Gold nanoparticles functionalized with gadolinium-diethylenetriamine pentaacetic acid-cysteine conjugate

Au@GdL

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Chemical name:	Gold nanoparticles functionalized with gadolinium-diethylenetriamine pentaacetic acid-cysteine conjugate	
Abbreviated name:	Au@GdL	
Synonym:		
Agent Category:	Nanoparticles	
Target:	Non-targeted	
Target Category:	Non-targeted	
Method of detection:	Multimodality imaging (magnetic resonance imaging/ computed tomography (MRI/CT))	
Source of signal / contrast:	Au and Gd(III)	
Activation:	No	
Studies:	• *In vitro* • Rodents	No structure is available.

Background

[PubMed]

The gold nanoparticles (AuNPs) functionalized with the gadolinium (Gd(III))-diethylenetriamine pentaacetic acid (DTPA) conjugate of cysteine, abbreviated as Au@GdL, are a magnetic resonance imaging (MRI)/computed tomography (CT) dual-

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imaging agent synthesized by Park et al. for MRI/CT multimodality imaging of tumors (1).

Development of hybrid imaging technology has triggered great effort in probe development to boost the benefits of hybrid instrument technology (2-4). In contrast to other agents, multimodal imaging agents for MRI/CT have rarely been explored, although MRI and CT are frequently applied to the same patients for precise diagnosis and treatment evaluation (5-7). Recently, AuNPs have been shown to induce strong contrast enhancement as X-ray contrast agents (8, 9). These particles exhibit a higher X-ray absorption coefficient than iodinated compounds (5.16 and 1.94 cm^2/g, respectively, at 100 keV). Furthermore, AuNPs are easily controlled with regard to size, shape, and surface modification (1). Gd(III) also possesses a higher X-ray absorption coefficient (3.11 cm^2/g at 100 keV) than iodine, although this value is lower than that of gold. Interestingly, when Gd(III) ions are bound to NPs, they exhibit a much higher relaxivity than that of clinically approved Gd(III)-chelates (1, 8). Sanchez et al. have shown that the water-soluble apoferritin-encapsulated gadolinium oxide-hydroxide NPs (Gd-Apoferritin) exhibit 10 and 70 times higher T1 and T2 relaxivity values, respectively, than those of classic Gd(III)-complexes (Omniscan® and Gd-DTPA) (8).

On the basis of these facts, Gd(III)-coated AuNPs have been hypothesized to be an efficient dual agent for MRI/CT imaging. Alric et al. demonstrated that Gd(III) chelate-coated AuNPs (Au@DTDTPA-Gd_{50}) provide strong X-ray absorption and R1 relaxivity (9). Approximately 50.7 mM Au@DTDTPA-Gd_{50} NPs (10 mg Au/ml) exhibits X-ray absorption equivalent to that of 280 mM iodine (35 mg iodine/ml). The R1 relaxivity of the particles as low as 5 mM Gd(III) is nearly the same as that of Omniscan® (3.90 $mM^{-1}s^{-1}$). These particles are small enough (2–2.5 nm) to circulate freely in the blood vessels without undesirable accumulation in organs such as lungs, spleen, and liver. Recently, Park et al. developed a similar MRI/CT dual-imaging agent with Gd(III) and gold reporters (Au@GdL) (1). Au@GdL was generated by encapsulating the gold core within a multilayered organic shell. The contrast enhancement in the MRI stem is from the Gd(III) entrapped in the shell, whereas the gold core provides strong X-ray absorption. Studies by Park et al. showed that Au@GdL had a long circulation time in blood and accumulated within tumor xenografts in animals (1). This chapter summarizes the data obtained with Au@GdL in MRI/CT imaging.

Related Resource Links:

- Multimodality imaging agents in MICAD
- Multimodality imaging clinical trials in ClinicalTrial.gov

Synthesis

[PubMed]

Park et al. described the synthesis of Au@GdL in detail (1). The ligand (L), a conjugate of DTPA with cysteine, was prepared by the reaction of DTPA-bis(anhydride) with cysteine

at 80°C for 6 h. The subsequent reaction of L with Gd_2O_3 for 6 h at 90°C led to the formation of GdL. The coating of AuNPs with GdL was accomplished by direct addition of GdL to citrate-coated AuNPs (~12 nm in diameter) with stirring for 24 h. Au@L NPs without Gd(III) were also synthesized similarly.

The Au@GdL NPs were well dispersed and spherical in shape with a mean diameter of 14 nm and a narrow size distribution. The total number of GdL per AuNP was ~2.9×10^3, which was further confirmed by the weight loss of 5.6% in the temperature range 100–800°C. A higher degree of oligomerization of thiols in L may be a partial explanation for such a high loading of Gd(III). The zeta potential of Au@GdL in water was −41.03 mV at pH 6.0, which was negatively large enough to ensure colloidal stability.

Both Au@GdL and Au@L exhibited greater X-ray attenuation than Ultravist®, an iodine-based CT agent used in the clinic, and the differences became greater as the concentration increased. At a concentration of 200 mM, both Au@GdL and Au@L showed attenuation almost three times greater than that of Ultravist®. When the comparison was made between Au@GdL and Au@L, the former showed greater attenuation, demonstrating a synergistic effect of Gd(III). An additional contrast enhancement of ~15% seemed to be contributed by 2% of Gd(III) (weight) bound on AuNPs.

At 293 K and 1.5 T, the R1 relaxivity of GdL (7.5 $mM^{-1}s^{-1}$) was twice as high as that of Omniscan® (3.30 $mM^{-1}s^{-1}$). The same R1 relaxivity increased dramatically to 17.9 $mM^{-1}s^{-1}$ with the formation of Au@GdL. When calculated in terms of the AuNP concentration, the molecular R1 relaxivity was 4.6×10^5. The high relaxivity demonstrated by Au@GdL may partially be rationalized in terms of the slower tumbling motion of GdL on AuNPs due to the formation of a rigid oligomeric framework as a result of disulfide bonds.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The cytotoxicity of Au@GdL was evaluated with 14-day-old chick cornea stroma primary cells and NIH-3T3 mouse embryonic fibroblast cells (1). No obvious decrease in cell viability was observed when the cells were exposed for 24 h in the concentration range of 10–1,000 μM Au@GdL. Instead, the relative cell viability increased with the increase of the Au@GdL concentration, indicating that Au@GdL stimulated the cell proliferation in the given concentration range, which is consistent with the reports in the literature (10).

Animal Studies

Rodents

[PubMed]

MRI/CT imaging was performed in mice ($n = 6$) after intravenous injection of Au@GdL.CT imaging at a dose of 1.75 mmol Au/kg showed clear contrast enhancement

in all organs (1). The most dramatic enhancement was observed in the liver. The maximum attenuation in the liver reached up to five times that of pre-injection and maintained that level for up to 6 h after injection. The majority of Au@GdL accumulated in the Kupffer cells of the liver as demonstrated with histological and electron microscopic analysis. Some particles accumulated in the kidney and spleen as a result of glomerular filtration function and macrophage activity, respectively.

In line with the observations from CT imaging, MRI at a dose of 0.03 mmol Gd(III)/kg showed a strong signal enhancement, specifically in the liver (1). In addition, prolonged signal enhancement of the abdominal aorta was observed because of the long-circulating blood pool effect of Au@GdL.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

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