Gold nanoparticle-mediated delivery of paclitaxel and nucleic acids for cancer therapy (Review)

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Abstract. Paclitaxel is a potent antineoplastic agent, but poor solubility and resistance have limited its use. Gold nanoparticles (AuNPs) are widely studied as drug carriers because they can be engineered to prevent drug insolubility, carry nucleic acid payloads for gene therapy, target specific tumor cell lines, modulate drug release and amplify photothermal therapy. Consequently, the conjugation of paclitaxel with AuNPs to improve antiproliferative and pro-apoptotic potency may enable improved clinical outcomes. There are currently a number of different AuNPs under development, including simple drug or nucleic acid carriers and targeted AuNPs that are designed to deliver therapeutic payloads to specific cells. The current study reviewed previous research on AuNPs and the development of AuNP-based paclitaxel delivery.

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1. Introduction

Cancer is the second most common cause of mortality worldwide, and lead to an estimated 18.1 incident cases and 9.6 million deaths in 2018 (1). Currently, surgery and cytotoxic chemotherapy are the primary treatments for cancer. However, 70% of cancer mortality occurs in low- or middle-income countries, which is due to delays in diagnosis and cancer being at a late stage at first presentation (2). Curative surgical resection may no longer be an option in such cases, leaving chemotherapy as the only treatment option (1-3). The global disease burden attributed to cancer underscores the importance of developing chemotherapeutic regimens with enhanced safety, tolerability and efficacy (3).

Paclitaxel is a first-line chemotherapeutic agent for solid tumors, but its use has been confounded by poor solubility, toxicity and the emergence of resistance during therapy (4,5). In order to improve efficacy and to decrease the emergence of resistance, clinicians combine paclitaxel with cisplatin and other antineoplastic drugs (6,7). As nanotechnology has progressed, multiple types of paclitaxel nanoparticles (NPs) have been developed to modulate drug release, promote drug encapsulation, improve bioavailability and target cancer cells by using frame materials of polyethylene glycol, polylactic acid, polyglycolin acid or liposomes (8). Examples include abraxane, which was synthesized by attaching six or seven paclitaxel molecules to albumin NPs of 130-nm diameter, and is considered to be among the most successful nanotherapeutics, as it has been approved as a first-line treatment for non-small cell lung carcinoma by the US Food and Drug Administration (8). Folic acid (FA)-poly NPs have been prepared to target ovarian tumor tissue, and NPs that carry rituximab and paclitaxel have been designed to target CD20-positive B-cell lymphoma (9).

Gold NPs (AuNPs) have received increasing attention as drug delivery vehicles for cancer therapeutics as they can be engineered to obviate drug insolubility, carry nucleic acid payloads for gene therapy, target specific tumor cell lines, modulate drug release and amplify photothermal therapy (PTT) (10,11). The development of gene therapy has generated increasing interest in the potential of AuNPs to deliver therapeutic nucleic acid payloads (10,11). AuNPs have been designed to carry p53, vascular cell adhesion molecule-1 and other mRNAs (10,11). Furthermore, poly(thymine)-functionalized AuNPs have been synthesized to target mRNA translation using a pcDNA6 vector expressing a bovine growth hormone polyadenylation signal (12). Consequently, it is important to investigate the potential of AuNPs to enhance paclitaxel drug delivery and gene therapy (12). In the current review, the role of paclitaxel in clinical oncology, and previous research on AuNPs and the development of paclitaxel AuNP-based drug delivery and its limitations are examined.

2. Mechanisms of paclitaxel action and drug resistance

Paclitaxel, which is isolated from Pacific Yew tree *Taxus brevifolia*, has been indicated to be a potent antimitotic agent in solid tumor cell lines (13). In 1992, paclitaxel was approved for ovarian cancer treatment by the US Food and Drug Administration (14). According to the National Comprehensive Cancer Network guidelines, paclitaxel is still a first-line chemotherapeutic, is combined with cisplatin, atezolizumab and other anti-neoplastic agents to treat lung, breast, gastric and colorectal cancer, and is also incorporated into pre- and post-operative chemoradiation protocols (15-18).

The antimitotic activity of paclitaxel is mediated via its disruption of microtubular function (19). Paclitaxel promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization (20). This inhibits the reorganization of the microtubule network, which is essential for interphase and mitotic cellular function (20). The polymerization of tubulin dimers decreases their concentration below that required for spindle assembly, thus arresting the cell cycle at the M/G2 phase (21-23). In addition, paclitaxel promotes tumor apoptosis by upregulating death receptor signaling and mitochondrial apoptotic pathways and increases beclin-1-mediated autophagy (21,24). These mechanisms of action have contributed to the emergence of paclitaxel as a first-line antineoplastic drug.

With repeated use, resistance commonly emerges during cancer therapy, and there are three major resistance mechanisms governing this resistance. The first, metabolic inactivation via the cytochrome P450 (CYP) system, was identified in 1994 (25). CYP3A and CYP2C were revealed to serve major roles in paclitaxel metabolism (26). It has also been demonstrated that paclitaxel treatment induces overexpression of CYP2C8 and CYP3A4/5, which is mediated by a nuclear receptor in multiple types of tumor cells, such as pancreatic ductal adenocarcinoma (PDAC), pancreatic adenocarcinoma 2 (PACO2) and PACO7, which are two primary PDAC cells propagated from immune-deficient NOD.Cg-*Prkdc*[scid]*Il2rg*[tm1Wjl] mice, leading to cell-autonomous detoxification (27). A second mechanism behind resistance is the overexpression of ATP

binding cassette (ABC) drug efflux transporters. ABCB1, ABCC1, ABCC2 and ABCG2 have been implicated in paclitaxel resistance *in vivo* and *in vitro* (28). ABCB1 and ABCC3 exhibit prominent activity in breast cancer resistance (28). A third mechanism for resistance is associated with drug transport that is mediated by solute carrier proteins. Changes in expression levels of solute carrier proteins may alter drug uptake and determine chemotherapeutic efficacy (29). Single nucleotide polymorphisms in genes that encode solute carriers (SLCs, including *SLC31A2*, *SLC43A1*, *SLC35A5*, *SLC41A2* and *SLCO1B3*) are associated with paclitaxel sensitivity and resistance *in vitro* (29). In addition, tumor suppressor genes such as *BRCA1*, *TP53*, *PTEN*, adenomatous polyposis coli, Cyclin Dependent Kinase Inhibitor 1A/2A, High in normal-1 and *Bax* also affect paclitaxel resistance (30,31). Furthermore, low solubility also limits the use of paclitaxel and all of the aforementioned factors decrease its efficacy. Therefore, it is essential to identify carriers to increase paclitaxel delivery and overcome insolubility and resistance. AuNPs have a number of advantages, including large surface area for drug and nucleic acid binding, non-toxicity and a unique property of amplifying PTT (10-12).

3. Development of AuNPs for antineoplastic drug delivery

In the past decade, NPs have been evaluated as novel drug delivery systems. The majority of these particles have a feature size <200 nm, which helps to overcome the mucus barrier, resulting in low reactogenicity and immunogenicity (32). A previous study demonstrated that NPs >200 nm in size induce a mucosal immune response and are taken up by dendritic cells, which secrete inflammation-associated factors, resulting in an immune response (33). In addition, NP carriers exhibit multiple pharmacokinetic advantages, including high loading efficiencies of lipophilic drugs such as 5-fluorouracil, which have low water solubility and intracytoplasmic bioavailability, protection of drugs from degradation, increased drug uptake by tumor cells, enhanced drug concentrations in tumor microenvironments, prolonged drug release and targeted delivery (34,35). The use of NPs for targeted drug delivery allows lower systemic drug exposures and minimal side effects (36). As cancer is the second leading cause of mortality worldwide, the future development and use of antineoplastic nanodrugs is essential (37,38).

Currently, there are four types of nanodelivery systems used or in development in oncology: Polymeric, magnetic, metallic and lipid NPs (36). AuNPs are non-toxic, can be easily synthesized into different sizes and shapes, have a large surface area to transport drugs, exhibit good biocompatibility and absorb near-infrared light (NIR) that can be converted to heat to enable focused thermal therapy (39). AuNPs are used in diagnostic imaging, targeted delivery of drugs, radio-isotopes and reactive oxygen species-generating enzymes, and plasmonic PTT and photodynamic therapy (40). Within the past year, >100 studies of AuNPs for drug delivery were identified. These studies are classified into 3 groups within the current review: Simple drug-carrying AuNPs, simple nucleic acid-carrying AuNPs and targeted (tissue directed) AuNPs.

Simple drug-carrying AuNPs. AuNPs were evaluated initially as antineoplastic drug carriers in 2004 (41). AuNPs with a diameter of 32 nm carrying tumor necrosis factor (TNF) have been used to target MC-38 colon carcinoma tumors *in vivo*, as the majority of TNF AuNPs target tumor cells with little accumulation in the liver and other organs in mice (41). Furthermore, TNF-carrying AuNPs have been indicated to be more effective against tumor cells compared with naive TNF (41). Studies have also been performed on AuNPs featuring optimization of either the particle or the drug payload (42,43). DM1, which is a maytansine analogue, was developed as a microtubulin inhibitor with the same mechanism of action as paclitaxel, but its toxicity and narrow therapeutic window limited its clinical development. Conjugation of DM1 with ultra-small (diameter, 2 nm) AuNPs prolonged the half-life of DM1, increased its cytotoxicity in Bel7404 and HepG2 cells and also improved its tolerability and efficacy in ectopic xenograft models of hepatocellular carcinoma (42). The conjugation of kaempferol, a flavonoid that damages DNA in malignant cells, to 2-nm gold nanoclusters decreases toxicity to normal cells, enhances toxicity to cancer cells and decreases proliferation, colony formation and migration of A549 lung cancer cells (43).

The amplification of PTT is a unique property of AuNPs that facilitates the development of a novel therapeutic modality, combined chemo-PTT (44). Gold nanoshell-coated wedelolactone liposomes combined with NIR-induced hyperthermia release 97.34% of wedelolactone in 8 h and exhibit an excellent antitumor efficacy *in vivo* (44). In conclusion, simple drug-carrying AuNPs are less toxic to normal cells and more toxic to cancer cells.

Nucleic acid-carrying AuNPs. As AuNPs have positive-charged surfaces whereas nucleic acids exhibit negative charges, AuNPs are easily adapted to deliver nucleic acid payloads (45). Small interfering RNAs (siRNAs), mRNAs and micro (mi)RNAs conjugated with AuNPs are used for diagnosis and gene therapy (45,46). Receptor tyrosine kinase-like orphan receptor 1 (ROR1) siRNA-HIV-1 Tat peptide-capped AuNPs have a hydrophilic arginine-rich section that facilitates DNA binding; increases the stability of ROR1 siRNA; enhances cellular uptake and induces apoptosis and necrosis in MDA-MB-231 cells (46).

Furthermore, surfactant-free AuNPs deliver plasmid DNA for tumor treatment (10). AuNPs capped with L-cystine methylester hydrochloride and loaded with p53 plasmid DNA increase p53 expression levels and induce A549 apoptosis, thus inhibiting proliferation without inducing cytotoxicity to normal lung cells (10). The conversion of amine-modified siRNA duplexes into dithiocarbamate ligands followed by conjugation with AuNPs increases siRNA stability and enhances targeted release of siRNA (47). Additional potential advantages of AuNP-based therapy have been demonstrated by the development of an intracellular self-assembly system of DNA and AuNPs (48). In a previous study (48), mRNA of survivin, which is an apoptosis inhibitor, and AuNPs in a complex with its complementary DNA sequence were transfected into cancer cells separately and spontaneously formed cytoplasmic aggregates. Survivin mRNA and AuNPs entered cells easily due to their small size, whereas the larger aggregates exhibited improved intracellular retention. This resulted in enhanced apoptosis and photothermal function, leading to cancer cell death rates of up to 93.3%, with minimal toxicity to normal cells (48).

17-N-allylamino-17-demethoxygeldanamycin (17-AAG) is a heat shock protein 90 (HSP90) inhibitor that blocks ATP binding and inhibits HER2(+) breast cancer cell proliferation (49). However, the anti-tumor effect of 17-AAG is decreased in the absence of Cullin-5 (Cul5), an E3 ubiquitin ligase that is required for HSP90 inhibitor function (49). Consequently, the delivery of 17-AAG and Cul5 DNA via AuNPs can sensitize 17-AAG-resistant breast cancer cells (49). Similarly, poly(sodium 4-styrenesulfonate) and poly(-diallyldimethylammonium chloride) have been used to coat gold nanoprisms carrying a siRNA targeting human program death-ligand 1 (hPD-L1), resulting in the downregulation of hPD-L1 expression and enabling photoacoustic imaging and PTT of lung cancer cells and cell-derived tumors (50).

Zhang *et al* (51) developed gold nanoshells that are designed for the PTT-stimulated release of siRNA to downregulate HER-2 expression levels and a genetic sequence to express the immunological adjuvant cytosine-guanine motifs to activate anti-tumor immune responses that are mediated by toll-like receptor 9 signaling. This integration of gene therapy, immunotherapy and PTT has been demonstrated to perform well in the treatment of a murine gastric cancer model (51). Consequently, in the presence or absence PTT, AuNPs may be used to carry tumor suppressor genes, oncogene-siRNA and miRNA to inhibit tumor cell proliferation (51).

Targeted AuNPs. In addition to simple AuNPs that are used for drug and nucleic acid delivery and PTT, multifunctional AuNPs have been designed for targeted delivery mediated by pH, short peptides, aptamers, antibodies and receptors (52-57). Glutathione (GSH)-coated Au-Fe$_3$O$_4$ nanoshells for doxorubicin (DOX) delivery feature a GSH layer on the nanoshell surface that is attached with an Au-S native bond, which is stable at physiological pH but rapidly broken down in acidic tumor microenvironments, resulting in local DOX release and cytotoxicity (52). AuNPs coated with biocompatible marine carbohydrate carrageenan oligosaccharide (CAO-AuNPs) have also been designed for pH-dependent drug release. For example, epirubicin (EPI)-CAO-AuNPs release their payload in acidic environments and more easily enter cells via endocytosis, inducing more potent cytotoxicity and increasing apoptosis compared with free EPI (53). A study by Pedrosa *et al* (53) used polyethylene glycol-coated AuNPs carrying a novel chemotherapeutic candidate (ZnD) and the monoclonal antibody cetuximab that targets epidermal growth factor receptor (EGFR) receptors that are overexpressed in cancer cells, and demonstrated that the addition of cetuximab facilitated both targeting and a second mechanism of action (antagonism of receptor-dependent EFGR signal transduction, resulting in interruption of the cell cycle, apoptosis and inhibition of metastasis and angiogenesis). This candidate was also demonstrated to be active against DOX-resistant tumors in a murine model (54). Afatinib (Afb) is a tyrosine kinase inhibitor that targets EGFR-positive lung cancer, and has disadvantages, including low bioavailability and high toxicity (54). In addition, the native structure of Afb prevents its direct conjugation to AuNPs. In order to mitigate these issues, an Afb analog containing
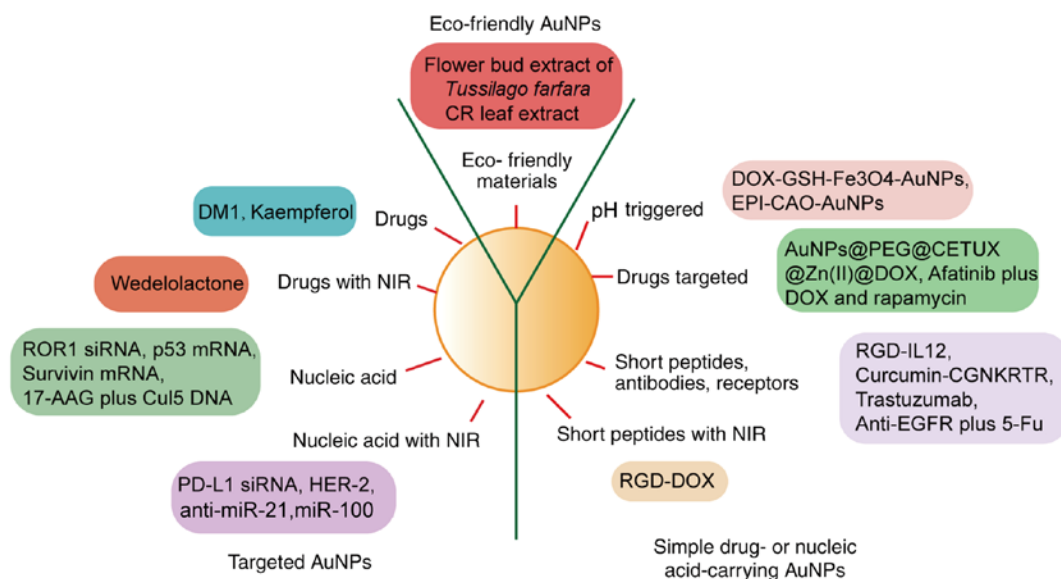
Figure 1. AuNPs are classified into three groups: Simple drug-carrying AuNPs, nucleic acid-carrying AuNPs and multifunctional AuNPs. Eco-friendly AuNPs may be synthesized using environmentally safe materials and production processes. AuNP, gold nanoparticle; NIR, near-infrared; ROR1, receptor tyrosine kinase-like orphan receptor 1; siRNA, small interfering RNA; 17-AAG, 17-N-allylamino-17-demethoxygeldanamycin; Cul5, Cullin5; PD-L1, program death-ligand 1; miR, microRNA; DOX, doxorubicin; GSH, glutathione; EPI, epirubicin; CETUX, cetuximab; RGD, arginylglyclaspartic; IL, interleukin; EGFR, epidermal growth factor receptor; 5-FU, 5-fluorouracil; PEG, polyethylene glycol; CGNKRTR, Nrp-1 receptor-specific short peptide.

a pedant alkynyl has been synthesized (55). The pedant alkynyl is coupled to an azide-functionalized lipoic acid moiety using a copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition to improve attachment to the AuNP surface with an alkylthiol-gold bond. Afb-AuNPs attenuate pro-inflammatory cytokine release and promote Afb cellular uptake and consequently, Afb-AuNPs exhibit a 3.7-fold increased potency in inhibiting EGFR mutant lung cancer cells, including PC-9 cells (55). Porous silicon NPs in a complex with gold nanorods have been designed for delivery of a three-drug combination of hydrophilic and hydrophobic drugs (Afb, DOX and rapamycin), and the inclusion of Afb, which targets HER-2 and EGFR. This construct confers targeted drug delivery to malignant cells, while gold nanorods facilitate PTT (56). This candidate has demonstrated positive results *in vitro* and *in vivo* (56).

The use of short peptides, antibodies and receptors in the design of targeted AuNPs is receiving increasing attention. Paris *et al* (56) recently investigated a novel strategy of targeting tumor angiogenesis rather than disrupting malignant cells. A tumor vascular endothelium-targeting nanoparticle was designed by incorporating an isoAspGly-Arg peptide that targets αβ-integrin-overexpressing cells (For example, tumor vascular endothelia), an anti-angiogenic drug (DOX), a vascular disrupting agent (fosbretabulin) and a gold nanorod. This enabled both drug delivery and PTT in a murine fibrosarcoma xenograft model and the results indicated a decrease in existing vasculature and the inhibition of neovascularization within tumors (57). Furthermore, delivery of interleukin-12 in RGD-peptide AuNPs may enhance adoptive T-cell therapy and improve its therapeutic potential (58). Neuropilin (Nrp)-1 receptor-specific short peptide-coated cucurbituril AuNPs deliver and release curcumin in Nrp-1-overexpressing melanoma cells (59). AuNPs coated with an anti-HER2 monoclonal antibody (trastuzumab)-cytotoxic drug [monomethyl auristatin E (MMAE)] conjugate and a cell-penetrating peptide (HIV Tat)

have been indicated to target HER-2-positive cells, increase cellular uptake and enhance the antimitotic potency and therapeutic index of free MMAE *in vitro* (60). Anti-EGFR-coated 5-fluorouracil-AuNPs have also been revealed to target colorectal cancer cells that overexpress EGFR, increase their apoptosis rate and improve their anti-tumor effects (9). DOX and anti-PD-L1 antibody-conjugated AuNPs enable drug delivery and PTT to target and induce CT-26 cellular apoptosis and inhibit cell proliferation (9). Furthermore, the attachment of glucose to polyethylene glycol (PEG) at the C6 position followed by installation on sub-50-nm nanocarrier enhances the delivery of polo-like kinase 1 siRNA to cancer stem-like cells, which overexpress glucose transporter 1 on their surface (61).

By carrying drugs in combination with specific nucleic acid sequences, short peptides, antibodies and receptors, AuNPs can aggregate at target tissues and cells to modulate drug release rate and improve efficacy.

4. Further innovations

Eco-friendly AuNPs. Protection of the environment has received increasing attention in recent years, and the use of eco-friendly materials has been investigated regarding the synthesis of AuNPs. The flower bud extract of *Tussilago farfara* has been used as a reducing agent to synthesize AuNPs that are suitable for anticancer drug delivery (62). Photosynthesized AuNPs from *Catharanthus roseus* (CR) leaf extract have also been studied, as CR is a plant that is used in traditional Chinese medicine (63). Without the addition of a chemotherapeutic or siRNA therapeutic payload, these AuNPs inhibit tumor proliferation by inducing mitochondrial-mediated apoptosis via reactive oxygen species (Fig. 1) (63). In addition, leaf extracts of *Ziziphus zizyphus*, *Coleus aromaticus*, *Indigofera tinctoria*, *Bauhinia purpurea* and *mulberry* have been used to synthesize environmentally friendly AuNPs (64-68).

Table I. Overview of PTX-AuNPs.

Study (Author, year)	Type of AuNP	Size, nm	Advantages	Targets	(Refs.)
Ding et al, 2013	GNPs with thiol capping	-	Prolonged circulation, stability across pH levels	T47D cells	(70)
Banstola et al, 2019	GNPs-pD-PTX-PLGA-Ms	19.50±4.00	PTT	Panc-1 cells	(37)
Bao et al, 2014	PTX-PEG400@GNPs in liposomes	281.10±5.40	Prolonged circulation, targeted delivery (hepatocellular carcinoma)	Sprague-Dawley rats, ICR mice	(69)
Gibson et al, 2007	PTX-PEG@GNP	155.00±24.20	Prolonged circulation, targeted intracellular release, improved tumor cell killing	HepG2 cells, ICR mice	(71)
Zhu et al, 2019	TL-PC-HDL-PTX	-	Improved drug release kinetics, enhanced long-term release	A-549, PC-9 and NCI-H358 cells	(82)
Farboudi et al, 2019	PTX-PNIPAAm-grafted-chitosan-GNPs	-	Improved dose precision, targeted delivery	T47D cells	(75)
Gupta et al 2012	MS-HAuNS-PTX	30.00-50.00	Increased plasma PTX levels and tumor necrosis apoptotic index; PTT	VX2 tumor-bearing rabbits	(81)
Heo et al, 2012	AuNPs-PTX-β-CD-biotin	-	Enhanced PTX efficiency	HeLa, A549 and MG63 cells	(76)
Liaskoni et al, 2018	B33-AuMOA-FA-PTX	174.56±37.59	Enhanced permeability and retention, accelerated release at acidic pH resembling tumor microenvironment and acidic intracellular compartments, induced apoptosis	A549 cells	(78)
Manivasagan et al, 2016	PTX-COS AuNPs	61.86±3.01	Sustained and pH-dependent drug release, potent cytotoxicity	MDA-MB-231	(79)
Paciotti et al, 2016	AuNPs-TNFα-PEG-Thiol-PTX analogs	~27.00	Targeted solid tumor, induced vascular leakage, prolonged release, enhanced potency	-	(77)
Pandey et al, 2017	AuNP-MSNPs-PTX	~200.00	Biocatalytic activity and robust framework for PTX loading	-	(84)
Peralta et al, 2015	PAC-AuNR-HSAPs	299.00±6.00	Increased loading efficiency and cell death with irradiation	4T1 cells	(80)
Venuri et al, 2019	AuNPs-Pacli	~87.60	Inhibited cell proliferation, apoptosis, angiogenesis, colony formation and spheroid formation	MCF-7 and MDA-MB 231 cells	(72)
Wang et al, 2019	PTX-PP@AuNPs	147.00±1.16	Controlled drug release, blocked TRPV6 cation channel, enhanced cell cycle arrest, elevated temperature and generated ROS	PC3 xenograft tumor mice	(85)
Yahyaei and Pourali, 2019	PLGA-GNP-PTX	-	Combined imaging and therapy in a single procedure	MCF7 cells	(86)
Wu et al, 2016	GNR@HPMOs-PTX@MSCs	~227.00	High PTX loading capability, PTT, improved dispersion and distribution in tumor tissue	MCF-7 cells	(87)

Table I. Continued.

Study (Author, year)	Type of AuNP	Size, nm	Advantages	Targets	(Refs.)
You *et al*, 2013	HAuNPs-PTX into glycolipid-like polymer micelles with NIR- EphB4	-	Increased drug delivery and toxicity to tumor cells, rapid and repetitive drug release, PTT	SKOV3 and A549 cells	(88)
Zhong *et al*, 2016	PTX-PAnP-FA	~184.70	Rapid drug release, targeted FA receptor over-expressed cells, combined drug release, imaging and PTT	HeLa cells	(74)
Zhu *et al*, 2019	PTX-TSL-siCOX-2(9R/DG-GNS)	-	Increased apoptosis at elevated temperatures, inhibited drug resistance	HUVECs and PTX-resistant HepG2 cells	(82)
Li *et al*, 2016	f-PGNPs	27.00±5.30	Potent cytotoxicity in drug-resistant cancer cells	Pgp-H460$_{PTX}$ and H460 cells	(73)

PTX, PAC or pacli, paclitaxel; AuNP, gold nanoparticle; PLGA, polylactic-co-glycolic acid; PTT, photothermal therapy; pD, Polydopamine; GNP, gold nanoparticles; Ms, microsphere; HAuNS, hollow gold nanospheres; AuMOA, gold nanoparticles functionalized with mercaptooctanoic acid; FA, folic acid; TNFα, tumor necrosis factor α; MSC, Mesenchymal stem cells; NIR, near-infrared; siRNA, small interfering RNA; f, fluorescent labeled; TRPV6, Transient Receptor Potential Cation Channel Subfamily V Member 6; PC, phosphatidylcholine; PEG, polyethylene glycol; β-CD, β-Cyclodextrin; COS, chitosan oligosaccharide; MSNPs, mesoporous silica nanoparticles; HDL, high density lipoprotein; -, not applicable.

Function of paclitaxel-carrying AuNPs. As the first-line chemotherapeutic agent for lung and ovarian cancer, paclitaxel has been evaluated as a payload for multiple types of NPs, including FA/polylactic-co-glycolic acid (PLGA) NPs and hyaluronic acid-coated paclitaxel-nanostructure lipid carriers (37,69,70). AuNPs are emerging as the paclitaxel carrier of choice because they are easy to synthesize across a range of sizes, absorb NIR, are highly biocompatible and are non-toxic. Table I outlines multiple paclitaxel-AuNP constructs that include nanoshells and nanorods that are added to frame materials, including PLGA, β-cyclodextrin (β-CD) and PEG, and are modified by thiol, chitosan and FA. Multi-NPs exhibit higher paclitaxel loading capability, enhanced cytotoxicity to cancer cells, decreased toxicity to normal cells, longer circulation time and improved targeting to tumor cells (69-76). PEG and gold nanoparticles (GNP) hybrid systems may solve the solubility and stability issues of AuNPs and increase their loading capacity (69,70). Conjugating AuNPs and paclitaxel via covalent bonding results in the attachment of ~70 molecules of paclitaxel per NP, facilitating enhanced antiproliferative and pro-apoptotic potency (71,72). AuNP delivery of paclitaxel has been previously demonstrated to prevent P-glycoprotein-mediated multi-drug efflux in H460 cells that is induced by exposure to drugs without nanoparticle carriers (73). A novel drug delivery strategy has been demonstrated by the design of NPs containing perfluorohexane (PFH), gold nanorods and paclitaxel, where FA was added to target malignant cells that overexpressed FA receptors (74). A cell culture study indicated that upon laser irradiation, PFH is vaporized, resulting in rapid intracellular drug release and apoptosis (74). Proof-of-concept was further demonstrated *in vivo* (74). Poly(e-caprolactonediol)-based polyurethane/poly (N-isopropylacrylamide)-grafted chitosan core-shell nanofibers exhibit pH/temperature dual-responsive activity and have been indicated to be highly active against breast cancer cells (75). Hybrid AuNPs coated with PEG, biotin (a growth promoter targeting biotin receptor-overexpressing cancer cells), paclitaxel and rhodamine B-linked β-CD (to improve paclitaxel solubility) exhibit increased cellular uptake and cytotoxicity in cancer cells, without toxicity to normal cells (76). The potential of AuNPs to deliver cytokine TNF has gained increasing attention. In addition to promoting apoptosis, TNF disrupts tumor vasculature and causes vascular leakage, which increases local delivery of systemically administered chemotherapy and also sensitizes the adjacent tumor to radiation and thermal-based therapies (77). Furthermore, AuNPs carrying TNF and paclitaxel analogs are more potent than free paclitaxel *in vivo* (77). CYT-21625, which is a PEG-Thiol gold NP carrying paclitaxel analog 5 and TNF, is stable in plasma and enhances drug delivery by a reductive cleavage mechanism that releases native paclitaxel into the tumor microenvironment (77). In B16/F10 tumor-burdened mice, CYT-21625 improves paclitaxel delivery to tumors and increases pharmacokinetic exposure compared with free paclitaxel and paclitaxel analog 5 (77). The dose of free paclitaxel required to exert a similar anti-tumor effect was demonstrated to be 16 fold-higher than CYT-21625 (77).

Targeted pH-triggered NPs have been synthesized by combining FA and pH-sensitive poly(2-vinylpyridine)-based-poly(ethylene oxide) with mercaptooctanoic acid (MOA) (78).

These AuNPs are stable in the normal physiological environment, efficiently penetrate targeted tumor cells and quickly release their payload in the acidic tumor environment (78,79). B33-AuMOA-FA-paclitaxel NPs exhibit enhanced permeability, retention and prolonged circulation, and efficiently target tumor cells and induce apoptosis in A549 cells (78). In addition, chitosan oligosaccharide-coated AuNPs exhibit release rates that are higher at pH 5.5 (96%), and lower at pH 6.8 and 7.4 (50-60%). This may be associated with enhanced cytotoxicity in a more acidic microenvironment (79).

Paclitaxel-carrying AuNPs have also been indicated to amplify PTT (80). Combined with PTT, it has been indicated that microsphere-hollow Au nanosphere-paclitaxel results in enhanced tumor necrosis in a rabbit liver tumor model (81). The addition of gold nanorods to human serum albumin NPs (HSAPs) carrying paclitaxel has also been revealed to enable PTT, and NIR treatment of murine 4T1 breast cancer cells that had been treated with paclitaxel/gold rod-loaded HSAPs was observed to increase cell death from ~82 to ~94% (80). Hybrid GNPs-Polydopamine-paclitaxel-PLGA-microspheres with NIR irradiation generate more reactive oxygen species by downregulating antioxidant enzyme expression levels, and enhancing cytotoxicity (37).

Furthermore, PTT using paclitaxel-loaded liposomes, which is modified with the addition of gold nanostars linking cyclooxygenase (COX)-2 siRNA with a targeting ligand (2-DG) and the transmembrane peptide 9-poly-D-arginine, has been identified to exhibit activity against drug-resistant cells (82). As COX-2 serves important roles in tumorigenesis, angiogenesis and the development of multi-drug resistance, its selection as a therapeutic target may yield substantial clinical benefits (82).

From 21 studies that examined paclitaxel AuNPs (Table I) (83-88), reports were identified that examined the synthesis of pH-sensitive drug systems and conjugates of antibodies, nucleic acids and receptors to target paclitaxel delivery into specific tissues and to modulate paclitaxel release, permeability and retention.

Association between blood-brain barrier (BBB) and AuNPs. AuNPs of varying sizes may have differential uptake in different tissue types, and size may also influence BBB penetration. The BBB allows neutral, lipophilic molecules and compounds with molecular weights <400 Da to cross, while preventing the entry of larger toxic molecules into the brain (89). A murine study demonstrated that AuNPs with diameters of 15 and 50 nm were delivered to the brain and other tissues, whereas BBB penetration of 200-nm diameter AuNPs was poor (90). Moreover, AuNPs coated with exosome-derived membranes exhibit improved BBB penetration as well as improved targeting of brain neurons (91). In addition to penetrating the BBB, AuNPs may also bypass the barrier via neuronal uptake and retrograde axonal transport to the central nervous system (92,93). Wheat germ agglutinin horseradish peroxidase-conjugated AuNPs deliver drugs to rat spinal cord and brainstem by bypassing the BBB via peripheral uptake and transport via the phrenic nerve (92). In a murine model of glioblastoma multiforme, polymer-coated gold-iron oxide nanoparticles carrying therapeutic miRNAs were successfully delivered to the central nervous system via intranasal administration, bypassing the BBB and augmenting the therapeutic effect of systemic temozolimide (93). In summary, AuNPs may provide alternative drug delivery platforms by either crossing or bypassing the BBB.

5. Limitations

Although AuNPs offer multiple advantages as drug carriers, safety is the foremost limitation to their widespread application. The majority of reports have indicated that AuNPs are non-toxic, however, additional studies have demonstrated toxicity (94-97). Toxicity may be associated with size, shape, conjugated materials and nucleic acids, dose and biodegradability (94,95). Nanostars are less toxic than nanospheres (96). In addition, surface charges and ligand types may influence toxicity. For example, cationic and polyelectrolyte-wrapped AuNPs are more toxic than electronegative and anionic 3-mercaptopropionic acid- and cationic3-mercaptopropylamine-wrapped AuNPs to Gram-negative and -positive bacteria (*Shewanella oneidensis* and *Bacillus subtilis*, respectively) (97). Based on these controversial findings, more detailed standardized criteria to evaluate AuNP toxicity are required.

6. Conclusion

Paclitaxel is a first-line anti-cancer drug for ovarian and breast cancer, as well as other types of solid tumor. However, poor solubility and resistance limit its widespread use. Currently, multiple types of paclitaxel NPs have been synthesized to increase efficacy, improve drug release kinetics and target specific tissues (8,98,99). Among NPs of various frame materials, AuNPs are receiving increasing attention as drug delivery systems because they are not immunogenic and are generally considered to be non-toxic. Furthermore, their mass production is facilitated by their ease of synthesis and controlled sizes. Of utmost importance are the capacity of AuNPs to carry nucleic acid payloads and their unique role in PTT (10,11). The current review divided AuNPs into 3 groups: Simple drug-carrying AuNPs, simple nucleic acid-carrying AuNPs and targeted AuNPs. The u use and functions of the three types were then further examined. The synthesis of paclitaxel AuNPs was subsequently discussed. Studies of paclitaxel AuNPs are increasingly focused on hybrid particles that incorporate multiple frame materials to improve solubility, prolong circulation times and enhance targeted release. Because cancer is a multigenic disease, nucleic acid-based therapy is a promising therapeutic modality that can be expedited by AuNPs (12,45,46). In addition, AuNPs enable the innovative modality of synergistic chemo-PTT (44). Furthermore, because the sizes of AuNPs are easily controlled, 15 and 50 nm AuNPs cross the BBB and AuNPs may bypass the BBB via retrograde axonal transport, AuNPs may offer novel drug delivery platforms for the treatment of central nervous system disease (90,92,93). However, the safety of AuNPs is still controversial. If accurate criteria to ensure non-toxicity can be developed, the pharmacokinetic and pharmacodynamic advances of AuNPs may enhance the therapeutic indices of paclitaxel and other cytotoxic agents, facilitate the development of gene therapy and PTT, and improve chemotherapeutic efficacy.

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ZGW, JYD, QJJZ and SSJ designed and wrote the original manuscript. YY, LJZ, JRZ, SQZ, JJW and YZ acquired data, generated the figure and table, and reviewed and edited the manuscript. ZGW and JYD, SSJ revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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