Invited Paper

**Cellular Uptake, Intracellular Trafficking and Biological Responses of Gold Nanoparticles**

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Promising application of gold nanoparticles (GNPs) in biomedical and environmental fields is increasing the likelihood of direct interaction with living systems. The knowledge about GNPs interacting with cells is quite limited and however, is necessary for risk prediction and evaluation of biological effects. Herein, we review recent advances in cellular effects of GNPs including cellular uptake, trafficking, subcellular distribution and cellular responses, and the relationship between physiochemical properties of GNPs and biological effects as well. To uncover these issues, it is quite instructive for safe and sustainable use of GNPs.

**Keywords:** GNPs; Uptake; Intracellular trafficking; Subcellular localization; Cellular response; Cytotoxicity.

**INTRODUCTION**

In recent years, a variety of engineered nanomaterials have been developed and widely applied in industrial, agricultural, environmental, and biomedical fields, own to their unique properties.¹⁻³ Nanoparticles (NPs; <100 nm in all three dimensions, ISO/TS 27687:2008) include carbon, semiconductor, and metal or metal oxide nanoparticles, and so on. Among these well-developed particles, GNPs are one kind of promising materials due to unique optical tenability, facile surface modification, and good biocompatibility.⁴⁻⁶ Their potential applications in biomedicine cover photothermal therapy of cancer,⁶ biosensing,⁷⁻⁸ gene and drug delivery,⁹⁻¹⁰ biological imaging.¹¹⁻¹³ However, some essential issues are raised about how GNPs interact with biological systems and whether the interaction can induce potential adverse effects on health and environment.

In particular, events at the cellular level induced by GNPs will largely expand our knowledge about these issues in detail. As we know, GNPs will have a tendency to form GNPs-protein corona in biological environment, which can be easily wrapped by cytoplasm membrane and internalized into cells in the form of vesicles. Then, these vesicles are trafficked to lysosomes, where GNPs will confront several choices like staying in lysosomes, escaping into cytoplasm or exclusion. The decision will be affected not only by the properties of GNPs like size, shape, surface physiochemical properties like surface coating and charge but also by cell types.¹⁵

Concerns about effects of GNPs on biological systems are very urgent and significant because these researches will encourage people to develop sustainable technologies, including promotion of much safer application of GNPs in biomedicine and predicting potential risks of novel nanomaterials and nanotechnologies. In this review, we will conclude recent progresses about the interaction between cells and GNPs, such as cellular uptake, trafficking and subcellular distribution, cellular response and surface physiochemical properties on biological effects.

1. **THE CELLULAR UPTAKE PROCESS**

Cell membrane is a dynamic structure with lipid bilayers and membrane proteins, segregating the cytoplasm from the exterior environment, serving as not only a protective barrier, but also a front line of the communications between cells and the microenvironment. To understand a
possible relationship between NPs and induced biological effect, it is important to know the processes involved in internalization of NPs. Several pathways have been considered to mediate the process in uptake of GNP, such as clathrin-mediated endocytosis, caveolae-mediated endocytosis, macropinocytosis, phagocytosis, and direct penetration.\textsuperscript{16,17} Generally speaking, these processes can be classified as specific (via receptor-ligand interaction) or non-specific ways. It is feasible to conjugate specific ligands to the surface of GNPs. These conjugated GNPs can target at cells via receptor-ligand interaction and be internalized efficiently. To study mechanism for uptake of GNPs, we also used specific inhibitors for endocytosis pathways in A549, human bronchial epithelial (16HBE) and mesenchymal stem cells (MSC) cells. We found that clathrin-mediated is the main pathway and lipid raft-mediated pathway (which is mediate by dynamin) is the secondary one during internalization of GNPs by all cells (Fig. 1).\textsuperscript{15}

The penetration of GNPs into cells can be adjusted by functionalizing surface of GNPs. The conventional way is to modify some ligand molecules on the surface of GNPs, which can increase specific recognition and trigger receptor-mediated endocytosis.\textsuperscript{18} One alternative approach is to adjust the hydrophobicity and hydrophobicity of surface coatings. Stellacci group simultaneously arranged hydrophilic and hydrophobic surface functional groups on GNPs to make their penetration into plasma membrane more effectively. The reason is that amphiphilic surface like membrane bilayers can make the fusion process much easier.\textsuperscript{19}

2. TRAFFICKING AND SUBCELLULAR DISTRIBUTION

After penetration into cells, intracellular trafficking of GNPs is the next concern. Usually, it is regarded that membrane-wrapped NPs are trapped in intracellular vesicles such as early and late endosomes, lysosomes, or phagosomes.\textsuperscript{20-21} Some studies also reported the presence of NPs in cytosol,\textsuperscript{19,22-24} in mitochondria,\textsuperscript{15,25} and in nuclei.\textsuperscript{23,26} The ways of entrance into cells and the subsequent distribution are crucial for their biological effects.\textsuperscript{25,27} Shukla et al. found that GNPs can be internalized in lysosomes and then the organelles move toward the nuclei with a peri-nucleu distribution in a time-dependent manner.\textsuperscript{28} Our results demonstrated that intracellular localization is a key factor in determining final fates of both GNPs (retention or exclusion) and cells.\textsuperscript{15} In short, after entering into A549 cells, GNPs are transported to lysosomes and then translocated to mitochondria. Their mitochondrial storage impairs mitochondrial structures and further influences their abilities to be excluded. Comparably, intracellular trafficking of GNPs in 16HBE and MSC cells is quite different from A549 cells. GNPs in both cells are localized at endosomes/lysosomes and then they remain there for some time for 16HBE, and about 60% are excluded for MSC cells. Our results showed that there are significant changes in lysosomal membrane permeation (LMP) after internalization of GNPs into lysosomes in A549 cells, but not in 16HBE and MSC cells, which provide a chance for GNPs to be released into cytoplasm. Finally, these GNPs can target at mitochondrial of cancer cells and induce apoptosis, while they cause few effects on normal or mesenchymal stem cells.

With respect to application, the surface of GNPs can be coated with membrane-disruptive molecules to release them from vesicular structures to cytosol. Alternatively, nanoparticles can be modified with peptides which allows for direct stepping over cell membrane and penetration into cells. In this way, it becomes more efficient to deliver molecules adsorbed on their surface to cytoplasm.

3. CELLULAR RESPONSES

As a systematic event, one puzzle is how cells respond to these internalized GNPs. To the best of our knowledge, biological effects of GNPs exhibit not only simply toxic forms, but also other forms, like cell type-associated response, changes in physiological or pathological behaviours such immunological responses and differentiation in-
duction, functional disturbance, inhibition in cell cycle, and so on. To understand these responses, we can collect more evidences to predict potential risk about nanomaterials. Moreover, beneficial response to GNPs can be used to develop their novel applications in nanomedicine. Next, we will discuss several types of cell responses to GNPs.

3.1. Toxic Responses

As mentioned above, the entrance of NPs into cells depends on either endocytosis or direct penetration. However, the latter process may cause significant toxicity to cells. Furthermore, intracellular GNPs may also cause cytotoxicity via other ways. Pan et al. studied the cytotoxicity of GNPs in four types of cell lines including HeLa, SK-Mel-28, L929 and mouse macrophage cells. TEM showed that the cells were swollen and lost their substrate contact. Incubated with GNPs for 12 h, some cells show membrane blebbing, cytoplasmic disintegration, and nuclear fragmentation which indicate cell apoptosis and secondary necrosis.

In addition, we found that CTAB-coated GNPs can target mitochondrial of A549 and consequently induce apoptosis, while show little toxicity in 16HBE and MSC cells. Synthesized gold nanorods (GNRs) contain a large amount of CTAB molecules in the solution, which exhibit high cytotoxicity. CTAB molecules develop bilayers on the surface of GNRs. Though we can remove most of free CTAB from solution, repeated centrifugation may cause irreversible aggregation of GNRs. What’s more, our group demonstrated that cytotoxicity of GNRs is strongly coating-dependent and almost shape-independent. As shown in Fig. 2, cytotoxic effects of CTAB on tumor cells are dose-dependent. By replacing CTAB on surface of GNRs by thiol molecules, we can easily calculate residual CTAB in suspended solution and those on GNRs surface by measuring their toxicity, respectively. After twice careful centrifugation of GNRs, residual CTAB (much fewer than that on surface) causes very limited effects on cell viability and their cytotoxicity actually come from CTAB on the surface of GNRs. The CTAB molecules alone can penetrate into cells, target at and damage mitochondria, and finally induce apoptosis. Furthermore, GNRs with different coatings, like CTAB, PSS and PDDAC molecules, were used to study the origin of toxicity. The other two types of GNRs exhibit less cytotoxicity than CTAB-coated ones (Fig. 3).

In fact, it is essential to distinguish the toxicity of the GNPs core from that due to ligands on the surface. It has been suggested that non-cationic GNPs can be used as reference nanoparticles for applications with lower toxicity compared to carbon nanotubes and quantum dots with higher toxicity. It is also feasible to modify their surface to decrease toxicity of GNPs, including replacement of toxic surface molecules by molecules with thiol and layer by layer modification with biocompatible polymers.
Besides, these biocompatible GNPs can be conjugated with multiple types of functional molecules to have promising biomedical applications in imaging, diagnosis and therapy.\textsuperscript{34,36}

3.2. Cell Type-Dependent Responses to GNPs

As we know, tissues or organs are consisted of multiple types of cells with different structures, functions, and behaviours. To understand impacts of nanoparticles on specific partitions \textit{in vivo}, one feasible way is to establish a model to compare the responses of different types of cells therein. That is to say, it is necessary to evaluate how different cells behave in front of GNPs. Recently, several groups have reported their discoveries about cell type-dependent response to GNPs. One impressive research indicated that GNPs can induce the apoptosis-involved death of lung epithelial cells (A549), while do not affect the fates of kidney epithelial cells (BHK21) and liver epithelial cells (HepG2).\textsuperscript{37} The induction of death in A549 cells indicated that responses to GNPs are cell type-dependent. However, the nature for selective responses needs further investigation. Interestingly, we noticed that the CTAB-coated GNPs can kill tumor cells while induce negligible effects on normal cells or stem cells.\textsuperscript{15} The reason is that the trafficking of GNPs in tumor cells is different from other cells, with destined localization in mitochondria of tumor cells, which causes damage in mitochondrial structure and functions and Triger apoptosis. Furthermore, Jiang et al. reported that numerous Herceptin–GNPs can be internalized by SK-BR-3 cells with highly expressed Herceptin receptors (ErbB2) rather than ErbB2-lowly expressed cells like HeLa. Their internalization into SK-BR-3 cells alters the downstream signaling and subsequent cellular response, like increased apoptosis and inhibition of cell cycle.\textsuperscript{38}

3.3. Influences on Physiological Functions

During the life time, adult stem cells are a type of original cells for tissue renewal and homeostasis and they have abilities of proliferation and differentiation into specific tissue cells. For example, Yang et al. found that GNPs in osteoblast-inducing medium can promote the differentiation of MSC stem cells into osteoblasts \textit{via} up-regulated p38 MAPK pathway, which may be derived of triggered mechanical stress due to internalized GNPs. And GNPs do not affect cell viability of MSC cells. Therefore, it showed us a direction to use nanomaterials to improve stem cell differentiation \textit{in vitro}.\textsuperscript{39}

Another interesting report from Pernodet et al. indicated that citrate coated GNPs can vitally affect the proliferation, morphological structure, spreading, migration, and protein synthesis of human dermal fibroblast cells. The reason for such strong cellular response was that intracellular presence of GNPs results in the disappearance of actin stress fibers and then disrupted extracellular matrix.\textsuperscript{40} Another group reported that GNPs can inhibit heparin-binding growth-factor (VEGF/bFGF)-mediated cell proliferation and disturbance of cell cycle because the binding of GNPs to their growth factors can efficiently block their functions to promote proliferation.\textsuperscript{41-42}

Latest work by Deng et al. demonstrated that poly(acrylic acid)-coated GNPs (PAA-GNPs) can induce strong inflammatory response after binding to and inducing unfolding of fibrinogen in plasma, while PAA-GNPs and fibrinogen themselves do not trigger this response.\textsuperscript{43} Detailed investigation pointed that 5 nm PAA-GNPs can insert into chains of fibrinogen by electrostatic interaction. Then, the interaction will change the secondary structure of fibrinogen with exposed γ C-terminus, which can recognize and bind to Mac-1 receptors on Thp-1 cells. Finally, Mac-1 receptor-mediated NF-κB activity will be activated, which up-regulates a number of pro-inflammatory genes. This research provides a novel mechanism to understand GNP-mediated immune response.

4. THE INFLUENCE OF PHYSIOCHEMICAL PROPERTIES TO BIOLOGICAL EFFECTS OF GNPS

Physicochemical properties of GNPs such as size, shape, surface charge and modification, play key roles in their uptake process and toxicity.\textsuperscript{2,18,32,44-45} Several researches have been conducted to probe GNPs-cell interactions in the past few years. It has been reported that the sign of surface charges can dramatically influence uptake of GNPs.\textsuperscript{32} In addition, different shapes,\textsuperscript{2,32} ligand structures,\textsuperscript{46} and compositions\textsuperscript{2,44} of GNPs can also lead to different degrees of cellular uptake. In particular, it is found that cationic and anionic GNPs follow different internalization pathways to enter cells.\textsuperscript{37} Interestingly, surface structure-regulated anionic GNPs can bypass endocytosis without obviously disrupting plasma membranes.\textsuperscript{19} Therefore, it is easy to understand the complicated relationship between properties of GNPs and biological effects. Next, we are going to summarize the advances of the influence of size, shape, surface charge and modifications on the bio-
### Table 1. Summary of cellular responses induced by physiochemical properties of gold nanomaterials

<table>
<thead>
<tr>
<th>NPs</th>
<th>Size, Aspect ratio</th>
<th>Surface coatings</th>
<th>Cell types</th>
<th>Exposure (concentration, duration)</th>
<th>Location</th>
<th>Cell responses</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>GNPs</td>
<td>3-8 nm</td>
<td>Lysine, PLL, FITC</td>
<td>RAW264.7</td>
<td>10, 25, 50, and 100 μM; 24, 48, 72 h</td>
<td>Lysosome</td>
<td>Nontoxic. Reduce the production of reactive oxygen and nitrite species, and do not elicit secretion of proinflammatory cytokines TNF-α and IL-1β.</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>7 nm</td>
<td>PVP</td>
<td>HEK293</td>
<td>10, 25, 50, 100 μM; 24 h</td>
<td>N/A</td>
<td>Nontoxic.</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>10 nm, 18 nm</td>
<td>Coumarin-PEG thiol, mPEG thiol</td>
<td>MDA-MB-231</td>
<td>50-200 μg/mL; 24 h</td>
<td>Peri-nuclear region</td>
<td>NPs are efficiently internalized. But essentially non-toxic up to 200 μg/mL.</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Citrate, biotin, L-cysteine, glucose, CTAB</td>
<td>K562</td>
<td>0-250 μM (Au atoms); 3 days</td>
<td>N/A</td>
<td>N/A</td>
<td>Citrate and biotin coatings show negligible toxicity at 250 μM; glucose and cysteine-modified GNPs are not toxic up to 25 μM; 18-nm CTAB-coated GNPs display significant toxicity.</td>
<td>35</td>
</tr>
<tr>
<td>13 ± 1 nm</td>
<td>Citrate</td>
<td>Human dermal fibroblasts</td>
<td>0-0.8 mg/mL; 2-6 days</td>
<td>N/A</td>
<td>N/A</td>
<td>Cell area, density, morphology, and actin stress fibers decrease and vacuoles increase with large dose of GNPs.</td>
<td>40</td>
</tr>
<tr>
<td>15 nm</td>
<td>BSA</td>
<td>NIH-3T3</td>
<td>0, 1, 10, 100 μM; 3 h</td>
<td>N/A</td>
<td>N/A</td>
<td>100% viability.</td>
<td>60</td>
</tr>
<tr>
<td>20-25 nm;</td>
<td>BSA, targeting peptides</td>
<td>Hep G2, HeLa, NIH-3T3, COS-7</td>
<td>0.1, 12 h; 150 pM, 3 h;</td>
<td>N/A; 6 h</td>
<td>Nucleus</td>
<td>Cell viability reduced by 20% in HeLa cells; but only 5% in NIH-3T3 and Hep G2.</td>
<td>61-62</td>
</tr>
<tr>
<td>N/A</td>
<td>PEI</td>
<td>SK-BR-3</td>
<td>0.05, 0.1, 0.5 nM; 24 h</td>
<td>N/A</td>
<td>Endosome, lysosome</td>
<td>Enhance transfect efficiency; but decrease 20-30% viability after transfection. Cystamine-modified GNRs were reasonably nontoxic and biocompatible, while Herceptin-modified GNRs show a dose-dependent toxicity since Herceptin induces apoptosis of breast cancer cells.</td>
<td>63</td>
</tr>
<tr>
<td>GNRs</td>
<td>60 × 13 nm</td>
<td>Cystamine, herceptin</td>
<td>SKBR3, CHO, C2C12, HL60</td>
<td>20-174 pM; 24 h</td>
<td>N/A</td>
<td>PSS showed substantial cytotoxicity. Only HL60 showed a toxic response at high concentrations of the PEGylated particles.</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>45 × 18 nm, 40 × 12 nm</td>
<td>PSS, PEG-SH</td>
<td>SKBR3, CHO, C2C12, HL60</td>
<td>20-174 pM; 24 h</td>
<td>N/A</td>
<td>PSS showed substantial cytotoxicity. Only HL60 showed a toxic response at high concentrations of the PEGylated particles.</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Aspect ratio: 1.1–4.0</td>
<td>PDDAC, PSS, CTAB</td>
<td>SKBR3, CHO, C2C12, HL60</td>
<td>20-174 pM; 24 h</td>
<td>N/A</td>
<td>PSS showed substantial cytotoxicity. Only HL60 showed a toxic response at high concentrations of the PEGylated particles.</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Aspect ratio: 15 × 58 nm</td>
<td>CTAB, PEG-SH</td>
<td>A549, 16HBE, mesenchymal stem cells (MSC)</td>
<td>50-200 μM (gold amount); 24, 48, 72 h</td>
<td>N/A</td>
<td>CTAB-coated GNRs kill A549 while pose negligible impact on 16HBE and MSC cells. PEG-GNRs have almost no toxicity.</td>
<td>15</td>
</tr>
</tbody>
</table>
logical effects of GNP{s}, which are summarized as shown in Table 1.

4.1. Size

GNPs could be synthesised in different sizes by controlling reaction conditions. In Fig. 4, GNPs are synthesised with size ranging from 14 to 100 nm. Chithrani et al. studied the relationship between particle size and internalization of GNPs. They quantified the uptake of different size GNPs in HeLa cells. Results showed that cellular uptake is heavily dependent on the size of GNPs. With the increase of the particle size, cells intake more GNPs, however, the uptake reduced with a size larger than 50 nm. The maximum uptake occurred for GNPs with a size of 50 nm. It is also showed that uptake rates of larger particles is lower than those of smaller ones.2

In addition, Jong et al. reported that sizes of GNPs affect their distribution in organs.48 They injected rats with different size of 10, 50, 100, and 250 nm GNPs, 24 h later, blood and various organs were collected for gold quantity by inductively coupled plasma mass spectrometry (ICP-MS). Results showed that majority of GNPs were found in liver and spleen. Interestingly, difference in distribution of GNPs was found between 10 nm and the larger ones. The 10 nm GNPs were observed in various organ systems while the larger GNPs were only present in blood, liver and spleen, demonstrating that organ distribution of GNPs is size-dependent and 10 nm GNPs have the most widespread distribution.

Moreover, Pan et al. studied the effects of size on cytotoxicity of GNPs.14 They performed a systematic study of colloid GNPs stabilized by triphenylphosphine derivatives with size ranging from 0.8 to 15 nm. Four cell lines including epithelial cells, connective tissue fibroblasts, melanoma cells, and macrophages were used to determine their toxicities. The result showed that most cells are sensitive to 1.4 nm GNPs. In contrast, 15 nm GNPs are non-toxic at up to 100 fold-higher concentrations. In addition, they found the cellular response is size dependent. For instance, 1.4 nm GNPs cause strong necrosis quickly within 12 h, while 1.2 nm particles mainly induce programmed cell death by apoptosis.

4.2. Shape

As is shown in Fig. 5, various shapes of GNPs can be synthesised, including CG (Colloid GNPs), GNRs, nanoshells, nanobowls, and so on. Does shapes of GNPs affect their biological effects is not certain.66 Chithrani et al. studied the shape effect of GNPs on intracellular uptake. They showed that uptake is shape-dependent via receptor-mediated endocytosis.2 Comparably, cells can intake more spherical GNPs than GNRs. Meanwhile, cells prefer excluding GNRs than spherical-shape GNPs. Moreover, GNRs with increasing aspect ratio have a

![Fig. 4. Transmission electron microscopy imaging and measurements of GNPs in cells. (A) The graph of number of GNPs per vesicle diameter vs nanoparticles size. (B-F) TEM images of GNPs with sizes 14, 30, 50, 74, and 100 nm trapped inside vesicles of a Hela cell, respectively. Reproduced with permission from Reference 5. Copyright 2006, Nano Lett.](image)

![Fig. 5. TEM images of 15-nm CG (a), 15 × 50-nm GNRs (b), 160(core)/17(shell)-nm silica/gold nanoshells (c, SEM), 250-nm Au nanobowls with 55-nm Au seed inside (d), silver cubes and gold nanocages (inset) (e), nanostars (f), bipyramids (g), and octahedrals (h). Reproduced with permission from Reference 66. Copyright 2010, J. Quant. Spectrosc. Radiat. Trans.)](image)
decreased rate for uptake and less internalized amount of NPs in cells. One possible explanation is that GNRs have a larger contact area with receptors on cell membrane than the spherical GNPs.

In addition, we studied cytotoxic effects of GNRs with ranging aspect ratio from 1.1 to 4.0. The result showed that cytotoxicity of GNRs does not show any distinguishable differences, which meant shape-independent cytotoxicity.32

4.3. Surface Charge

Surface charges of GNPs have a vital influence on affinity constant between nanoparticles and cell membranes because cell membrane is negatively charged. PMF analysis showed that cationic GNPs are more favoured by PC/PG bilayers than anionic GNPs. So cationic GNPs are much easily absorbed onto bilayers than the anionic ones.47 Furthermore, increased charge density of GNPs can affect both the level of penetration and membrane disruption (in Fig. 6). It was reported that internalization rate of cationic GNPs is five time-faster than that of anionic ones. It suggested that mechanisms for internalization of GNPs with different charges may be distinct. Anionic GNPs are internalized by endocytosis, while a number of cationic GNPs escape from this pathway by direct diffusion into cells that will cause damage in plasma membrane and result in strong cytotoxicity. In conclusion, these studies show that cationic particles are moderately toxic, whereas anionic particles are relatively non-toxic.49

4.4. Surface Modification

GNPs could be modified with compounds, nucleic acid, peptide, antibody, etc. These surface modifications have a vital influence on toxicity, endocytosis, and other biological effects of GNPs. It was reported that GNPs coated by CTAB molecules when synthesized by seed-growth method were found to be cytotoxic35,50-51. However, after further coated with negatively charged PSS (sodium polystyrene sulfonate), their cytotoxicity decreases greatly.32,44 Further coated with positively charged PDDAC(poly diallyldimethyl ammonium chloride) with positive charges, GNPs do not cause obvious cytotoxicity.32 What’s more, PEG-SH coated GNRs could decrease the toxicity of harmful CTAB/GNRs.52 In addition, Dreden used a thiol-PEGylated tamoxifen derivative to conjugate with GNPs.53 The compound can be used to selectively target estrogen receptor on the surface of positive breast cancer cells with up to 2.7-fold enhanced drug potency in vitro. Shenoy et al. indicated that after incubating methoxy-PEG-thiol or coumarin-PEG-thiol GNPs with MDA-MB-231 cells for 24 h, functionalized GNPs are engulfed by nonspecific endocytosis, and localize in cytoplasm and perinuclear region.54 Connor et al. studied effects of surface modification on their uptake and cytotoxicity in human leukemia (K562) cells. The surface modifiers include CTAB, cysteine, citrate, biotin, and glucose. After incubating with cells for three days, the GNPs with citrate and biotin surface did not show any toxic at 250 μM. However identical content of gold salt (AuCl₄⁻) solution appeared to be over 90% toxic.35

CONCLUSION AND PROSPECT

GNPs possess some attractive properties: firstly, GNPs are inert, which makes them relatively biocompatible; secondly, they can be easily synthesized and colloially stable; thirdly, they can be conjugated with biological

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GNPs possess some attractive properties: firstly, GNPs are inert, which makes them relatively biocompatible; secondly, they can be easily synthesized and colloially stable; thirdly, they can be conjugated with biological
molecules in a straightforward way; Moreover, GNPs possess unique optical properties, in particular the surface plasmon resonance. All these properties make GNPs very available in gene delivery and intracellular regulation, hyperthermia therapy, and biosensing using optical and electronic approaches. Recent studies have reinforced the concept that size, shape and surface modification, and charge are critical factors for materials properties. Undoubtedly, they are crucial aspects that can heavily affect the interaction between NPs and biological systems, like uptake, trafficking, intracellular localization, and cellular responses. Nevertheless, we can control the size, shape, surface modification of GNPs to regulate biological effects responses. Nowadays, more and more reports have been focusing on not only for risk evaluation, but for smart applications. We can control the size, shape, and surface modification of GNPs to regulate biological effects responses. Nevertheless, we can control the size, shape, surface modification of GNPs to regulate biological effects responses.

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