Review

Jie Yang[a], Haijun Zhang[a] and Baoan Chen*

Application of nanoparticles to reverse multi-drug resistance in cancer

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Abstract: Multi-drug resistance (MDR) poses a large obstacle to various human malignancies. For a long period, combination of multiple therapeutic agents has been the conventional method used to reverse MDR in cancer. However, it is still not an effective method as rather than cancer its serious side effects causes patient's death. Nanoparticles (NPs) are emerging as a class of therapeutics for cancer, including overcoming MDR. In the present review, we focus on the application of NPs to reverse MDR in cancer. Several kinds of NPs developed for the reversal of MDR are summarized. In addition, investigations *in vitro* and *in vivo* are also shown to highlight the advancement in the application of NPs to reverse MDR.

Keywords: cancer; multi-drug resistance (MDR); nanoparticles (NPs).

1 Introduction

Though chemotherapy is successful to some extent in certain cancer types, it still has several limitations [1]. Firstly, chemotherapeutic agents do not have sufficient selectivity for tumor so the normal tissues can also be hurt. Secondly, the tumor tissues cannot get to the effective drug concentration due to the frequent occurrences of multi-drug resistance (MDR). In this case, we have no choice but to get high drug doses.

Multi-drug resistance is also called as pleiotropic drug resistance, which is a phenomenon whereby treatment with one agent confers resistance not only to that drug and other(s) of its class but also to several other unrelated agents [2]. Many factors contribute to the mechanisms of MDR, such as overexpression of efflux transporters, which is a popular source [3]. The other mechanisms involve DNA repair, upregulation of the tumor enzymatic repair systems, and so on.

As MDR has been a great obstacle in the cancer therapy, a variety of methods have been developed to solve the problem, including P-glycoprotein (P-gp) inhibitor, protein kinase C inhibitor, and other traditional drugs. However, most of them are administered at high doses which in turn could cause serious side effects – even patient's death.

Advances in nanotechnology have opened up unprecedented opportunities in controlled drug delivery and novel combination therapy strategies [4]. Research in nanomedicine has not only become a frontier movement but is also a revolutionizing cancer therapeutic [5]. It is also inspiring that recently nanoparticles (NPs) are widely evolving in an attempt to overcome MDR. So far, many kinds of NP systems have been designed and applied to overcome MDR in cancer. The results showed prominent advantages as compared with conventional drugs. These drug-loaded NP systems exhibit prolonged systemic circulation lifetime, sustained drug release kinetics, and selective tumor accumulations through both passive and active mechanisms [4]. A variety of NP platforms just like polymeric NPs, mesoporous silica NPs (MSNPs), solid lipid NPs (SLNPs), micelles (MI), and others are introduced in this review, and their *in vitro* and *in vivo* studies to overcome MDR are also summarized.

2 Nanoparticles for drug delivery systems

Nanoparticulate systems are versatile which include polymeric NPs, MSNPs, SLNPs, MI, liposomes, and polymer-drug conjugates. There are about two dozen clinically

[a]**Jie Yang and Haijun Zhang:** These authors contributed equally to this work.
***Corresponding author: Baoan Chen,** Department of Hematology and Oncology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing 210009, People's Republic of China, Phone: +86 25 83272006, Fax: +86 25 83272006, e-mail: cba8888@hotmail.com
Jie Yang and Haijun Zhang: Department of Hematology and Oncology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing 210009, People's Republic of China

Table 1: Characteristics of nanoparticle systems.

Nanoparticles (NPs)	Characteristics
Polymeric NPs	The versatile platform for the delivery of chemotherapeutic drugs including small molecular weight drugs and macromolecules like genes and proteins
Mesoporous silica nanoparticles	Inorganic nanocarriers which have tunable size and shape, their high pore volume and surface area resulting in high drug loading
Solid lipid nanoparticles	Release drug in the acidic microenvironment of multi-drug resistance cells
Micelles	Small size and usually have high payload capacity, improved stability, greater solubilization potential for different hydrophobic drugs and long circulation
Lipid NPs	Long circulation, preferential accumulation in tumor tissues via enhanced permeability
Biocompatible inorganic material-based nanosystems	
(1) Iron oxide magnetic NPs	Electrical, magnetic, and/or electrochemical properties and good stability
(2) Gold nanoparticles	A kind of versatile platform for cancer drug delivery because of its tunable properties

approved therapeutic products [4]. They are often composed of nontoxic, biodegradable constituents and possess varying loading capacities [6]. Although all of them have the same aim, i.e. to get effective intracellular drug concentration with minimum drugs, each NP system has its unique character and strength. Thus, these must be taken into consideration during the productive process so that they can be qualified for different combinatorial therapeutics. The characteristics of different NP systems are shown in Table 1.

2.1 Polymeric nanoparticles

Polymeric NPs are the versatile platform for the delivery of chemotherapeutic drugs including small molecular weight drugs and macromolecules like genes and proteins [7]. The drug delivery platform has controlled, sustained, and targeted property. Among them, some antitumor drugs can self-assemble into NPs. For example, the amphiphilic iTEP-Sali conjugates self-assembled into NPs. Then the free Sali with two additives, N-dimethylhexylamine and α-tocopherol were encapsulated into the NPs. The result showed improved tumor accumulation and pharmacokinetics in mice model bearing orthotopic breast tumor [8].

Traditional chemotherapeutics could also load onto NPs and then achieve surprising results on reversing MDR in cancer. In *in vitro* and *in vivo* studies, the multifunctional self-assembled NP system increased the sensitivity of MCF7/ADR cells against doxorubicin (DOX) obviously. It enhanced the accumulation of drugs in tumors and showed remarkable antitumor efficacy in mice bearing MDR tumor. At the same time, the result indicated lesser side effects than drug combination therapy [9].

Multifunctional nanoassemblies (MNAs) have small particle size, sustained-release characteristics, and high drug encapsulation efficiency, especially for cationic hydrophilic drugs. As a result of these excellent characteristics, the Vincristine (VCR)-loaded MNAs (VCR-MNAs) prolonged the retention time in systemic circulation and improved its cellular uptake and cytotoxicity in resistant cancer cells in the experiments performed in MCF-7/ADR cells and mice model [10]. Another study showed that VCR-folate (Fol)/R7 NPs could significantly enhance drug cellular uptake and cytotoxicity in MCF-7 and MCF-7/ADR cells compared with the NPs that were individually modified by Fol or R7 [11]. Recently, Yuan et al. developed a novel strategy of using taxol-loaded NPs for overcoming MDR. In their study, CBT (2-cyanobenzothiazole)-taxol showed a 4.5-fold or 1.5-fold increase in anti-MDR effects compared with taxol, on taxol-resistant human colon tumor (HCT) type 116 cancer cells or tumors that were not being toxic to the cells or the mice, respectively [12].

In another study, multifunctional NPs used a single-molecule modification of TPGS [tocopheryl polyethylene glycol succinate (average molecular weight 1000)]. They delivered a hydrophobic drug of paclitaxel (PTX) and a hydrophilic drug of fluorouracil (5-FU). The result showed an efficient effect on overcoming MDR in tumor [13]. Compared with (lactide-co-glycolide)-D-a-TPGS(PLGA–TPGS) *in vitro* and *in vivo*, PLGA-TPGS/PPNPs (Poloxamer type 235 porous NPs) were found to have an increased level of uptake of drugs in docetaxel (DTX)-resistant human breast cancer cell line (MCF-7/TXT) [14].

Apart from the above studies, biomolecules are also loaded onto NPs and utilized to show their ability to overcome MDR in several other studies [15–17]. As the study developed by Yin et al. showed, NPs also had the

ability to delivery reduction-responsible cationic PAEs (b-amino esters)-loaded MDR-1 and Survivin-targeting RNA (shSur). Experiments performed on male BALB/c nude mice and MCF7/ADR cells showed down-regulation expression of P-gp and Survivin. The IC_{50} value of DOX lowered as well [18].

2.2 Mesoporous silica nanoparticles

Mesoporous silica nanoparticles are inorganic nanocarriers which have tunable size and shape. Their high pore volume and surface area result in high drug loading. At the same time, they show multifunctionalization for targeted and controlled delivery [7]. Because of the above characteristics, they have been widely studied for cancer treatment.

For instance, compared with free CPT-11 (irinotecan hydrochloride), the polymer-lipid supported MSNPs (PLS-MSNPs) system showed a 7.1-fold higher cytotoxicity and a stronger cell cycle arrest in MCF-7/BCRP cells [19]. Besides, rod-shaped MSNPs that loaded DOX indicated good drug delivery efficiency and uptake in breast cancer MCF-7/MDR1 cells and mice model [20]. In another study, conjugating TAT peptide onto the surface of MSNPs (MSNPs-TAT) could make a nuclear-targeted drug delivery system. It was observed that direct intranuclear drug DOX delivered in MCF-7/ADR cancer cells [21]. P-gp iRNA and the chemotherapeutic drug were loaded at the same time using the MSNPs. The delivery system resulted in an obviously synergistic inhibition of tumor growth [22]. Another study carried out in MCF-7/ADR cells demonstrated that PTX/TET (tetrandrine)-CTAB (cetyltrimethylammonium bromide) at MSNP could increase the concentration of drugs or NPs which could inhibit the efflux function of P-gp. The mechanism showed that TET could arrest MCF-7/ADR cells at G1 phase so that it could enhance the antitumor activities of PTX and CTAB [23]. In addition, several other experiments in breast cancer MCF-7/ADR cells using MSNPs also showed different levels of suppression to tumor [23–26].

2.3 Solid lipid nanoparticles

Solid lipid nanoparticles have the ability to release the drug in acidic microenvironment of MDR cells. They can deliver anticancer drugs in order to overcome the P-gp mediated MDR [7]. The DOX-loaded SLNPs with a mean hydrodynamic diameter of ~100 nm and a low polydispersity index (under 0.20) were synthesized by Chen et al. They showed a high drug-loading efficiency which ranged from 80.8% to 90.6% so that they could deal with the MDR in tumor [27]. In another study, three kinds of SLNPs such as PVS (PTX and VP co-loaded SLNP), PSV (PTX loaded SLNP, later added VP), and PVSV (PTX and VP co-loaded SLNP, later added VP) were prepared to overcome MDR by the combination of PTX and VP [28]. The experiment *in vitro* indicated that PVSV had significantly higher cytotoxicity and cellular uptake in MDR cells than other two kinds.

2.4 Other nanoparticles

The other NPs we would like to introduce here are MI, lipid NPs, inorganic NPs including iron oxide magnetic NPs, gold NPs (AuNPs), and so on.

Micelles are small sized particles which usually have high payload capacity, improved stability, greater solubilization potential for different hydrophobic drugs, and long circulation [7]. Researchers have performed many experiments in order to achieve more drug accumulation and retention in MDR cancer cells. In response to the intracellular reductive environment, such drug carrier released the incorporated DOX. As a result, it significantly enhanced the cytotoxicity of DOX to the MDR cancer cells [29].

Lipid NPs have long circulation, and preferential accumulation in tumor tissues via enhanced permeability. The hepatocellular carcinoma cells experiment showed enhanced cytotoxicity, decreased IC_{50}, and resistant index using DOX and curcumin (Cur) co-delivery lipid NPs (DOX/Cur-NPs) [30]. Later the mice model study confirmed the effect of the DOX/Cur-NPs. A study in K-562 leukemia cells showed that Edelfosine lipid NPs induced a caspase-mediated apoptosis to overcome MDR [31].

Biocompatible inorganic material-based nanosystems provide another good choice in effectively circumventing the drawbacks of traditional organic materials in biomedical therapy, especially in overcoming the MDR of cancer cells which was related to their unique structure, specific biological behaviors, and characteristics of their compositions [32].

Iron oxide magnetic NPs have been widely studied recently. They possess magnetic and/or electrochemical properties. The DOX-loaded superparamagnetic iron oxide NPs showed greatest release at pH between four and five compared with the result in endosomes/lysosomes. The NP-DOX had the ability to circumvent the MDR that was associated with overexpression of the ATP-binding cassette (ABC) transporters, especially ABCB1, ABCB5, ABCB8 and ABCC1, in C6 glioma cells [33]. In another study, Fe_3O_4 NPs have been used for the delivery of DOX against HeLa cells that were highly drug resistant. The study indicated

improved cellular uptake and drug intensity profile that had greater percentage of apoptotic cells [34]. Cheng et al. researched on the magnetic iron oxide NPs that were co-loaded with daunorubicin (DNR) and 5-bromotetrandrin. This nanosystem was utilized in K562/A02 cells. The result showed enhanced accumulation of intracellular DNR and downregulation of the expression of P-gp and transcription of the MDR1 gene [35]. Later, the co-polymer wogonin and DNR co-loaded onto Fe_3O_4 magnetic NPs were studied in K562/A02 cells to overcome MDR [36]. Nano-zinc oxide (nano-ZnO) and nano-copper oxide (nano-CuO) are common metal oxide nanomaterials. Experiments showed that nano-CuO, nano-ZnO, $CuSO_4$, and $ZnSO_4$, even at very low concentrations (0.5 ppm), increased calcein-AM (CAM, an indicator of ABC transporter activity) accumulation was observed at different development stages in the sea urchin embryos in order to overcome MDR [37].

AuNPs are a kind of versatile platform for cancer drug delivery. DOX was tethered onto the surface of AuNPs with a poly(ethylene glycol) spacer by way of an acid-labile linkage (DOX-Hyd at AuNPs), and the drug delivery system was developed. The study achieved enhanced accumulation and retention of the drug in MCF-7/ADR cancer cells as it was compared with free DOX [38].

3 Evaluation of overcoming MDR *in vitro* and *in vivo*

Nanoparticles are promising in overcoming MDR, and a large amount of evaluation has been carried out in different malignant tumors *in vitro* and *in vivo*.

3.1 Experiments *in vitro*

Multi-drug resistance in female genital system tumor poses a more troubling situation during the therapy causing therapeutic failure and finally death. On the contrary, NPs dramatically enhanced cancer cells' death *in vitro* so that we can consider the nanomedicines as a promising therapy to treat MDR in the female genital system tumor.

For example, in order to determine the cytotoxic abilities of the DTX-loaded NPs, *in vitro* cell cytotoxicity experiments were carried out in both A2780 and drug-resistant A2780/T cells. The result showed that DTX-loaded NPs exhibited higher cell cytotoxicity against the two types of cells than the free DTX. The effect had obviously concentration-dependent tendency [39]. In another study, in a MDR ovarian cancer cell line, the OVCAR-3, lapatinib/PTX nanocolloids induced an enhanced inhibition of cell growth compared with the PTX-only treatment [40]. Kobayashi et al. researched on the effect of DOX or DOX/NP on ovarian cancer (SKOV-3) cell cultures and its respective MDR counterpart $SKOV\text{-}3_{TR}$. The result indicated various degree enhancement of accumulation of DOX [41].

The breast tumor is another kind of malignancy which threatens women's life greatly. The breast tumor incidence shows younger trend. Large dose of traditional chemotherapy drugs resulting in severe side effects and MDR can kill the patients constantly. With the aim to solve the above problem, studies using NPs have been carried out *in vitro*.

One of these experiments was performed in MCF-7 and MCF-7/ADR cells that overexpressed P-gp. The aim was to investigate the MDR reversal effect induced by VCR-MNAs, including the cytotoxicity, cellular uptake, and uptake mechanism. The NP system efficiently increased the cytotoxicity to overcome MDR by enhancing the cellular accumulation of VCR in MCF-7/ADR cells [10]. In another study performed by Misra et al., the developed cationic NPs that were loaded with MDR1-siRNA and DOX were studied in MCF-7/ADR cells. Its improved uptake of DOX and cytotoxicity indicated that it is a promising co-delivery system against MDR in breast cancer [42]. Experiment *in vitro* was also carried out on P-gp (MDR1) overexpressing human breast carcinoma cell line MDA-MB435/LCC6/MDR1 and its parental cell line MDA-MB435/LCC6/WT. The study demonstrated that DOX-loaded NPs enhanced the cytotoxicity of DOX. The result gave us a positive message that the drug-loaded NPs could overcome MDR in cell line besides MCF-7/ADR cells [43].

Some studies were also carried out in other different tumor cells. Their results gave us a positive hint that NPs could reserve MDR in tumor therapy. Compared with taxol, CBT-taxol induced obviously an increase in anti-MDR effects on taxol-resistant HCT 116 cancer cells [12]. In the study by Shen et al., the iRGD-conjugated TPGS mediated the co-delivery of PTX and shSur on A549 and A549/T cells. As a result, the nanosystem performed successfully in enhancing the accumulation of PTX and shSur, downregulating the expression of surviving and inducing cell apoptosis in tumor tissue [44]. Another couple of studies with the DOX-loaded NPs performed in different cell lines included NCI/ADR-RES cells and K562 and K562/ADR cells. Although they chose different cell lines, both of them got similar consequences. The DOX-loaded NPs succeeded in enhancing the DOX accumulation and cytotoxicity so that they could reverse MDR in the two kinds of tumor therapy [45, 46].

In addition, some other kind of NPs was utilized in different studies *in vitro*. Several experiments with MSNPs *in vitro* were carried out in MCF-7/ADR cells [20, 23, 47]. Even

though the details were different, they got similar results that the MSNP systems increased the antitumor effect of drugs via different mechanisms. MCF-7 and MCF-7/ADR cells were utilized in the experiments that researched the SLNPs with different drugs. The nanosystems displayed a good capability of inhibiting the proliferation of MDR cells [27, 28]. As the study showed, the redox-responsive micellar nanodrug carrier significantly enhanced the influx of DOX and decreased its efflux in the MCF-7/ADR breast cancer cells. The result demonstrated that drug-loaded MI system could overcome MDR [29]. Studies on AuNPs have been carried out to overcome MDR for some time as well. The DOX-tethered responsive AuNPs indicated an excellent increase of DOX accumulation in MCF-7/ADR cancer cells compared with free DOX [38]. In other studies that DOX-loaded iron oxide NPs in the rat glioma C6 cells and C6/ADR cells [33], Fe_3O_4 NPs for the delivery of DOX in drug-resistant HeLa cells [34], magnetic iron oxide NPs co-loaded with DNR, and 5-bromotetrandrin in MDR leukemia K562/A02 cells [35], their results indicated the iron oxide NP system did good for increasing the drug concentration, reducing the tumor volume, and suppressing the tumor growth.

3.2 Experiments *in vivo*

Furthermore, a number of experiments *in vivo* that researched the application of nanomedicines to reserve MDR in cancer have been performed. Among them, the polymeric NPs were studied widely.

Several traditional drugs obtained better curative effect *in vivo* as they were loaded onto NPs. For instance, the experiment showed an increase in anti-MDR effects on tumors with CBT taxol compared with taxol on mice model and it was not toxic to mice [12]. In the MCF-7/ADR tumor-bearing mice model, the NP co-loaded DOX and shSur. It improved the accumulation of DOX and shSur in tumor tissues [48]. Punfa et al. also made efforts to develop drug-loaded NPs for overcoming MDR. In their study, they chose female BALB/c mice dramatically and found that the combined treatment of PTX with Cur(Cur-NPs-APgp) decreased tumor cells' viability and growth compared with PTX treatment alone [49]. Apart from the above experiments, the nude mice model with orthotopic, MDR breast tumor xenografts were utilized in another study. It demonstrated that PTX/Lonidamine-loaded EGFR-targeted NPs were able to decrease the tumor volume and reduce the expression of hypoxic and proteins associated with MDR [50]. In the *in vivo* investigation performed by Liang et al., the MCF-7/ADR xenografted nude mice model was utilized. The result confirmed that HTTP-50 NP showed much higher accumulation in tumor tissue and exhibited obviously enhanced antiresistance tumor efficacy with less systemic toxicity which was compared with HTTP-0 NP and Taxotere [51].

In addition to the studies mentioned earlier, many other experiments using mice model bearing MDR cells showed the advantage of nanomedicines. In recent years, cancer stem cells (CSCs) that were a subpopulation of cancer cells have been linked with MDR in tumor. Female BALB/c mice induced by CSCs were used for animal experiment to demonstrate the depletion effect of NP-delivered Sali CSCs in breast tumors. The NP-delivered Sali CSCs were more efficiently than free Sali [8]. Yang et al. established a human xenograft MDR ovarian cancer model with the female nude mice bearing ovarian tumors. Their study showed that ethyleneimine(HA-PEI)/ethylene glycol(HA-PEG) NPs could deliver MDR1 siRNA into MDR ovarian cancer cells successfully [52]. In our group, we chose nude mice bearing MDR leukemia cell K562/A02 xenografts. DNR-Tet-Tf-PEG-PLL-PLGA NPs were injected and the injection successfully inhibited the tumor growth and induced apoptosis in tumor cells. As a result, the NPs succeeded in overcoming MDR to some extent [53].

Next, we would like to introduce some other nanosystems which were utilized in different studies *in vivo* and their superiority in overcoming MDR.

On BALB/c nude mice MCF-7/BCRP drug resistance tumor model, the PLS-MSNPs were shown to enhance the intracellular delivery of antitumor drug and its efficacy [19]. Another experiment *in vivo* chose the rats that were established by implanting Walker 256 cancer cells in the back of them. The result showed enhanced chemotherapeutic efficiency of anticancer agents and circumvent of the cells of MDR [26]. In the study by Chen et al., the MCF-7/MDR xenografted tumor on BALB/c nude mice was inhibited in volume which treated with pH-responsive cholesterol-PEG adduct-coated SLNPs(C-PEG-SLNPs) loaded DOX [27]. In the study that explored the ability of iron oxide NPs to overcome MDR, the BALB/c mice were randomly assigned to different groups in order to be injected with given drugs through tail vein. The experiment's result indicated that Fe_3O_4 NPs-loaded DOX were promising for drug delivery in highly drug resistant HeLa cells [34].

4 Conclusion

The NP drug delivery system has been successfully utilized in various experiments *in vitro* and *in vivo* to overcome MDR. Different NP systems have their specific characters so that we can choose the most appropriate NP system to load antitumor drugs. Nanocarriers have effectively

overcome the problem of poor intracellular concentration, lack of targeting cancer tissues, low bioavailability, and so on. We can decrease the drug dose sharply and reduce the side effects with nanocarriers. The NPs alleviated the challenge of MDR in clinical cancer treatment. Benefiting from the advancements in nanomedicine, in future, more number of cancer patients may be able to prolong their life.

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Bionotes

Jie Yang
Department of Hematology and Oncology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing 210009, People's Republic of China

Jie Yang is a graduate student of Southeast University School of Medicine specializing in blood research in the group of Professor Baoan Chen. She is currently working on nanoparticles drug delivery system to reverse multi-drug resistance.

Haijun Zhang
Department of Hematology and Oncology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing 210009, People's Republic of China

Haijun Zhang is an associate professor and PhD supervisor at Zhongda Hospital, Medical School, Southeast University, China. He is engaged in clinical treatment and basic research into tumors, and is devoted to the field of nanobiotechnology-based cancer theranostics. He has published more than 20 SCI-indexed papers in renowned journals such as Biomaterials. He is a peer reviewer for numerous journals.

Baoan Chen
Department of Hematology and Oncology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing 210009, People's Republic of China,
Phone: +86 25 83272006,
Fax: +86 25 83272006,
cba8888@hotmail.com

Baoan Chen (MD/PhD) is a renowned hematologist and oncologist in China. He is the director of Faculty of Oncology of Southeast University, leader of Department of Hematology of the Affiliated Zhongda Hospital of Southeast University, head of MDS Research Institute. Professor Chen has rich experience in hematological malignancies' diagnosis and treatment.