GOLD NANOPARTICLES IN THE DIAGNOSIS AND TREATMENT OF CANCER

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Due to chemical stability, low toxicity, and relative simplicity of synthesis/modification techniques, gold nanoparticles (NP) enjoy a wide range of biomedical applications, including *in vitro* diagnostics, targeted drug delivery, contrast-enhanced radiation therapy, and photothermal therapy. The high ratio of the gold NP surface area to their volume facilitates design of complex nanoplatforms for various therapeutic and diagnostic purposes. Unique electrical and optical properties of gold NP known as surface plasmon resonance assist medical diagnosis. In this work we look at the basic methods for gold NP synthesis and modification, including the so-called green chemistry, talk about the pharmacological aspects of their application and highlight their potential as diagnostic agents. We believe that due to their unique properties, gold-based nanoplatforms for targeted drug delivery and theranostics have indisputable advantages over other nanoparticles.

Keywords: gold nanoparticles, nanodiagnostics, nanotherapy, targeted drug delivery, theranostics, cancer research

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НАНОЧАСТИЦЫ ЗОЛОТА ДЛЯ ДИАГНОСТИКИ И ТЕРАПИИ ОНКОЛОГИЧЕСКИХ ЗАБОЛЕВАНИЙ

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Химическая стабильность, низкая токсичность, относительная простота методов синтеза и модификации наночастиц (НЧ) золота способствуют их использованию в различных областях биомедицины, таких как диагностика *in vitro*, адресная доставка лекарств, фототермическая и фотодинамическая терапия. Высокое соотношение площади поверхности к объему этих НЧ существенно облегчает создание на их основе комплексных наноплатформ, используемых сразу в нескольких терапевтических и диагностических направлениях. Уникальные электрические и оптические свойства НЧ золота, известные как локализованный поверхностный плазмонный резонанс особенно актуальны для диагностики различных заболеваний. Рассмотрены основные методы синтеза и модификации НЧ золота, в частности методами «зеленой химии», фармакологические аспекты их применения и использования в качестве диагностических агентов. По нашему мнению, именно благодаря своим уникальным свойствам наноплатформы для адресной доставки лекарственных препаратов и тераностики, созданные на основе НЧ золота, имеют неоспоримые преимущества перед другими типами наночастиц.

Ключевые слова: наночастицы золота, нанодиагностика, нанотерапия, адресная доставка лекарственных средств, тераностика, онкология

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The use of gold nanoparticles (NP) in biomedicine was pioneered in the study investigating the possibility of direct microscopic visualization of Salmonella surface antigens using antibodies conjugated to colloidal gold [1]. That study gave rise to an independent field of scientific knowledge focusing on the applications of gold NP in biomedical research, diagnostics, biosensors, photothermal and photodynamic therapy, as well as targeted delivery of pharmaceutical drugs or genetic material [2].

The interest in gold NP has been growing ever since, yielding an increasing number of publications every year (Fig. 1).

Gold NP can be categorized into two major groups based on their structure and application. The first group comprises NP conjugated to molecules that have various functions and properties. Such platforms are employed in the targeted delivery and controlled release of tumoricidal agents [3], locally induced hyperthermia against cancer [4], medical imaging, and sensor design [5]. It is important that methods for gold NP synthesis should be robust and reliable and the surface of the synthesized particles could be effortlessly modified. Today, gold NP from this group can be functionalized with oligonucleotides, peptides and polyethylene glycol.

The second group consists of hollow NP with a dielectric or magnetic core and a gold shell. These are used to encapsulate therapeutic agents. The size of gold NP varies from 20 to 500 nm, which facilitates their biodistribution following passive targeted delivery. Advantageously, these multilayer particles are polyfunctional: their functions are distributed between the core and the shell.

Gold NP are characterized by increased absorption and scattering cross-sections; their absorption spectra depend on their shape and size. Au^0 nanospheres of 10–25 nm in diameter

absorb light at 520 nm, whereas gold nanorods absorb in the near infrared region of the spectrum. This can assist *in vivo* diagnosis and further treatment.

Modified gold NP are lowly immunogenic and highly biocompatible. Particles sized 10–22 nm can serve as carriers for vaccine delivery [6]. It has been demonstrated that Au^0 NP enhance the immune response *in vivo*, especially against viral infections, such as tick-borne encephalitis, HIV and hepatitis B.

Unique electrical and optical properties of gold NP and their ability to form stable complexes with biomolecules are actively exploited in biosensor design. For example, Au^0 nanoparticles encapsulated in graphene oxide were used to design a DNA biosensor for the detection of biomarkers, including proteins found on the surface of breast cancer cells.

It is known that inflammation causes elevated blood plasma levels of C-reactive protein of humans. In clinical practice, this protein serves as a marker of many pathologies, including cardiovascular disorders [7, 8]. A novel sensor for the electrochemical detection of troponin I (a specific biomarker of myocardial tissue injury) in the blood plasma is based on capturing the signal emitted by Au^0 NP localized on the electrode surface [9].

Methods for gold NP synthesis

Gold NP can be synthesized using two major techniques: dispersion and condensation. Dispersion occurs as a result of applying a high-voltage electrical current or a similar destructive physical force to the metal. Condensed gold NP are synthesized from ions of gold salts by chemical reduction or following mild physical stress (radiolysis, sonication, etc.) [2]. Dispersion yields heterogeneously sized particles. Because of this major drawback, condensation remains the preferred method for gold NP synthesis.

Au^0 NP obtained through condensation are colloidal particles of 5 to 20 nm in diameter derived from gold halides, such as hydrogen tetrachloroaurate produced as gold is dissolved in aqua regia. Among the chemical reducing agents used for condensation are sodium citrate and borohydride, ascorbic and ethylenediaminetetraacetic acids, and alkaline solutions of hydrogen peroxide. Ultra-dispersed sols of 2–3 nm in diameter are synthesized from sodium or potassium thiocyanates.

The rate of NP synthesis depends on the concentration of the reagents and the chemical composition of the reducing agent. A low rate of nucleation and a high rate of particle condensation yield relatively small quantities of big particles. At a low rate of condensation, small particles are likely to form in large quantities.

Gold 8–120 nm-sized NP for medical applications are usually synthesized by reducing hydrogen tetrachloroaurate in the presence of sodium citrate; the method was originally proposed to fabricate NP of 20 ± 1.5 nm in diameter [10]. Large gold NP of > 80 nm in size can be synthesized by condensation using isoascorbic acid as a reducing agent and gum arabic as a protective colloid.

Monodisperse gold NP sols are sometimes synthesized using two-phase techniques. In the first step, metal-containing reagents are transferred from an aqueous to an organic phase (hexane, toluene); in the second step, solutions of surfactants and a reducing agent (butanol) are added to the reaction mixture. The surface of nanoclusters is capped with hexadecylamine. Its amino groups interact with the metal surface in such a way that nonpolar hydrocarbon tails remain outside the surface [11].

The size and shape of gold nanoparticles are affected, among other things, by the type of a reducing agent used for their synthesis. For example, sodium citrate and hydrogen peroxide will yield spheres, whereas hydroxylamine will produce cubic crystals with well-shaped facets [12].

NP are stabilized with thiols and disulfides. High affinity of sulfur to gold promotes formation of a gold thiolate monolayer on the surface of the particles. Gold halides can be reduced using both chemical and physical methods; the latter include exposure to ultrasound, ultraviolet and infrared ionizing radiation, laser photolysis and electrochemistry. The NP yielded by these methods do not have any trace amounts of chemical reagents of their surface.

The use of microorganisms, cells of plants, animal or humans has given rise to a unique, advanced biotechnological approach to the synthesis of gold NP relying on the principles of "green chemistry" [13, 14]. Interestingly, green chemistry techniques are hardly ever used for the synthesis of other NP types.

A recently published review takes a close look at the application of plant extracts in the synthesis of metal NP [15]. Plants contain bioactive compounds, such as flavonoids, phenols, citric and ascorbic acids, polyphenols, terpenes, alkaloids, and reductases, that can act as reducing agents [16]. Biotechnological production of NP has certain advantages over chemical methods due to the ability of plant extracts to play the role of both reducing and stabilizing/isolating agents (see the Table).

Plants produce NP intra- and extracellularly [23]. To stimulate intracellular biosynthesis of NP, plants should be grown in organic media or on metal-enriched soils (cell/tissue engineering, hydroponics) [24]. Extracellular methods of NP synthesis rely on leaf extracts [25]. Biotechnologically produced

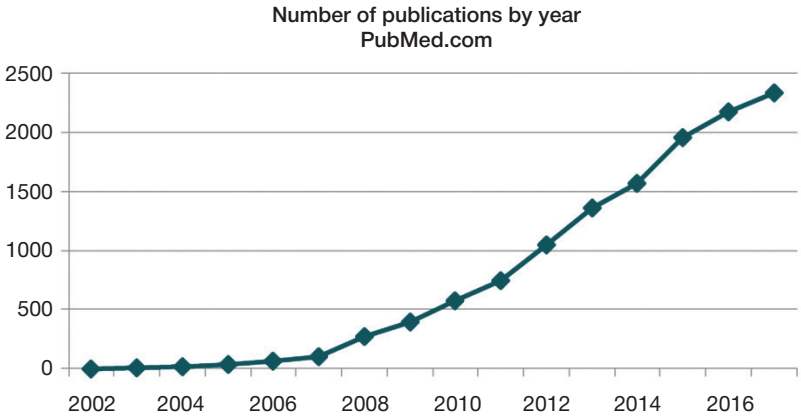

Fig. 1. The number of research articles on the use of gold NP in biomedicine published between 2002 and 2017 (figures provided by PubMed.com)

gold NP have various sizes and shapes: spheres, rods, cubes, and triangles.

A simple, cost-effective and reproducible technique for the synthesis of almost monodisperse gold nanocubes of 20 nm in diameter is based on the use of extracts derived from fresh or dried mango (*Mangifera indica*) leaves. It takes only 2 minutes to fabricate such NP by adding the leaf extract to the solution of $HAuCl_4 \bullet 3H_2O$; importantly, the colloid remains stable for over 5 months. Smaller and uniformly distributed particles can be obtained from a dried leaf extract of the same plant [26].

The size of NP synthesized by green chemistry techniques depends on what extract is employed as a reducing and stabilizing agent. The olive leaf extract yields Au^0 NP of 50–100 nm in size; the geranium extract, about 12 nm; white willow seeds, 50–80 nm [26]. Production of gold NP can be assisted by pollen, seed, flower, bark, and root extracts [27]. Another method of NP synthesis relies on chitosan that acts as a reducing and stabilizing agent. Positively charged chitosan-containing particles help to mitigate the adverse effects of the chemotherapy drug 5-fluorouracil [28].

Au^0 nanospheres are a product of $HAuCl_4$ reduction in colloidal solutions. At the first stage of synthesis, the rapid reduction of hydrogen tetrachloroaurate results in a supersaturated gold solution. Then reduction slows abruptly and the new phase condensates producing very small NP nuclei of less than 2 nm in diameter. The rate of nucleation in the new phase is determined by the degree of saturation of the solution and the concentrations and chemical structure of the reducing agent. At a low rate of nucleation and a high rate of condensation, a small amount of relatively large particles is produced. Higher rates of nucleation and smaller rates of condensation are more likely to yield large quantities of small NP.

Nonspherical colloidal gold NP are synthesized on hard silica or aluminum oxide matrices under artificially created anisotropic conditions by electrochemical methods [29]. Nanorods are synthesized on soft matrices (micellar solutions of surface-active agents) through chemical reduction.

The last few years have witnessed a rapid evolution of nanomedicine involving the use of ultra-small NP with a diameter of less than 6 nm. Gold nanorods with a diameter of < 6 nm have the same electrical and optical properties as their large counterparts, but are devoid of their flaws which is important for biomedical applications [30]. Gold nanothreads are thermally derived from gold NP adsorbed on the surface of nanotubes. Tubular gold nanothreads with an external diameter of 10 nm can be obtained by thermally removing residual nanotubes. DNA molecules can also be used as a matrix for nanothread synthesis.

Spherical gold nanoshells consist of a dielectric nucleus of 100 nm in diameter coated with a thin layer of gold. The optical properties of such particles can be tuned by varying the diameter of the nucleus and the thickness of the shell. Gold nanoshells hold great promise for biomedical research, diagnosis and therapy. One of the methods for nanoshell fabrication consists of 4 major steps: first, spherical silica cores are synthesized and then their surface is functionalized with amino groups onto which gold particles are absorbed [31].

The physical and chemical properties of synthesized NP and their average diameter and shape are traditionally controlled and measured by electron microscopy and spectrophotometry. The NP size can also be assessed by laser correlation spectroscopy (dynamic light scattering). Differential centrifugation, scanning/atomic force microscopy, small/wide X-ray scattering, X-ray diffraction analysis, mass spectroscopy, and other methods are less common.

Methods for gold NP surface modification

Adsorption and hemadsorption are two major methods for Au^0 NP surface modification. Adsorption of biomolecules onto the NP surface facilitated by hydrophobic and electrostatic interactions stabilizes nanoparticles. A strong negative charge of the gold NP surface ensures stable adsorption of a wide range of high molecular weight compounds.

Biocompatibility of Au^0 NP can be improved by functionalizing their surface with coatings, layers, and linkers. The same strategy is employed for creating diagnostic or therapeutic platforms. At the molecular level, surface modifications are required to confer specificity, sensitivity and biological compatibility to the nanoparticles.

Gold NP are capable of interacting with immunoglobulins, lectins, enzymes, hormones, lipoproteins, etc. As carriers, they have numerous advantages over other platforms. Gold NP improve the solubility of therapeutic agents and protect them from deterioration on the way to the target. Gold NP can actively or passively accumulate in the target organ and enable controlled release of the carried drug. Their magnetic and photothermal properties expand the arsenal of therapeutic techniques that can be applied to a patient and reduce the toxicity of a carried drug ensuring the desired therapeutic effect at lower drug doses.

Methods for Au^0 NP surface modifications can be covalent and noncovalent. Advantageously, noncovalent methods do not require a therapeutic agent to be modified, too, and ensure easy release of the drug from a carrier, which is a prerequisite for successful therapy. Charged or hydrophilic groups accumulated on the surface of nanostructures increase their solubility and facilitate interactions with biomolecules. Amphiphilic polymer coatings also improve the solubility of the complex, promote nonspecific interactions with biological

Table. Plant extracts for the synthesis of gold NP

Common name of plant	Latin name of plant	Part of plant used for extract preparation	Gold NP diameter, nm	References
Rose geranium	*Pelargonium graveolens*	Leaves	45	[17]
Lemon verbena	*Lippia citriodora*	Leaves	36	[17]
Garden sage	*Salvia officinalis*	Leaves	29	[17]
Pomegranate	*Punica granatum*	Fruit	32	[17]
Dragonhead	*Dracocephalum kotschyi*	Leaves	11	[18]
Cinnamon	*Cinnamomum zeylanicum*	Leaves	25	[19]
Pomelo	*Citrus maxima*	Fruit	15–35	[20]
Black cherry	*Prunus serotina*	Flowers	10–20	[21]
Date palm	*Phoenix dactylifera*	Pollen	20–50	[22]

macromolecules, increase compatibility of the nanostructures with proteins and their affinity to cell membranes. Polyethylene glycol coatings enhance the efficacy of NP uptake by body cells, prevent NP aggregation in the medium characterized by high ionic strength and increase their circulation time in the blood stream.

Surface-modified Au^0 NP demonstrate an improved ability to penetrate blood vessel walls and cell membranes. Nanoparticles interact with therapeutic agents and reduce their cytotoxicity. The most common method for gold NP surface modification is thiolation by bifunctional thiols, whose additional functional group allows them to conjugate to biomolecules. The surface of gold NP can be stabilized with modified dextran. The appeal of such structures is grounded in their ability to reversibly change their properties depending on the temperature or pH of the environment.

Modification of gold nanostructures by self-assembled monolayers or complex molecular aggregates is described in detail in a number of works [32]. Also, there is a plethora of functional molecular linkers, including aryl diazonium salts, that can be used to modify the surface of gold NP [33, 34].

Gold nanoparticles in diagnostics and therapy

Aurotherapy of arthritis was first attempted in 1929. Its underlying mechanism is based on the ability of gold compounds to inhibit macrophages *in vivo* and suppress pathological immune response.

Gold nanorods actively absorb in the near infrared spectrum for which the human body is relatively transparent. Therefore, they are ideal for photothermal therapy (selective destruction of pathogens by heating). For example, gold NP complexes with antibodies can kill intracellular *Toxoplasma gondii* that causes toxoplasmosis. Antibodies allow NP to selectively bind the target. Exposed to laser radiation, NP get heated inducing death of up to 83% of toxoplasma cells.

Until recently, gold NP were not used in cancer research. An increased interest in these particles is evoked by their unique optical and electronic properties (surface plasmon resonance) that can revolutionize the approaches to the diagnostics and treatment of cancer. Theranostic platforms combining diagnostic and therapeutic functions enable control over patients' response to treatment [35].

The epidermal growth factor receptor (EFGR) expressed on the surface of many cancer cells can be exploited as a diagnostic marker in the treatment of malignancies. The selective effect of gold NP on tumor tissue may be explained by the specifics of tumor architecture and growth. Cancer cells grow rapidly forming gaps between each other and fenestrations on their surfaces. This phenomenon is referred to as enhanced permeability and retention, EPR. It allows NP to easily penetrate a cancer cell. Increased acidity inside the cancer cell is also a beneficial factor aiding targeted and timely release of therapeutic agents into the lesion.

Once gold NP have bound to their target, the affected organ is irradiated with low-energy infrared laser beams. This energy is absorbed by the nanoparticles, which emit ultrasound and thermal waves in response. The emitted ultrasound waves lay the basis for the photoacoustic imaging of malignancies whereas the produced heat kills cancer cells (photothermal therapy). Locally induced hyperthermia stimulates targeted release of drugs entrapped in a gold capsule [36].

Photoacoustic imaging can be performed with gold nanorods. But the best therapeutic effect is achieved by using star-shaped gold NP sized 25 nm with 5–10 sharp-tipped branches. Owing to the large surface area of such NP, increased amounts of a therapeutic agent can be loaded onto the "star" whose shape stimulates light absorption and ensures targeted drug delivery.

Biocompatible gold NP functionalized with molecules that can selectively interact with cancer cells are an ideal tool for hyperthermia-based therapy against cancer [37].

Inhibition of metastases with gold nanoparticles by increasing the rigidity of nuclear membranes of cancer cells

As the tumor grows, its cells migrate to neighboring tissues and organs forming metastases. Therefore, curbing their metastatic spread is a critical clinical task. Au^0 HP modified with ligands consisting of L-arginine, glycine and L-aspartic acid (RGD peptide) and nuclear localization signal (NLS) peptides were used to design a drug that increased the rigidity of nuclear cancer cell membranes. It stimulated overexpression of A/C lamin proteins and reduced the ability of cancer cells to metastasize. Free RGD peptide is often employed in cell biology research and biotechnology as it is capable of inhibiting intercellular interactions [38]. Inhibiting the spread of metastases leaves a doctor and a patient more time to fight cancer [39].

Gold NP as platforms for molecular diagnostics and therapy of cancer

In clinical practice, diagnosis and treatment do not take place simultaneously. Theranostics is a combination of the two comprising an entire range of medical services from early diagnosis to therapy to follow-up observation. Theranostics involves the use of targeted therapy and diagnostic tests based on the so-called nanoplatforms and has an important role in oncology.

Au^0 NP-based platforms have certain advantages over other carriers due to their unique optical characteristics, high efficiency of photothermal conversion and a high value of X-ray absorption coefficient. The energy absorbed by the particle is partly emitted as scattered light and partly turns to heat. Thus, gold NP find their application in both diagnostics and treatment based on optical hyperthermia. By tuning the shape of NP, one can vary their analytical and therapeutic parameters.

Some authors have demonstrated that gold NP sized about 13 nm are ideal for theranostics. They are potent contrasting agents for CT and X-ray modalities and can be successfully used to create theranostic platforms [40–42].

Photothermal therapy

Conventional chemotherapy is a systemic treatment that affects every organ. Chemotherapy drugs have serious adverse effects. Au^0 NP are a suitable material for biocompatible and highly effective photothermal platforms that can absorb and convert near infrared light to heat causing a local rise in temperature, which destroys cancer cells. This phenomenon is known as optical hyperthermia [43].

Chinese researchers have designed unique theranostic nanoplatforms capable of simultaneous detection and killing of cancer cells. The hollow gold NP components of the platforms contain iron oxide that has paramagnetic properties; the surface of these NP is functionalized with antibodies against some cancer cells. The NP are administered to a patient by injection. Their migration to organs and tissues can be monitored by CT thanks to the properties of iron oxide. Heated by infrared

light, the NP localized in the tumor destroy cancer cells (the phenomenon of optical hyperthermia, see above) [44].

Another type of nanoplatforms was created based on the traditional anticancer drug doxorubicin and gold NP encapsulated in heat-sensitive liposomes. This nanoplatform combines a thermal tumoricidal effect with the effect produced by doxorubicin that is released directly into cancer cells following their irradiation with infrared light. The concentration of the drug in the tumor increases as the liposome membrane degrades [45].

So far, two gold-based intravenous drugs (AurImmune™ and AuroLase™) have been approved for clinical use [46, 47].

The therapeutic effect of Au^0 NP is based on the narrowing of blood vessels that supply nutrients to the tumor and inhibiting angiogenesis in the affected organs and tissues. Normally, angiogenesis is moderately intensive. It is stimulated when tissue needs regenerating, in thrombosis and inflammation, scarring and other regenerative processes; it is also vital for the growth and development of an individual. In cancer tissues angiogenesis is very vigorous; therefore, cancer cells are continuously supplied with sufficient amounts of blood and nutrients boosting their growth.

The majority of existing angiogenesis inhibitors are represented by antibodies against VEGF. (vascular endothelial growth factor) and cause serious adverse reactions. Unlike most of them, gold NP suppress VEGF function without producing a toxic effect on the cells [48].

Radioactive gold and its application in cancer research

Colloidal solutions of radioactive gold are used as tumoricidal agents. Au^0 has found its medical application in oncology in the form of a radioactive isotope ^{198}Au obtained through the irradiation of the naturally occurring Au^0 with neutrons. The half-life of ^{198}Au does not exceed 3 days. It emits β- and γ-rays that help to locate the isotope inside the body. Radioactive gold colloids selectively accumulate in the cells of the mononuclear phagocyte system and connective tissue and therefore can be used for diagnostic and therapeutic purposes. Radionuclide-based diagnostic procedures utilize colloidal solutions with Au^0 NP concentrations of 3–6 mg/ml and a particle size of 10–30 nm.

Mono- and polydisperse colloidal Au^0 NP solutions produce a therapeutic effect on cancer patients. Radioactive concentration of the drug must not exceed 4 mCi/ml; it is achieved by diluting the initial drug with 0.25—0.5% solutions of novocain or sodium chloride.

CONCLUSIONS

Rapid evolution of technologies for the synthesis of gold NP has yielded an abundance of diversely shaped, sized and structured nanoparticles with various optical properties. Modification of NP surfaces with specific molecules is critical for the biomedical application of NP, as it improves their stability *in vivo* and specificity to a biological target. At present, thiolated derivatives of polyethylene glycol and some other molecules are considered to be the best NP stabilizers. Particles modified with polyethylene glycol circulate in the blood stream longer and are better protected against immune cells. Gold NP conjugates are potent biomarkers of cancer, Alzheimer's disease, AIDS, hepatitis, TB, diabetes mellitus, and other disorders. Plasmonic photothermal laser therapy is now being tested in the clinical setting. The success of this technology is determined by how fast researchers will be able to develop reliable methods for *in vivo* targeted drug delivery and to improve control over photothermolysis *in situ*. We believed that diagnostic and therapeutic targeted drug delivery platforms based on gold NP and synthesized by green chemistry techniques hold the best promise for nanobiomedicine.

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