Gold Nanoparticles for Cancer Theragnosis

Subjects: Oncology

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Research on cancer theragnosis with gold nanoparticles (AuNPs) has rapidly increased, as AuNPs have many useful characteristics for various biomedical applications, such as biocompatibility, tunable optical properties, enhanced permeability and retention (EPR), localized surface plasmon resonance (LSPR), photothermal properties, and surface enhanced Raman scattering (SERS). AuNPs have been widely utilized in cancer theragnosis, including phototherapy and photoimaging, owing to their enhanced solubility, stability, biofunctionality, cancer targetability, and biocompatibility.

Keywords: gold nanoparticle (AuNP) ; cancer therapy ; theragnosis ; photothermal treatment (PTT) ; photodynamic therapy (PDT) ; cancer imaging

1. Introduction

Gold, one of the historically precious materials of everyday human life, is utilized as currency, jewelry, accessories, and valuables, as well as in industries owing to its distinct characteristics. Biomedical applications of gold have a long history. As early as 700 BC, in Etruria, gold was used in dental treatment [1]. The use of gold in ancient times for in vivo transplantations can be attributed to its extraordinary physicochemical properties. Gold can be molded into a desirable shape, has no toxicity to the human body, does not rust, and has no undesirable taste. The rapid development of nanotechnology has enabled the manufacture of gold nanoparticles (AuNPs) in different sizes and shapes, leading to their expanded and diversified use in many fields [2][3][4][5].

2. Key Properties of Gold Nanoparticles (AuNPs) Important for Cancer Theragnosis

2.1. Biocompatibility

Nanomaterials (NMs) for body transplants and injections should have biocompatible and bioinert properties. Since NMs can interact with mammalian cells and tissues in ways different from those of their bulk counterparts, their potential toxicity is still controversial. The toxicity of metals in the body is mostly due to their capacity to form metal cations that damage cell membrane. However, gold is relatively stable in the body because of its high reduction potential and is less likely to ionize than other metals. Previous studies have verified that gold is relatively safe both in vitro and in vivo, although the size and concentration of AuNPs should be within the recommended ranges [6][7][8][9]. Due to the nature of inorganic NMs, their decomposition and release in the body could be potentially hindered [10]. In addition, little is known about the processing and degradation of AuNPs after uptake by cells [11]. Murphy et al. emphasized the potential toxicity of AuNP [12] by demonstrating that a 13 nm citrate-capped AuNP showed non-cytotoxicity and promoted formation of abnormal actin filaments which led to decreased cell behavior. Meanwhile, toxicity can be different within a cell type or species; a 33 nm citrate-capped AuNP was found to be nontoxic to hamster kidney and human hepatocellular liver carcinoma cells, but cytotoxic to human carcinoma lung cell line. Therefore, more studies are required that investigate both the mechanism of action of the metabolic process of AuNPs and strategies that could enhance their biodegradation and release such as those that capitalize on surface chemistry, shape modulation, and size control [13].

Surface engineering of AuNPs has been reported as a good strategy for enhancing biocompatibility and functionality through interaction with cells or tissues. Surface ligands determine the physicochemical properties of AuNP surface, such as hydrophilicity, zeta potential, and dispersion in solution. Surface properties determine interactions among cells and AuNPs, cell membrane binding and permeability, immune reaction, and in vivo localization [14]. Appropriate surface engineering of AuNPs can markedly improve their biocompatibility and responsiveness to cells. Surface engineering of AuNPs is generally processed by functionalization with various moieties such as polymers, surfactants, proteins, peptides, or other ligands [15][16][17][18][19]. One example introduced by Liu et al. synthesized multidentate zwitterionic chitosan oligosaccharide (CSO) modified AuNPs by surface engineering [20]. The zwitterionic CSO was prepared by conjugating 2-acryloyloxyethyl phosphorylcholine (APC) to CSO with an amino group by a Michael addition reaction and further

conjugated to lipoic acid (LA) by reacting the carboxylic acid group with the amine group using carbodiimide chemistry. The resultant LA-CSO-PC exhibited hemocompatibility, high cell viability, and cell membrane integrity at concentrations ≤0.12 mM, suggesting that surface engineering can facilitate the preparation of AuNPs as biomedicine.

The size and shape of NPs are crucial factors affecting biocompatibility; they are dramatically changed by endocytosis, protein absorption, gene regulation, and physical damage to membrane integrity [21]. For example, Vácha et al. demonstrated that passive endocytosis varied depending on the size and shape of the NPs. Differential membrane-binding strengths were observed, and spherocylindrical-shaped NPs were found to be more efficiently endocytosed than sphere-shaped NPs; moreover, the transport of NPs with sharp edges was suppressed [22]. Vecchio et al. quantitatively compared size-dependent toxicity of citrate-capped AuNPs and found that, as the particle size decreased, the cell viability decreased and the amount of reactive oxygen species increased; this relationship was especially proportional within a size range of 5 to 80 nm [23]. Sangabathuni et al. showed that AuNPs, depending on their shape, had different toxicity, biodistribution, and sequestration, in Zebrafish [24], and that nanorods uptake and clearance were faster, but nanostars decomposition was slower and stayed longer in the body.

2.2. Physicochemical Characteristics

2.2.1. Enhanced Permeability and Retention (EPR) Effect

The EPR effect is a phenomenon in which liposomes, macromolecular drugs, and NPs accumulate in cancer tissues for a longer period of time than in normal tissues. It is known that 200 nm–1.2 μm sized particles tend to accumulate more in tumors, depending on the tumor type; 200 nm is often considered to be a favorable size for the EPR effect [25][26][27]. The EPR effect is induced by certain characteristics of tumors, such as aberrant vasculature with extensive production of vascular permeability factors that stimulate extravasation and lack of lymphatic drainage, and wider lumen between tissues [28]. Consequently, injected AuNPs can remain longer and are tumor-specifically retained; thus, they can be applied as a passive tumor targeting strategy. Many studies have reported that the AuNPs without any tumor-targeting domain are relatively more abundant in cancer tissues, owing to the EPR effect [29][30][31].

2.2.2. Localized Surface Plasmon Resonance (LSPR)

SPR (surface plasmon resonance) is defined as the oscillation of electron on a conductive metal surface that forms an interface with a non-conductive substrate. SPR leads to a unique optical phenomenon in which light is scattered or absorbed when a conductive metal is irradiated with light of a specific wavelength that matches the plasmon oscillation cycle. Although most metallic materials absorb light in the ultraviolet region, Au absorbs light in the visible region, facilitating wider application in optical imaging. LSPR is one of the unique characteristics of nanomaterial. Unlike bulk Au, the surface size of an AuNP is very small and its plasmons do not move; instead, the plasmons oscillate collectively with a specific wavelength at the NP surface, which is variable depending on the particle size and formulation. Because the absorption and scattering of light by AuNPs depend on their size and formulation, they are widely applied as contrast agents in X-ray imaging, computed tomography (CT), photoacoustic tomography (PAT), and fluorescence imaging in vivo and in vitro [32][33][34][35][36][37].

2.2.3. Photothermal Effect

Accurate temperature control is a key factor for successful photothermal treatment of cancer. Therefore, understanding the photothermal properties of AuNPs is important. The photothermal effect is caused by photon irradiation and conversion of absorbed energy to thermal energy. Localized heating can result in the elimination of a targeted tissue; therefore, it can be applied as a noninvasive therapy. In addition, the generated heat is confined around the particles, enabling localized thermal toxicity to targeted cancer tissues. Basically, the light absorbed by AuNPs is converted to heat to induce a photothermal effect. In particular, the photothermal effect of AuNPs is strengthened by LSPR, as the oscillating excited electrons scatter each other. The quantized collective and coherent oscillation of the conduction band electrons is driven by light when resonance condition matches, and then the photothermal effect of the AuNP is significantly enhanced. The photothermal effect by LSPR enhances the localization of heat because, although the released energy has high intensity, the total capacity is small [38].

Among Au-based nanomaterials, nanospheres have an absorbance peak near 520 nm and do not absorb strongly in the near-infrared (NIR) range well, meanwhile, nanorods or nanoshells can strongly absorb NIR light for electron oscillation allowing deeper penetration of tissues. Therefore, in vivo imaging using Au nanorods or Au nanoshells is more feasible than AuNPs. However, nanorods and nanoshells are rarely fabricated as small size to be cleared from the body [39]. A possible solution could be rod-shaped assembly of AuNPs that could absorb NIR light efficiently by plasmon coupling of individual AuNPs [40]. Taken together, AuNPs hold a particular interest in the photothermal effect owing to their extraordinary photon-to-thermal energy conversion efficiency under NIR irradiation [41][42].

2.2.4. Surface Enhanced Raman Scattering (SERS)

The typical Raman cross-section is 10^{-30} cm^{-2} sr^{-1}, which is 10^{14} times smaller than the average cross-section of fluorescent dye (10^{-16} cm^{-2} sr^{-1}). It has the limitations of slow acquisition speed and difficult applicability in biological imaging [43]. However, when a localized surface plasmon of metal nanoparticles has a specific resonance condition (when the frequency of incident light and the frequency of collective motion of the conduction band electrons accord), the surface plasmon generates an induced electromagnetic field. Therefore, when AuNP is irradiated with light of a specific wavelength, the electromagnetic field on its surface is amplified such that the Raman signal is amplified when an organic substance attaches to the AuNP surface. Studies have confirmed that the SERS effect could amplify Raman cross-section to a degree similar to that of a fluorescent dye [44][45][46]. SERS Raman spectroscopy has achieved high resolution comparable to that of fluorescence microscopy and has potential for application in spectroscopic cancer diagnosis [47][48][49].

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