Fig. 1 Four AuNPs structures. (a): gold nanorods; (b): gold nanoshells; (c): gold nanocages; (d): gold nanostars [4].

3. Synthesis Methods of AuNPs

From the perspective of the synthesis route, the synthesis methods of AuNPs used for PTT can be classified into “top-down” and “bottom-up,” each corresponding to different techniques and specific methods [12]. Top-down methods represent starting materials of relatively large volume, which are gradually broken down by external conditions such as laser or irradiation until the nanoscale; bottom-up methods represent the need to obtain initial substances at the nanoscale or even smaller, which undergo a series of specific treatments to form the finally desired AuNPs, and in this process special attention must be paid to preventing nanoparticle aggregation that leads to synthesis failure [12]. Below, this paper will focus on the bottom-up route and describe four methods for synthesizing AuNPs: sodium citrate reduction, the biphasic method, seed-mediated growth, and seedless growth.

3.1. Sodium Citrate Reduction

Sodium citrate reduction, also known as the Turkevich method, uses sodium citrate to reduce chloroauric acid and synthesizes AuNPs under heating and stirring conditions. In this method, tuning the molar ratio of sodium citrate to chloroauric acid enables control over the size of the synthesized AuNPs (showing a negative correlation). This ratio simultaneously influences the surface plasmon resonance (SPR) peak, which exhibits a blue shift as the molar ratio increases. Sodium citrate reduction is a classical, mature, and relatively simple method; however, the size and structure of the AuNPs synthesized are relatively difficult to control, and the reproducibility is poor when synthesizing larger AuNPs [13].

3.2. Biphasic Method

The biphasic method, also known as the Brust–Schiffrin method, consists of two steps: as shown in figure 2, first, tetraethylammonium bromide is used to transfer tetrachloroaurate ions from the aqueous phase to the organic phase, and then sodium borohydride is used to reduce them in the organic phase to obtain AuNPs [14]. In this approach, tuning the molar ratio of dodecanethiol (as the primary reducing agent) to chloroauric acid and varying the duration of the reaction allows precise control over the volume and particle size of the resulting AuNPs [15]. The biphasic method can synthesize AuNPs with diameters as small as 1.0–1.5 nm [14]; however, its reaction process is relatively complex and will pose cost issues in clinical practice.

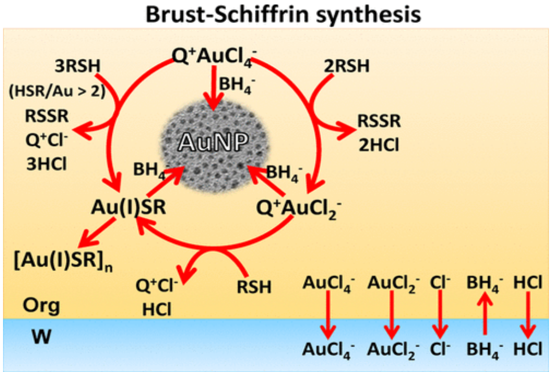

Fig. 2 Ion reactions in the biphasic method [14].

3.3. Seed-mediated Growth

Seed-mediated growth is considered one of the most commonly used synthesis methods for AuNPs: trivalent gold ions are first rapidly reduced by sodium borohydride to form gold nanoparticle bromide seeds, and then a large amount of AuNPs is reduced on the seeds by ascorbic acid. In this method, by adjusting the number of seed particles, the length and diameter of the synthesized AuNPs can be tuned (a negative correlation), and their appearance will also be correspondingly affected. Seed-mediated growth is a well-tested method that mainly produces AuNRs; however, this method requires a specific CTAB concentration [15].

3.4. Seedless Growth

Similar to seed-mediated growth, seedless growth is a more specialized method for synthesizing AuNRs; it directly reduces chloroauric acid with sodium borohydride in a vessel containing hydroquinone to synthesize AuNPs [16]. In this method, by adjusting the amounts of sodium borohydride and silver ions (as shown in figure 3), the thickness of AuNPs can be constrained, and their LSPR peaks can be correspondingly tuned [16]. Seedless growth is an emerging method specialized in the synthesis of AuNRs; the AuNRs it produces have advantages in optical tunability and yield, thus showing potential for application in PTT [16]. However, this method has been less studied and therefore requires further development.

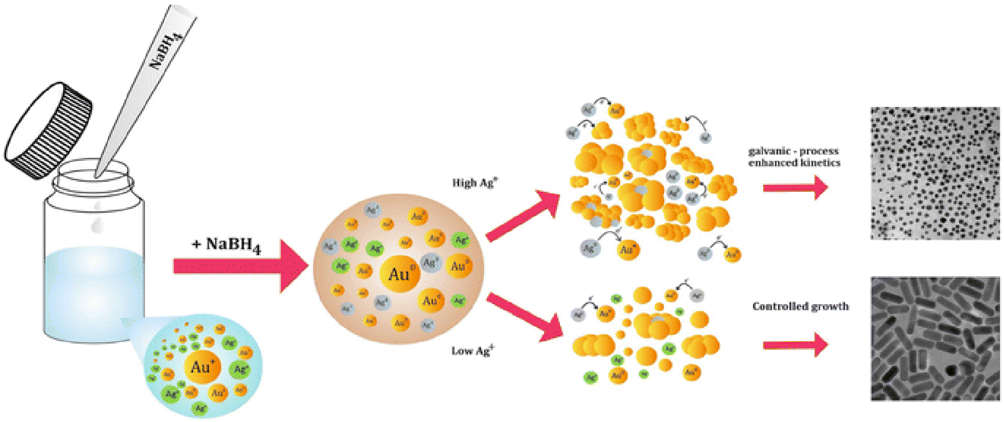

Fig. 3 Controlling the final product in seedless growth by adjusting the amount of silver ions [16].

4. Surface Modification of AuNPs

After AuNPs are synthesized, they usually cannot be directly used in the human body for PTT treatment; relevant surface modification is required to realize their biological functions and improve their biocompatibility [17]. Surface modification of AuNPs covers a wide range; this paper selects its main aspects and divides them into four parts for discussion, namely surface anchoring, hydrophilic outer coating, functionalization, and biological ligands. Surface anchoring refers to molecules that fix AuNPs by forming strong and stable interactions with the gold surface; hydrophilic outer coating refers to a hydrophilic shell that prevents AuNPs from aggregating in bodily fluids and resists fouling; functionalization refers to the incorporation of components that endow AuNPs with new functions such as probing, imaging, and drug loading; biological ligands refer to molecules that can specifically recognize biological targets (strictly speaking, these belong to functionalization, but due to their importance they are discussed separately in this paper).

4.1. Surface Ancoring of AuNPs

In PTT applications, AuNPs will be exposed to various chemical conditions such as pH and temperature, and surface ligands are needed to increase their solubility and make them stable; due to their good coordination, thiols used to be the standard surface anchoring molecules for AuNPs [18]. The N-heterocyclic carbenes synthesized by Michelle J. MacLeod et al. are an emerging class of surface ligands; they are easy to synthesize and can form strong chemical bonds with many hydrophilic outer coatings or functionalization components and therefore have potential for application in PTT [18]. In addition, lipoic acid synthesized by Zhicheng Jin et al. can significantly accelerate phase transfer and improve the stability of AuNPs, likewise showing very good prospects [19].

4.2. Hydrophilic Outer Coating of AuNPs

After AuNPs enter bodily fluids, they will participate in human circulation, and adding a hydrophilic outer-coating layer can prolong their circulation lifetime, thereby promoting targeted therapy in PTT [20]. As shown in figure 4, Ji-Gang Piao et al. developed a novel pH-sensitive stealth shell, which increased the cellular uptake efficiency of AuNPs in acidic tumors and thus enhanced their accumulation in cancer cells [20]. In addition, polyethylene glycol (PEG) is a more classic and commonly used hydrophilic outer coating because it is not easily adsorbed by proteins and has strong water solubility [21].

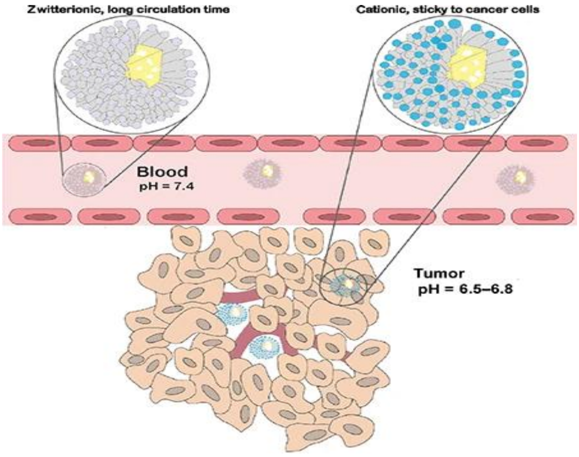

Fig. 4 AuNPs with a pH-sensitive stealth shell accumulating in acidic tumors [20].

4.3. Functionalization of AuNPs

Although AuNPs already have superior performance in photothermal conversion efficiency, their small specific surface area limits their drug-loading capacity; therefore, the functionalization of AuNPs has been continuously studied [22]. As shown in figure 5, Que Lin et al. recently proposed a newly designed drug delivery platform integrating gold nanorods with an upper critical solution temperature (UCST) polymer for potential biomedical applications, which can rapidly release its loaded antitumor drugs during PTT treatment, thereby exhibiting outstanding anticancer capability [22]. In addition, the lipoic acid molecules developed by Rubén Ahijado-Guzmán et al. can realize oligomer self-assembly of AuNPs, thereby reducing the light irradiation intensity required for PTT [23].

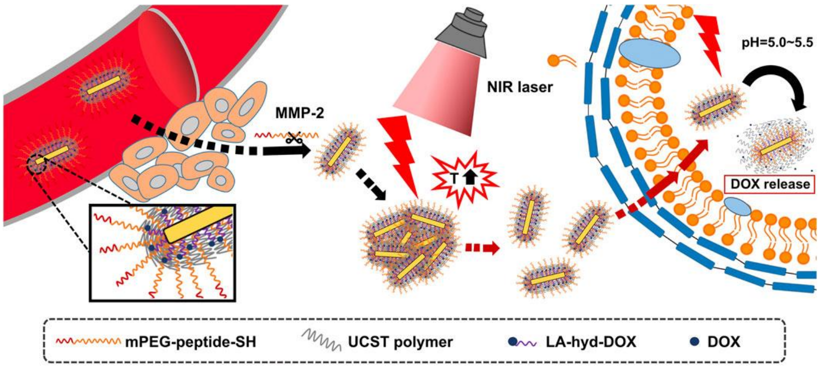

Fig. 5 A new drug delivery platform utilizing gold nanorods and a polymer exhibiting an upper critical solution temperature for biomedical use. [22].

4.4. Biological Ligands of AuNPs

If only bare AuNPs are used during PTT treatment, targeting will be lacking [24]; therefore, biological ligands capable of biospecific recognition are particularly important, as they can do their utmost to preserve the health of tissues surrounding the lesion. Xinmei Kang et al. developed a novel nanocomposite abbreviated as TGN, composed of gold nanorods, porphyrin, and trastuzumab; this composite can recognize HER2-positive breast cancer cells, thereby achieving selective ablation of tumors [24]. In addition, Yajie Zhang et al. recently developed AS1411 aptamer-based AuNPs, which can actively target and accumulate in gastric cancer cells for therapy through the interaction between AS1411 and nucleotides [25].

5. Conclusion

In AuNP-based photothermal therapy, gold nanorods are the most widely studied and applied structures because of their pronounced ability to absorb and scatter near-infrared light; in addition, more emerging structures such as gold nanoshells and gold nanocages are also continuously developing. When choosing synthesis methods, bottom-up approaches such as seed-mediated growth are widely adopted because they can regulate the formation of AuNRs with smaller diameters, and seedless growth is expected to become an approach superior to seed-mediated growth in the synthesis of AuNRs. Surface modification of AuNPs is flourishing and requires corresponding modification processes according to needs, while classic modification processes such as using thiols for surface anchoring and using polyethylene glycol to add a hydrophilic outer coating are still frequently chosen due to their high maturity. This paper summarizes four structures of AuNPs applied to PTT—gold nanorods, gold nanoshells, gold nanocages, and gold nanostars; four synthesis methods—sodium citrate reduction, the biphasic method, seed-mediated growth, and seedless growth; and four types of surface modification—surface anchoring, hydrophilic outer coating, functionalization, and biological ligands. This can help readers who are unfamiliar with PTT and AuNPs and wish to understand the field to gain an overall, generalized initial grasp, while also giving experts in the field some suggested research directions and enhancing the impact of PTT in cancer therapy. However, many deficiencies of AuNPs still remain to be studied—for example, AuNPs are currently mostly based on AuNRs while other structures are less studied; in synthesis, it is difficult to achieve large-scale, reproducible production of AuNPs with defined parameters, which hinders their widespread clinical application; and AuNPs have certain toxicity, which relies on more advanced surface-modification methods to reduce. In the future, AuNPs should develop more diversified structures, advance deeply in scaling up and reproducibility of synthesis, and, according to the needs of different cancer treatments, develop more corresponding surface-modification strategies, so as to promote the further development of PTT, a therapy that is expected to benefit society.

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