Gold Nanoclusters in Tumor Theranostic and Combination Therapy

Subjects: Materials Science, Biomaterials Contributor: Sisi Liu, Junyao Wang, Yuxin Song, Shuya He, Huaxin Tan

The rising incidence and severity of malignant tumors threaten human life and health, and the current lagged diagnosis and single treatment in clinical practice are inadequate for tumor management. Gold nanoclusters (AuNCs) are nanomaterials with small dimensions (\leq 3 nm) and few atoms exhibiting unique optoelectronic and physicochemical characteristics, such as fluorescence, photothermal effects, radiosensitization, and biocompatibility.

Keywords: gold nanoclusters ; cancer diagnosis ; combination therapy

1. Introduction

The high incidence and mortality rate of cancer pose grave risks to the lives and well-being of all humans. It has long been a focus of research in life science to improve the accuracy of the early detection of malignant tumors and to address the dearth of effective tumor treatments ^[1]. With the rapid development of nanotechnology, the diversity of structures and functions of biological nanomaterials has been further enriched and spread at an alarming rate to life sciences and clinical medicine, especially new nanomaterials that integrate multiple modes of diagnostic and therapeutic strategies in one, making precise diagnosis and treatment integration and synergistic treatment possible, and this is eagerly anticipated around the globe ^{[2][3]}.

Gold nanoparticles (AuNPs) are a type of colloidal or agglomerated particle with diameters between a few and hundreds of nanometers, composed of gold cores and surface shell layers. Due to their unique optical properties (surface plasmon resonance, surface-enhanced Raman scattering, etc.) and excellent catalytic properties, they hold great promise in a variety of applications, including biosensing, bioimaging, disease diagnosis, and treatment [4][5][6][Z].

Gold nanoclusters (AuNCs) are gold nanomaterials with significantly smaller dimensions (\leq 3 nm) and typically comprise a few to tens of atoms ^[B]. Due to the quantum-limited effect, AuNCs have superior fluorescence properties and are utilized in a variety of scientific fields, including environmental detection, molecular labeling, and bioimaging ^{[B][10][11][12][13]}. In addition, because AuNCs are smaller than the renal threshold, they are easier to eliminate from the body than AuNPs, resulting in greater biosafety and in vivo application potential ^[14]. Physical, chemical, and biological techniques are now used by production enterprises and lab researchers to create AuNCs. In situ synthesis employing biomolecules (DNA, proteins, peptides, etc.) as templates are one of the chemical techniques that is gaining popularity among researchers ^[15]. The principal causes are as follows. Firstly, the biomolecular template contains numerous active functional groups, such as -SH, -COOH, -NH₂, and -OH, which can bind gold atoms and improve their stability ^{[18][19]}. Secondly, some reducing amino acids (e.g., tryptophan, tyrosine) can reduce Au³⁺ ions to Au atoms in the presence of an appropriate pH environment, avoiding the use of strong reducing agents (e.g., NaBH4, CTAB) and have an improved biocompatibility ^[20]. Thirdly, the physical and chemical properties of AuNCs, such as the number of atoms, particle size, and optical properties, can be rapidly modified by adjusting the template amino acid or nucleotide sequences ^{[21][22][23]}. Lastly, the biological activities and functional binding sites of biomolecules provide a rich platform for further multi-functionalization of AuNCs ^{[24][25]}.

Meanwhile, for tumor tissue enrichment, small AuNCs with high permeability and long retention are preferable. Surfacemodified AuNCs can reduce the reticuloendothelial system (RES) and non-specific uptake, as well as specifically bind to overexpressed tumor cell receptors to enhance tumor cell accumulation, resulting in an enhanced cytotoxic effect against tumor cells ^{[26][27]}. The AuNCs can be rapidly excreted via the kidney, thereby minimizing damage to healthy tissues ^[14]. In comparison to large AuNPs, AuNCs possess a larger specific surface area and, consequently, greater surface energy. Due to this surface effect, the surface atoms of AuNCs are reactive and readily bondable with other atoms. Large payloads of drugs, genes, and other therapeutic molecules can be effectively trapped and protected from enzymatic degradation in complex physiological microenvironments ^{[28][29][30]}. Various internal and external stimuli may be used to regulate the release of drug-carrying molecules from functionalized AuNCs (e.g., pH, glutathione, light) ^{[31][32]}. As a result, they can be used as carriers for efficient targeted transport of therapeutic molecules, to enhance drug aqueous solubility, to prevent drug leakage in healthy tissues prematurely, and mitigate potential side effects.

Indeed, numerous reviews have been conducted on the design and application of AuNCs, particularly in terms of fluorescence imaging. Nonetheless, an increasing number of studies are currently attempting to fully integrate the various properties of AuNCs (Scheme 1).



Main Features

Scheme 1. Primary preparation strategies, distinctive properties, and combined applications in diagnosis and therapies of AuNCs(created with BioRender.com).

2. AuNCs as Imaging Agents in Tumor Theranostic

Since the successful construction of ultra-small AuNCs, the unique photoelectric effect resulting from their quantum size effect has been valued by researchers and utilized in a variety of sensing, detection, and bioimaging fields ^{[33][34][35][36]}. AuNCs are ideally suited for integrated medical applications in diagnostics and treatment due to their superior biocompatibility and functional versatility ^{[37][38]}. The atomic-level investigation of AuNCs has accelerated recently. Due to their precise size and composition, researchers have discovered that AuNCs have outstanding self-assembly and crystallization properties which endow them with more unique and diverse fluorescence properties ^{[39][40]}. To start, the researchers summarize the recent studies on the integration and visualization of AuNCs for diagnosis and treatment based on different imaging modalities of AuNCs, respectively (**Table 1**).

 Table 1. Application of AuNCs.

Multifunctional Nanoplatform	Role of AuNCs	Therapeutic Agent	Size (nm)	Imaging Mode	Cancer Types	Therapy Method	Activity	Ref
AuNCs-Ag@Keratin-Gd	Imaging	NM	5	FL, MRI	Breast cancer	Chemotherapy	In vivo and in vitro	[37]
CDGM NPs	Imaging, drug delivery	CAD, Ce6	2	FL	Lung cancer	PDT	In vivo and in vitro	[41]
AuS-U11	PTT-carrier	U11 peptide, cyanine dye Cy5.5, 5-ALA	10	FL	Pancreatic carcinoma	PTT, PDT	In vivo and in vitro	<u>[42]</u>
Au NBPs@PDA/AuNCs	Imaging	Au NBPs@PDA	2.1, 3.3	FL	Breast cancer, hepatocarcinoma	PTT	In vitro	<u>[43]</u>
Dox@HG-CAHs	Imaging	HA-ALD, Dox	2.8	FL, CT	Osteosarcoma	PTT, chemotherapy	In vivo and in vitro	[44]
AuNCs-LHRHa	Imaging, PTT	LHRH analogues	2.4	FL, CT	Prostatic cancer	PTT	In vitro	[45]
GTSL-CYC-HER2	Changed the zeta potential of liposomes, superior photothermal effect	HER2-modified thermosensitive liposome, cyclopamine	NA	CT, PTI	Breast cancer	Chemotherapy, PTT	In vivo and in vitro	[46]
Ce6&AuNCs/Gd-LDH	Imaging	Ce6	~2	MRI, FL	Hepatocarcinoma	PDT	In vivo and in vitro	<u>[47]</u>
AuNCs-ICG	Imaging, radiosensitizing effects	ICG	~1	FL, PAI, CT	Breast cancer	PDT, RT	In vivo and in vitro	<u>[48]</u>
Qu-GNCs	Imaging	Qu	1–3	FL	Lung cancer	Chemotherapy	In vitro	[<u>49</u>]
Fe3O4@PAA/AuNCs/ZIF-8 NPs	Imaging	DOX	NA	MRI, CT, FL	Hepatocarcinoma	Chemotherapy	In vivo and in vitro	[50]
AuNCs@GTMS-FA	Imaging, phototherapeutic agents	FA	2.8	FL	Breast cancer	PTT, PDT	In vitro	[<u>51</u>]
AuNCs/Dzs-Dox	NSET effect, shelter therapeutic cargos	Dzs-Dox	~1.76	FL	Breast cancer	Gene therapy, chemotherapy	In vivo and in vitro	[52]

Multifunctional Nanoplatform	Role of AuNCs	Therapeutic Agent	Size (nm)	Imaging Mode	Cancer Types	Therapy Method	Activity	Ref
HG-GNCs/GO-5FU	Bioimaging, phototherapeutic	HA, 5FU	2	FL	Lung cancer, breast cancer	Chemotherapy, PDT, PTT	In vitro	<u>[53]</u>
AuNCs@mSiO ₂ @MnO ₂	Photosensitizer	MnO ₂ nanozyme	NA	MRI	Breast cancer	PDT	In vivo and in vitro	<u>[54]</u>
Au8NC	Radiosensitizing effects	Levonorgestrel	~2	FL	Esophagus cancer	RT	In vivo and in vitro	[55]
Au ₄ -IO NP-cRGD	Imaging, radiosensitizing effects	IO nanocluster	2	FL, MRI	Breast cancer	RT, chemotherapy	In vivo and in vitro	[<u>56</u>]
PML-MF nanocarrier	Imaging	IO@AuNPs	NA	FL	Cervical cancer	PPTT, chemotherapy	In vitro	[<u>57]</u>
WLPD-Au ₂₅	Photosensitizer, drug delivery	WS2 nanoparticles, Dex, Captopril	2.5	СТ	Breast cancer	PTT, PDT	In vivo	[<u>58</u>]
AuNCs/Cas9-gRNA	Imaging, drug delivery	Cas9–sgRNA plasmid	~1.56	FL	Osteosarcoma	Gene therapy	In vitro	<u>[59]</u>
K-AuNCs	Imaging, drug delivery	К	1–3	FL	Lung cancer	Chemotherapy	In vitro	[<u>60]</u>
EA-AB	Imaging	EB	NM	FL, MSOT Imaging	Breast cancer	Chemotherapy, PTT	In vivo and in vitro	[61]
Ce6-GNCs-Ab-CIK	Drug delivery	Ce6, CD3 antibody	NA	FL	Gastric cancer	Chemotherapy, PDT	In vivo and in vitro	[62]
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 References Au₄Cu₄/Au₂₅@Lip
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Biomed. Anal. 2020, 190, 113522. AuNCS are widely used for drug delivery and controlled release in vivo and ex vivo as one of the metallic nanomaterials 12/ith/une.ppayest tesseareschist.goldAsaooelusters spebialmagingnappsizationanoBreitsteires.] Allanceschive la 2020 tel 10 dia 81:546 or 120 Phingto Bal, who is a the second where the second states and states and second second states and second s molectules ultrusthan bub Garberese high put free thread ungeration and waters be deaded. With a crubstantia intra big 1265 small-

molacity drugs via reasonable surface modification [49]. In addition, AuNCs can be targeted for in vivo tumor transport via

passive accumulation (e.g., enhanced permeability and retention effect) or active targeting (e.g., modified target 15. Liang, G.; Jin, X.; Zhang, S.; Xing, D. RGD peptide-modified fluorescent gold nanoclusters as highly efficient tumor-molecules), thereby enhancing the bioavailability of drugs [50][67]. Moreover, the ultra-small nanostructures enable precise targeted radiotherapy sensitizers. Biomaterials 2017, 144, 95–104. targeting of subcellular organelle structures, such as the nucleus and mitochondria, supplement selection, and therapeutic

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2. 4. Auncs as Therapeutic Agents in Combined Therapy for the stabilized gold

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release and fluorescent dye into gold nanoclusters for endomicroscopy-guided photothermal/photodynamic therapy to In factority discussion discussion and the second discussion and the

distributed according to the different shapes of tumors needs to be further investigated. In conclusion, more animal 43. Wang, J., Gao, Y., Liu, P., Xu, S.; Luo, X. Core-Shell Multifunctional Nanomaterial-Based All-in-One Nanoplatform for experiments and preclinical trials are needed for the practical translation of AuNCs to ensure that the multifunctional Simultaneous Multilayer imaging of Dual Types of Tumor Biomarkers and Photothermal Therapy. Anal. Chem. 2020, system of AuNCs can be efficiently and safely applied in the clinic.

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Crosslinking-Assembled Hydrogels Based on Gold Nanoclusters for Synergistic Osteosarcoma Multimode Imaging and As These amentions allows them to be used as ideal photothermal agents for multimodal imaging and therapeutic implementation. Therefore, examples of combined treatment 45. Wang, Z.; He, L.; Che, S.; Xing, H.; Guan, L.; Yang, Z.; Li, X.; Zvyagin, A.V.; Lin, Q.; Qu, W. AuNCS-LHRHa nanobased on the photothermal action of AUNCs will not be repeated in this section prostate cancer. J. Mater. Chem. B 2022,

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