Nanomedicines for Overcoming Cancer Drug Resistance

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Clinically, cancer drug resistance to chemotherapy, targeted therapy or immunotherapy remains the main impediment towards curative cancer therapy, which leads directly to treatment failure along with extended hospital stays, increased medical costs and high mortality. Therefore, increasing attention has been paid to nanotechnology-based delivery systems for overcoming drug resistance in cancer. In this respect, novel tumor-targeting nanomedicines offer fairly effective therapeutic strategies for surmounting the various limitations of chemotherapy, targeted therapy and immunotherapy, enabling more precise cancer treatment, more convenient monitoring of treatment agents, as well as surmounting cancer drug resistance, including multidrug resistance (MDR). Nanotechnology-based delivery systems, including liposomes, polymer micelles, nanoparticles (NPs), and DNA nanostructures, enable a large number of properly designed therapeutic nanomedicines. Nanomedicines have paved the way for effective treatment of cancer by rationally designing strategies such as passive targeted drug delivery, active targeted drug delivery, co-delivery of combinatorial agents and multimodal combination therapy, and have broad prospects in overcoming drug resistance. It is believed that nanomedicines will be an attractive strategy for reversing or overcoming cancer drug resistance.

Keywords: nanomedicine ; chemotherapy ; drug

1. Mechanisms in Drug Resistance of Chemotherapy

Nowadays, chemotherapy is still the most widely used strategy for treating cancer; however, the biggest obstacle to this traditional strategy is the development of cancer drug resistance [1][2][3]. The mechanisms of drug resistance to chemotherapy are extremely complex [3]. Generally, the emergence of chemoresistance may be classified by the following pathways: (1) increased drug efflux by ATP-dependent pumps mediated by transmembrane transporters of the ATP-binding cassette (ABC) superfamily [4][5][6]; (2) reduced drug uptake mediated by altering specific cellular targets [7][8][9]; (3) inactivation of apoptotic pathways mediated by high expression of the Bcl-2 antiapoptotic family such as Bcl-2, Mcl-1 and Bcl-XL, which are mainly responsible for the reason why cancer cells can resist apoptosis [10][11][12]; (4) enhanced DNA repair ability that can contribute to the resistance of cancer by promoting genomic instability and mutation [13][14][15]; (5) alterations in specific drug targets [16][17]; (6) increased drug detoxification mediated by metabolism or biotransformation [18][19]. All in all, these resistance mechanisms can allow cancer cells to survive by easily changing different pathways, and ultimately resulting in chemotherapeutic failure.

2. Nanomedicines to Overcome Chemotherapy Resistance

Considering that chemotherapy resistance-related drug efflux proteins mainly reside in the nuclear membranes and blood, but not in the mitochondria [20][21], delivering chemotherapy agents into the mitochondria is an emerging strategy to surmount drug resistance to chemotherapy [22][23][24][25][26][27][28]. Yu et al. [29] constructed a weak acid-activated, charge-reversible, triphenylphosphonium (TPP)-based, “shell–core” nanosystem (DOX-PLGA/CPT/PD) for sequential facilitation of tumor accumulation, cellular uptake, mitochondria targeting, intracellular localization and surmounting drug resistance of MCF-7/ADR breast cancer. Firstly, positively charged mitochondrial-targeting lipid-polymer hybrid nanoparticles (PLGA/CPT) were prepared from PLGA and C_{18}-PEG_{2000}-TPP (CPT) [30]. Then, DOX was loaded into PLGA/CPT nanoparticles to obtain DOX-PLGA/CPT. Lastly, positively charged PEI-DMMA (PD) shell was wrapped on the surface of positively charged DOX-PLGA/CPT to obtain negatively charged DOX-PLGA/CPT/PD with a diameter of ~150 nm. When DOX-PLGA/CPT/PD was treated at pH 6.5, the hydrolysis of amide in PD occurred, facilitating the elimination of electrostatic interaction between PLGA/CPT and PEI, ultimately resulting in the deshielding of PD to reveal DOX-PLGA/CPT and transformation of the charge from −24 to +19.2 mV. Then, they studied the pharmacokinetics of DOX-PLGA/CPT/PD, and, the results showed that DOX-PLGA/CPT showed significantly slower clearance with a half-life time 15.84 h. After incubation with MCF-7/ADR cells at pH 6.5, DOX-PLGA/CPT/PD showed effective lysosome escape, excellent mitochondrial-targeting capacity and superior cytotoxicity for overcoming DOX resistance by up-regulating the apoptosis-related proteins as well as down-regulating the antiapoptotic protein Bcl-2. Encouraged by the in vitro antitumor effect of DOX-PLGA/CPT/PD, Yu et al. evaluated the in vivo effect in MCF-7/ADR cell-bearing mice. The results show that

DOX-PLGA/CPT/PD showed the best inhibitory effect on tumor growth and exhibited the best treatment effect, with a tumor inhibition rate (TIR) of 84.9% with no obvious side effects.

Studies show that the exposure of tumor cells to chemotherapy drugs can result in hypoxia-inducible factor-1 (HIF-1) activation and stabilization [31][32], where HIF-1 plays an important part in drug resistance by regulating multidrug resistance protein (MRP), P-glycoprotein (P-gp), Bcl-2, etc. [33][34][35]. Moreover, HIF-1 can up-regulate the level of glutathione, which can bind with heavy metal ions, including cisplatin [36][37]. Therefore, inhibiting HIF-1 pathways during chemotherapy might be a promising method to circumvent chemo-resistance [38][39][40][41][42]. Acriflavine (ACF), a potent HIF-1 inhibitor, has been proven to bind to HIF-1α and thereby impede HIF-1α/β dimerization [43][44], which can be a useful strategy for sensitization of chemotherapy. In this regard, Zhang et al. [45] developed a new type of microporous silica-based co-delivery system (PMONA) to reverse the acquired resistance to cisplatin. Firstly, cisplatin was loaded into the polymeric mPEG-silane functionalized mesoporous silica nanoparticles inner core by reverse microemulsion method, where polymeric mPEG-silane was applied to maintain stability during blood circulation. To achieve tumor-specific glutathione (GSH)-triggered drug release, tetrasulfide bond-bridged organosilica was integrated to obtain the nanoparticles. Finally, ACF was loaded into the inner area of mircopores by electrostatic interactions to obtain ACF-loaded nanoparticles with a diameter of ~45 nm. After internalization by cancer cells, the outer organosilica shell of PMONA could be degraded by intracellular GSH, resulting in nanoparticle disassembly, drug release and synergistic regulation of multiple cancer-related signaling pathways. As shown in an in vitro release experiment, cisplatin and ACF had faster and higher cumulative release rates in a medium containing 10 mM GSH than in a medium containing 10 μM GSH, which confirmed that the tetrasulfide bond in organosilica enabled GSH-responsive disassembly and drug release. After incubation with A459 cells, PMONA exhibited stronger cell cytotoxicity, induced more apoptosis than the single drug-loaded nanoparticles by suppressing HIF-1-related proteins and decreased the level of intracellular GSH. Inspired by the result that ACF strengthens the curative effect of cisplatin in vitro, Zhang et al. assessed the in vivo antitumor effect in A459 cell-bearing mice. The results indicated that PMONA showed the best inhibitory effect on tumor growth and exhibited the best therapeutic effect with limited side effects. Additionally, the immunohistochemical experiment showed that PMONA enhanced cell death and apoptosis in tumor tissues mainly by down-regulating the levels of P-gp, MRP2, HIF-1-activated glutamate-cysteine ligase modifier subunit (GCLM), vascular endothelial growth factor (VEGF) and cystine transporter (xCT). Taken together, these results confirmed that ACF could combat cisplatin-acquired resistance by inhibiting HIF-1 function.

Hyperthermia, a non-invasive treatment strategy, has shown a competitive advantage in reversing drug resistance in cancer by suppressing the expression of drug efflux transporters [46][47][48][49][50][51]. Therefore, hyperthermia combined with chemotherapy is a hopeful treatment strategy for overcoming chemotherapeutic resistance [52][53][54][55][56][57]. Huang et al. [58] constructed smart, thermoresponsive, pH low insertion peptide (pHLIP)-modified gold nanocages (DOX@pPGNCs) to realize synergistic thermo-chemotherapy and overcome chemotherapeutic resistance. Firstly, thermoresponsive poly (di (ethylene glycol) methyl ether methacrylate-co-oligo (ethylene glycol) methyl ether methacrylate) ($PMEO_2MA$-OEGMA) polymer was anchored to gold nanocages to $PMEO_2MA$-OEGMA-modified gold nanocages, where $PMEO_2MA$-OEGMA served as a temperature-sensitive gate guard at a lower critical solution temperature of ca. 41.6 °C. In other words, the $PMEO_2MA$-OEGMA chains extended under 41.6 °C, sealing the pore of gold nanocages to prevent the leakage of drug into the blood; however, once the temperature increased up to 41.6 °C due to the NIR-induced photothermal effects, its chains shrunk, leading to opening of the pores of gold nanocages and fast DOX release. Then, pHLIP was used to decorate $PMEO_2MA$-OEGMA-modified gold nanocages to obtain pPGNCs, where pHLIP was a good candidate to enhance cancer cell internalization by conformational transition at the weakly acidic tumor microenvironment. Lastly, DOX was loaded into pPGNCs to obtain DOX@pPGNCs with a diameter of ~160 nm and a zeta potential of approximately −20 mV. $PMEO_2MA$-OEGMA was thermosensitive with a lower critical solution temperature of ca. 41.6 °C. In vitro release experiments indicated that the cumulative release of DOX increased from 3.7 to 20.1% after 5 min of NIR irradiation. More importantly, the rapid release of DOX was consistent under NIR irradiation in another cycle, indicating that $PMEO_2MA$-OEGMA was a very responsible gatekeeper to precisely control NIR-triggered DOX release from DOX@pPGNCs. Cytotoxicity experiments showed that the antiproliferation ability against MCF-7/ADR cells was strongest in the DOX@pPGNCs and NIR irradiation group at pH 6.5, suggesting that pHLIP could enhance cellular uptake of DOX@pPGNCs under a weak acid tumor microenvironment, and, upon NIR irradiation, DOX@pPGNCs could efficiently achieve synergistic thermo-chemotherapy to overcome cancer resistance. In vivo biodistribution experiments showed that DOX accumulation in tumor site of tumor-bearing mice treated with DOX@ pPGNCs and NIR irradiation was highest, confirming that NIR irradiation-triggered photothermal effects of gold nanocages could further strengthen DOX accumulation. Inspired by the above experimental results, Huang et al. further assessed the in vivo treatment effect in MCF-7/ADR cell-bearing mice. The results indicated that DOX@pPGNCs achieved the strongest antitumor efficacy with a TIR of 97.3%, indicating the highly effective synergistic thermo-chemotherapy in MCF-7/ADR cell-bearing mice.

Studies have shown that tumor cells can develop drug resistance by enhancing DNA repair [59][60][61][62][63][64], suggesting that drug resistance owing to DNA repair can be overcome by inhibiting the function of related proteins [65][66][67][68].

Recently, Wang et al. [69] constructed a smart delivery system for overcoming cisplatin-related “cascade drug resistance” (CDR) by mild hyperthermia (43 °C) triggered by NIR. Firstly, hydrophobic photothermal-conjugated polymer and biodegradable amphiphilic polymer were mixed to form F-nanoparticles (F-NPs) with photothermal performance. Secondly, biodegradable amphiphilic polymer and C16-CisPt-Suc (a Pt (IV) prodrug) were mixed to form Pt-nanoparticles (Pt-NPs). Lastly, Pt-NPs and F-NPs were mixed to obtain the mixed nanoparticles (F-Pt-NPs). On the basis of DLS data, the average particle size of F-NPs was 91.0 ± 2.6 nm, while that of the Pt-NPs was 105.1 ± 1.6 nm. In vitro experiments showed that, under the treatment of NIR, mild hyperthermia could efficiently facilitate cellular uptake of drug-resistant A549DDP cells, resulting in enhanced cytotoxicity and surmounting CDR of cisplatin by the consumption of GSH and the reduction of Pt (IV) to Pt (II). More importantly, mild hyperthermia could accelerate the binding of Pt to DNA and promote the formation of irreparable crosslinking of Pt-DNA strands, resulting in the destruction of DNA repair. In vivo experiments showed that, under mild hyperthermia conditions, F-Pt-NPs exhibited the best antitumor effect with a TIR of 94% with few side effects, further indicating that NIR-triggered mild hyperthermia could reverse CDR.

In recent years, substantial evidence has confirmed that drug resistance is closely related to the CSC phenotype [70][71]. One proven mechanism of multidrug resistance (MDR) in CSC is the increased expression of ABC transporters [72]. In addition, the CSC phenotype shows increased drug resistance to chemotherapy by modulating many other stem characteristics, including enhanced DNA damage repair capacity and up-regulation of antiapoptotic proteins [73][74]. Therefore, eradication of CSCs is an effective strategy to surmounting cancer drug resistance. Shen et al. [75] constructed an alltrans-retinoic acid (ATRA) and camptothecin (CPT) co-loaded nanoplatform (ATRA/CPT-NPs) to surmount chemotherapeutic resistance of both CSCs and bulk tumor cells. Firstly, ROS-responsive nitroimidazole-modified hyaluronic acid-oxalate-CPT conjugate (n-HA-oxa-CPT) was synthesized. Then, n-HA-oxa-CPT assembled into nanoparticles and physically encapsulated ATRA to obtain ATRA/CPT-NPs with a diameter of ~150 nm. Based on the difference levels of ROS between bulk tumor cells and CSCs, ATRA/CPT-NPS could sequentially release ATRA and CPT during the differentiation of CSCs. After uptake by hypoxia CSCs, ATRA was firstly released, which induced CSC differentiation into reduced stemness and chemoresistance, along with increased ROS level. Then, the increased ROS in differentiated CSCs triggered CPT release for enhanced cytotoxicity towards the differentiated cells with decreased drug resistance. On the other hand, after uptake by bulk tumor cells with hypoxia and high ROS, ATRA/CPT-NPS could simultaneously release ATRA and CPT, resulting powerful synergistic anticancer effects. In their study, ATRA/CPT-NPs showed the strongest inhibition efficacy on the orthotopic BCSC-enriched tumor mouse models, suggesting that the differential drug release realized by ATRA/CPT-NPs was very important to strengthen the synergistic efficacy of ATRA-triggered CSC differentiation and CPT-triggered cytotoxic activity for the treatment of poorly differentiated and highly chemo-resistant heterogeneous tumors.

Additionally, a summary of nanomedicines studied for overcoming chemotherapeutic resistance in recent years is displayed in **Table 1**.

Table 1. Recent advances in nanomedicines for overcoming chemotherapeutic resistance.

Nanoformulation	Name	Particle Size	Payload	Reversal Mechanism of Drug Resistance	Cell Line	Tumor Model	Referen
Polymeric micelles	ACP-Dox and Apa micelles	104 ± 2 nm	DOX and apatinib	Inhibit P-gp activity	MCF-7/ADR cells	MCF-7/ADR tumor-bearing mice	[76]
	HA-PLGA (PTX and FAK siRNA)-NPs	232.9 ± 6.9 nm	PTX and FAK siRNA	siRNA-mediated silencing of FAK	HeyA8-MDR and SKOV3-TR cells	Drug-resistant, patient-derived xenograft (PDX) model	[77]
	ACP-R837 and PPP-DOX	~110 nm	R837 and DOX	Synergistic chemo-immunotherapy	4T1 cells	4T1 tumor-bearing mice	[78]
	NC-DOX	~122 nm	DOX and IR780	Combined chemotherapy/PTT/PDT	MCF-7/ADR cells	MCF-7/ADR tumor-bearing mice	[79]
	Dox-Cur-NDs	55.1 ± 3.0 nm	DOX and CUR	Down-regulate the expression of P-gp	A2780 ADR cells	A2780 ADR tumor-bearing mice	[80]
Polymeric nanoparticles	[FeFe]TPP/GEM/FCS NPs	176.0 ± 17.2 nm	Gemcitabine and [FeFe]TPP	Reduce the of function P-gp efflux pump	T24 cells	T24 tumor-bearing mice	[81]
	IGU-PLGA-NPs	199.6 nm	Iguratimod	Facilitate BBB penetration and inhibit GSCs proliferation and stemness	U87 and U251TMZ-R cells	U87 tumor-bearing mice	[82]

Nanoformulation	Name	Particle Size	Payload	Reversal Mechanism of Drug Resistance	Cell Line	Tumor Model	Referen
Liposomes	rTLM-PEG, PTX liposomes	/	PTX and trichosanthin	Reverse caspase 9 phosphorylation and induce caspase 3-dependent apoptosis	A549/T cells	A549/T tumor-bearing mice	[83]
	PTX/NO/DMA-L	146.3 ± 0.82 nm	PTX and DETA NONOate	NO-mediated down-regulation of P-gp	A549/T cells	A549/T tumor-bearing mice	[84]
	CBZ liposomes	108.53 ± 1.5 nm	CBZ	G2/M phase arrest	MCF-7 and MDA-MB-231 cells	Female SD rats	[85]
	Lip (Ap-Dox)	128.6 nm	Ap-Dox complex	Bypass the P-gp-mediated drug efflux	MCF-7/ADR cells	MCF-7/ADR tumor-bearing nude mice	[86]
	(DEX and DTX)-Lip	74.02 ± 0.41 nm	DTX and dexamethasone	Overcome stroma obstacles	Multidrug-resistant KBv cells and 4 T1 cells	Multidrug-resistant KBv and metastatic 4 T1 tumor models	[87]
	FPL-DOX/IM	159 ± 6 nm	DOX and imatinib	Inhibit ABC transporter function	MCF-7/ADR cells	MCF-7/ADR tumor-bearing mice	[88]
	PpIX/Dox liposomes	55.9 ± 20.9 nm	DOX and PpIX	Disrupt the structure of P-gp	MCF-7/ADR cells	MCF-7/ADR tumor-bearing mice	[89]
Nanogels	LNGs-PTX-siRNA	~100 nm	PTX and MDR1 siRNA	Knockdown MDR1	DROV cells	DROV tumor-bearing mice	[90]
	CDDP/DOX-NGs	~100 nm	CDDP and DOX	Combination chemotherapy	MCF-7/ADR cells	MCF-7/ADR tumor-bearing mice	[91]
	HA/Cis/Dox	45 ± 9.9 nm	DOX	GSH-induced DOX release	A2780cis cells	/	[92]
Inorganic nanoparticles	SiPT75	75.5 ± 19.8 nm	TPPS	Elude the drug efflux pumps and retards exocytosis of cells	A549/DDP cells	A549/DDP tumor-bearing mice	[93]
	H-MSNs-DOX/siRNA nanoparticles	~100 nm	P-gp siRNA and DOX	siRNA-mediated silencing of P-gp	MCF-7/ADR cells	MCF-7/ADR tumor-bearing mice	[94]
	Pt-AuNS	~85 nm	Pt	GSH depletion and GPX4 inactivation	MCF-7/ADR cells	MCF-7/ADR tumor-bearing mice	[95]
	FA-GT-MSNs@TPZ	~60 nm	TPZ	Synergistic radio-chemo-photothermal therapy	Hypoxic SMMC-7721 cells	SMMC-7721 tumor-bearing mice	[96]

Nanoformulation	Name	Particle Size	Payload	Reversal Mechanism of Drug Resistance	Cell Line	Tumor Model	Referen
Hybrid nanoparticles	$S_{CA4P}NP_{BTZ}$	~150 nm	BTZ and CA4P	Inhibit the overexpression of BCRP/ABCG2	A549 cells	Human A549 pulmonary adenocarcinoma xenograft model and PDX model of colon cancer	[97]
	cNPs	286 ± 79 nm	Afatinib, rapamycin and docetaxel	Synergistic treatment	HER2-positive breast cancer cells, EGFR-positive NSCLC cells and SKBR-3/AR cell lines	HER2-positive breast cancer mouse model	[98]
	4T1-HANG-GNR-DC	103.1 ± 7.6 nm	CDDP and DOX	Synergistic chemo-photothermal therapy	4T1 cells	4T1 tumor-bearing mice	[99]
	IR780/DTX-PCEC@RBC	~150 nm	IR780 and DTX	Combination therapy	MCF-7 cells	MCF-7 tumor-bearing mice	[100]
	cNC@PDA-PEG	170.5 ± 1.4 nm	Paclitaxel/lapatinib	Combination therapy	MCF-7/ADR cells	/	[101]
	miR497/TP-HENPs	125 ± 6 nm	miR497 and triptolide	Synergically suppress mTOR signaling pathway	SKOV3-CDDP cells	SKOV3-CDDP tumor-bearing mice	[102]

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