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Multifunctional Gold nanoparticle: as novel agents for cancer treatment

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Abstract

One of the most important problems in the therapy of cancer is that along with cancer cells, healthy cells are destroyed, for example, in radiation therapy, the radiation site can be more limited; However, radiation also damages some healthy cells, causing severe side effects for patients, so in recent years a method that can only target cancer cells has become one of the forefront of cancer research. Gold nanoparticles are one of the best drug delivery ever known. These gold particles are very small (one hundredth the size of a red blood cell) and can cross the body's natural and physiological barriers or hard tissues. Gold nanoparticles in cancer cells not only make it easier to image cancer cells, but they can also kill cancerous tumors by heating them. For the direct growth of gold nanoparticles inside a cancerous tumor, polyethylene glycol is used as the carrier of gold ions, which is essentially gold salt that dissolves in a liquid. When this carrier reaches the cancer cell, the cellular-acidic microenvironment converts gold from ionic to plasmonic gold nanoparticles. Another feature is the potential usefulness of gold nanoparticles, which can absorb light and then release energy in the form of heat. This property can make nanoparticles an ideal tool for accurate cancer therapy. Because gold nanoparticles can be purposefully inserted into cancer cells and then exposed to light, they can selectively kill cancer cells through thermal.

Keywords: Nanoparticles; Cancer therapy; Gold

1 Introduction

Cancer is a disease known for the abnormal growth and control of cells. It is DNA damage that can be caused by environmental factors. Cancerous tumors can form on tissues or grow in the body's circulatory system. The main methods of therapy include surgery, chemotherapy and radiation therapy. Tumor resection in surgery is very effective in primary tumors, but is limited to known and accessible tumors, and therefore cancer cells may not be completely removed. Chemotherapy is the use of chemical drugs to fight cancer. Drugs that are systematically administered circulate in the body to kill rapidly dividing cells, especially cancer cells. These drugs are highly toxic and may also damage healthy cells and therefore have significant side effects. Radiation, the use of high-energy ionization (X-rays, gamma rays, or electrons) to damage cells and tissues at a molecular level, is often used as a complementary approach to removing postoperative cancer cells. Radiation can damage healthy tissue near cancer cells or in the radiation pathway [1-6]. X-rays cause the primary and secondary electrons to be excited, which in turn produce free radicals in the body that damage DNA and the body's proteins and biological molecules. Therefore, the use of x-rays should be done with utmost care [7-11]. Photothermal therapy (PTT) is an invasive therapy strategy in which photon energy is converted to heat enough to destroy cancer cells. Heating sources such as near-infrared or visible light, radio waves, microwaves, and ultrasound waves are used to create moderate temperatures in a specific target area to kill cancer cells, which is clinically known as thermal therapy [1, 12-14]. Lack of heat distribution in all diseased cells as well as heat therapy of healthy cells is a challenge that exists in most methods of thermal therapy, even regional methods. Photothermal therapy with gold nanostructures can solve this problem to some extent. Because nanoparticles have the ability to enter tumor tissues and cancer cells in a targeted and specific way, and as a result, only affect cancer cells. Nanoparticles act as energy exchangers that convert radiated energy into heat in cancer cells. Gold nanostructures are excellent tools for photothermal therapy cancer by absorbing light in the visible and near-infrared region, as well as generating heat rapidly in picoseconds or less [15-19]. Gold nanoparticles are of different types such as nanospheres, nano shells, nano rods, nano-cages, nano-stars, nano-dendrites, nano-clusters and other types. Many biomolecules such as chains, DNA, proteins, peptides and aptamers can be attached to a gold nanoparticle, indicating the high biocompatibility of gold nanoparticles. Gold nanoparticles also have a high absorption of incident light due to their ability to form plasmon on their surface, which makes them a good choice for the therapy of disease. The first study in this field was performed in 2003 and showed the death of cancer cells with 100 laser pulses with an energy of 0.5 joules per square meter, while adjacent cells that lacked nanoparticles but were irradiated with laser survived [20-22]. Despite the important applications of adsorbed nanoparticles in the near infrared region, in photothermal therapy (PTT), indirect heating of these nanomaterials, which is applied

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while using targeting techniques, is a challenge. Because it can cause the death of healthy cells due to heat. This is because the nanomaterials do not accumulate completely in the tumor. Some of the nanoparticles remain in the environment and are likely to be absorbed by healthy cells, leading to undesired heating and destruction. Another limitation of this technique is that it is difficult and impossible to perform for deep tumors. Because the laser light penetrates only a few centimeters into the soft tissue. In addition, some studies have estimated that 5,000 nanoshells per cell are needed to achieve the right heat to kill the tumor. Factors affecting nanoparticle pharmacokinetics, biological distribution and toxicity of substances in the body should be clarified. Gold nanoparticles need to leave tumor vessels, enter cells, and potentially leave lysosomes in the body. Long-term studies are needed to evaluate the toxicity and mutagenic potential of nanoparticles because the particles may remain for months [23, 24]. The aim of this study was to use gold nanoparticles in the therapy of cancer.

2 Function of thermal therapy

Cancer cells and healthy cells have different membrane potentials. This means that when the water around them vibrates, they are affected differently. Cancer cells are less stable than heat than healthy cells. thermal therapy effectively takes advantage of this difference. Fever has several effects on the body when the body is attacked by pathogens or even cancer cells. Fever causes a temperature above 38 degrees and stops the telomeres at the end of the cells. This means that it prevents viral pathogens from multiplying. Fever is associated with the release of T cells by the immune system, which can kill a variety of bacterial pathogens and help clear bacterial toxins. T cells cannot attack viruses, but it is the fever that prevents viruses from multiplying. Unlike our normal cells, cancer cells are less resistant to heat, which justifies the use of methods such as thermal therapy. thermal therapy raises body temperature to tolerable levels of normal cells. When the interstitial water around the cells heats up, this water begins to vibrate and enters the cell according to the membrane potential of the cell in question. Because thermal therapy raises body temperature only to the tolerable levels of healthy cells, this hot water does not enter healthy cells and only enters cancer cells. The inflow of water continues until the cancer cell eventually bursts and dies. Thermal therapy thus kills cancer cells. The use of thermal therapy increases the performance of other methods of cancer therapy [25-28]. A summary of the different forms of gold nanoparticles and the application of PTT is given in Table 1.

Table 1. Summary of different forms of gold nanoparticles and application of PTT

Type of Gold	Size	Therapy	Brief Mechanism	Application	Ref.
Gold nanorods	10 × 38 nm	PTT	Nontargeted, NIR wavelength	In vivo cancer treatment	[29, 30]
Gold nanocages	45 nm edge length, 5 nm wall thickness	PTT	PEG coated nanocage specific targeted, NIR wavelength	In vivo cancer treatment	[31, 32]
Gold sphere	20 nm	PTT	Specific targeted, NIR fs wavelength	In vitro cell eradication	[33, 34]
Gold nanoshell	50 nm	PTT	PEG coated, nontargeted, NIR wavelength	In vivo cancer treatment	[35-37]
Gold nanoflower	145 × 123 × 10 nm	PTT	Nontargeted, NIR wavelength	In vitro and in vivo cancer treatment	[38-40]

3 Thermal therapy radiation frequency (RF) with gold nanoparticles

Radiation frequency ablation is one of the most common methods of cancer therapy. In this method, a needle probe is inserted into the tumor, which is used to raise its temperature and destroy the tumor. It is useful for the therapy of primary and metastatic tumors of small tumors of the lung, liver and kidney. It has also been suggested for the therapy of pancreatic and bile duct cancers. Radiation frequency ablation causes gentle and effective removal of benign bone tumors, reduces bone destruction and reduces recurrences compared to surgical techniques. When gold nanoparticles are exposed to radiation frequency (RF) electric fields, they increase the thermal of the surrounding environment. Thermal therapy radiation frequency is different from traditional radiation frequency therapy. In the traditional type, thermal is dissipated through a probe and there are no nanoparticles. Direct exposure of the tumor to the field at a low frequency of 350-500 kHz can help destroy tumor cells in a variety of cancers. However, this method can cause severe pain in the patient due to thermal damage and the cells may not be completely destroyed, also power 35 watts causes the destruction of cancer cells [41, 42].

4 Types of gold nanoparticles

4.1 NanoSphere

Convenient synthesis, production in sizes from more than 1 nm to above 100 nm, the maximum absorption of light in the range of 600-500 nm has made gold spherical nanoparticles the most widely used type. The maximum absorption wavelength of these structures is transmitted to higher waves as the particle size increases. Gold spherical nanoparticles absorb visible light several million times more than organic dyes, and nearly 100% of the light absorbed in these structures is converted to thermal (Figure 1). These nanoparticles are very stable under light radiation and also have high biocompatibility. The combination of these and other properties makes these particles one of the best choices for photothermal therapy. Photothermal therapy with gold spherical nanoparticles is possible with both continuous wavelength lasers and pulsed lasers. Due to the absorption of surface plasmon resonance of these particles in the visible region (wavelength about 500 nm), their application is limited to superficial cancers such as skin cancers and is not suitable for deep cancers; Because visible light (wavelength 500 nm) is not able to pass through body

tissues. Therefore, it is used only for superficial tumors that can be irradiated with light [43, 44].

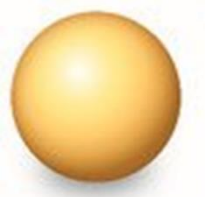

Figure 1. Schematic of a gold nanosphere [45]

4.2 NanoCage

Gold nanocages are a new structure of hollow nanostructures with porous walls that result from the reaction of galvanic substitution between silver nanocubes with gold chloride salt. The wall thickness of nanocages can be changed by changing the concentration of gold chloride used, which determines the maximum adsorption of nanoparticles. Large absorption cross section, excellent optical and thermal properties and environmental compatibility have made gold nanocages have a broad perspective in the fields of optics, medicine, tumor diagnosis and therapy and other related fields. The process of making nanocages is controllable and can be easily produced in relatively large quantities Figure 2 [46, 47]. Nanocages are actually nano-boxes with shortened corners.

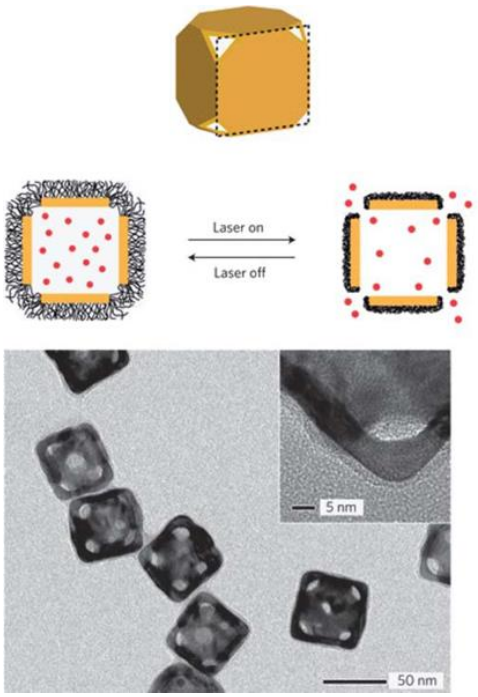

Figure 2. Schematic image and properties of gold nanocages for controllable release [48].

4.3 NanoRod

Due to the high cross-sectional area of absorbed light, the controllable absorption in the near-infrared region, as well as the strong photoluminescence excitation of two photons suitable for in-vivo 3D imaging, are of great interest for thermal therapy applications. These structures have two absorption peaks that are attributed to the resonance of plasmons across the nanorod and the resonance of plasmons along the nanorod. The determining factor in the maximum absorption associated with the resonance of longitudinal plasmons is the length-to-width ratio of nanorods [47, 49, 50]. A schematic of a gold nanorod coated by a bilayer of positively charged CTAB molecules is shown in Figure 3.

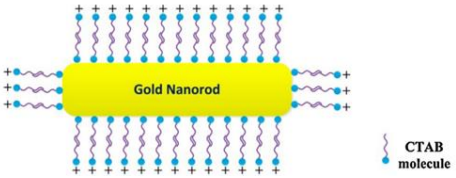

Figure 3. Schematic of a gold nanorod coated by a bilayer of positively charged CTAB molecules [51]

5 Applications of gold nanoparticles

5.1 Gold nanorods in photothermal therapy of squamous cell carcinoma

Gold nanorods were prepared using the attached seed growth technique. The seeds were prepared by rapid reduction of gold chloride salt (Hydrogen Aurichloride Chloaurate Acid ($HAuCl_4$)) and using cold ice Sodium TetraHydroborate ($NaBH_4$). Growth solution containing cetyl trimethyle ammonium bromide (CTAB), $AgNo_3$, $HAuCl_4$ and ascorbic acid were gently mixed to give a clear growth solution. The seeds are then added to the growth solution and the reaction lasts up to 2 hours. The synthesized rods were observed with a length of 50 × 12 nm and a ratio of 4 and an absorption wavelength of 800 nm. Excess sodium tetrahydroborate was removed by centrifugation twice and the cleaned rods were coated with polyethylene glycol by covalent bonding of gold thiol. There are two methods of injection: direct injection into the tumor and intravenous injection through the mouse tail. Immediately after direct injection, the near-infrared region is irradiated. In intravenous injection, light is irradiated 24 hours after injection. Changes in tumor size were recorded over 89 days. In direct injection, the tumor size was reduced by more than 31% and in intravenous injection, the tumor size was reduced by 74% [52, 53]. Figure 4 shows the therapy of cancer with gold nanorods.

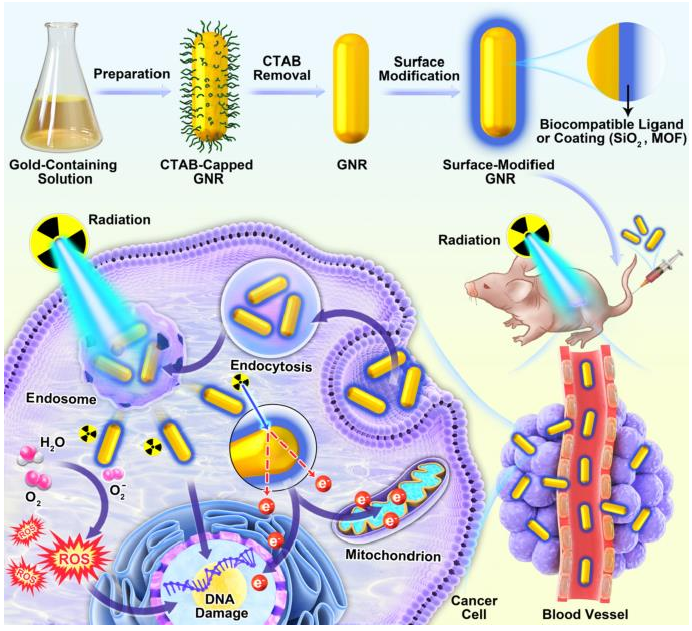

Figure 4. Cancer therapy with gold nanorods [54]

5.2 Gold nanocages in cancer therapy

In biological systems where water has a higher thermal conductivity, gold nanocages are not melted but increase local

temperature, which can provide therapeutic effects on cancer cells paired with gold nanoparticles (Figure 5) [55, 56]. Recently, the destruction of selective intracellular cancer cells using immunological gold nanocages has been demonstrated. Comparing the three structures available for photothermal therapy in the near-infrared region, gold nanorods have two advantages over nanocages and nanoshells. The process of making nanorods is very easy, with a suitable protocol, in just two hours at room temperature, these structures are made with different and adjustable aspect ratios. To make nanoshells, it is very difficult to create a completely homogeneous shell in terms of thickness around the silica core, and to make nanocages, the initial process of making silver nanocubes requires a temperature above 150 ° C for 20 hours [49, 57, 58].

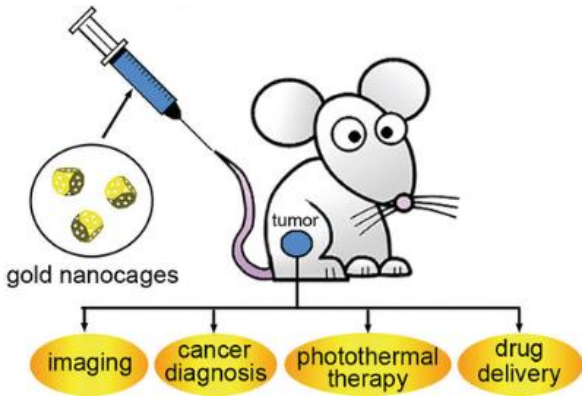

Figure 5. Gold nanocages in cancer therapy [59]

6 Conclusion

Cancer therapy in recent years with the development of nanotechnology and the use of nanoparticles in the field of medical sciences, efficient and low-risk techniques with greater effectiveness than conventional methods in this field have been studied. Among these, gold nanoparticles have received more attention due to their good plasmonic properties, easy synthesis, ability to functionalize with different materials for the intended purpose, low toxicity, high biocompatibility and easy access to its nano-dimensions. The use of gold nanoparticles has shown a clear vision in the development of new methods for the rapid therapy of cancer. Researchers hope that with the presence of gold nanoparticles in medicine and the emergence of new techniques in cancer diagnosis, these nanoparticles will be a good alternative to traditional therapy of this disease.

Ethical issue

Authors are aware of, and comply with, best practice in publication ethics specifically with regard to authorship (avoidance of guest authorship), dual submission, manipulation of figures, competing interests and compliance with policies on research ethics. Author adhere to publication requirements that submitted work is original and has not been published elsewhere in any language.

Competing interests

The authors declares that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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