Applications of nanoparticle drug delivery systems for the reversal of multidrug resistance in cancer (Review)

YINGHONG HUANG¹, SUSAN P.C. COLE², TIANGE CAI³, and YU CAI¹,4

¹Department of Traditional Chinese Medicine, College of Pharmacy, Jinan University, Guangzhou, Guangdong 510632, P.R. China; ²Department of Pathology and Molecular Medicine, Division of Cancer Biology and Genetics, Queen’s University Cancer Research Institute, Kingston, ON K7L 3N6, Canada; ³Department of Biological Sciences, College of Life Sciences, Liaoning University, Shenyang, Liaoning 110036; 4Cancer Institute of Jinan University, Guangzhou, Guangdong 510632, P.R. China

Received March 28, 2015; Accepted April 29, 2016

DOI: 10.3892/ol.2016.4596

Abstract. Multidrug resistance (MDR) to chemotherapy presents a major obstacle in the treatment of cancer patients, which directly affects the clinical success rate of cancer therapy. Current research aims to improve the efficiency of chemotherapy, whilst reducing toxicity to prolong the lives of cancer patients. As with good biocompatibility, high stability and drug release targeting properties, nanodrug delivery systems alter the mechanism by which drugs function to reverse MDR, via passive or active targeting, increasing drug accumulation in the tumor tissue or reducing drug elimination. Given the potential role of nanodrug delivery systems used in multidrug resistance, the present study summarizes the current knowledge on the properties of liposomes, lipid nanoparticles, polymeric micelles and mesoporous silica nanoparticles, together with their underlying mechanisms. The current review aims to provide a reliable basis and useful information for the development of new treatment strategies of multidrug resistance reversal using nanodrug delivery systems.

Correspondence to: Mr. Yu Cai, Department of Traditional Chinese Medicine, College of Pharmacy, Jinan University, 601 Huangpu Avenue West, Guangzhou, Guangdong 510632, P.R. China
E-mail: caiyu8@sohu.com

Ms. Tiange Cai, Department of Biological Sciences, College of Life Sciences, Liaoning University, 66 Chongshan Mid-Road, Shenyang, Liaoning 110036, P.R. China
E-mail: caitiange@163.com

Abbreviations: MDR, multidrug resistance; SLNs, solid lipid nanoparticles; NLCs, nanostructured lipid carriers; PLN, polymer-lipid hybrid nanoparticle; MSNs, mesoporous silica nano drug delivery systems

Key words: nanoparticle drug delivery system, MDR, SLN, NLC, PLN, polymeric micelles, MSNs, liposomes, phospholipid bilayer, cancer, applications

1. Introduction

At present, chemotherapy remains the optimal choice for cancer therapy, and tumor multidrug resistance (MDR) is a major factor that reduces the efficacy of chemotherapy (1). MDR is a phenotype that tumor cells acquire, which confers resistance to certain chemotherapy drugs, as well as concurrent cross-resistance to additional antitumor drugs that have different structures or mechanisms of action (2,3). The complexity of MDR has impeded the study of reversal agents (3-5). In recent years, the application of nanotechnology for drug carrier design has resulted in the development of novel nanoparticle drug delivery systems that aim to reverse MDR (6-8). Inorganic nanodrug delivery systems, lipid-based systems and polymer nanodrug delivery systems are the most common nanodrug delivery systems, which exhibit non-toxic, biocompatible and highly stable properties (8,9). The application of nanoparticle drug delivery systems is increasing due to their advantage of controlled and targeted drug release (9,10). Studies have demonstrated that entrapped small molecule drugs (10-200 nm in diameter) are more conducive to drug uptake and efflux; these nanodrug particles function via passive and active mechanisms, whereas in the systemic blood circulation they exhibit sustained release that subsequently enhances intracellular drug accumulation in tumor cells, yielding an improved effect (1,11-14). In the present review, the application of nanoparticle drug delivery systems in reversing the MDR of tumors is reviewed, which may provide an improved understanding of novel strategies for cancer therapy.
2. MDR and applications of nanodrug transmission systems

Cancer MDR may be caused by a number of complex factors, including ATP-binding cassette (ABC) transporters, multi-drug resistance protein [P-glycoprotein 1 (P-gp)], MDR-associated proteins (MRPs), breast cancer resistance protein (ABCG2), glutathione transferase, metallothionein, DNA topoisomerase II and catalytic enzymes (2,3,5). These substances exhibit various functions in the induction of tumor cell MDR (Fig. 1). Cellular MDR is divided into the ATP-dependent efflux pumps and non-ATP-dependent efflux pumps types. The ‘pumps’ type use the energy obtained from ATP hydrolysis to efflux drugs via ATP-dependent transport proteins, such as P-gp, MRPs and BCRPs, which decreases the intracellular drug concentration and subsequently results in drug resistance. The ‘non pumps’ type do not depend on the energy from ATP hydrolysis while activating the anti-apoptotic proteins, such as Bcl-2, and efflux drugs directly (2,7,9).

Nanoparticle drug transmission systems may alter drug uptake in tumor cells (12). The system delivers the chemotherapy drug directly to tumor cells, which functions to reverse MDR (10). Entrapment affects the pharmacokinetic properties of drugs; free drugs cross the cell membrane passively and are easily identified by the efflux pumps located on the cell membrane or captured by ABC transporter proteins, whereas drug-loading nanoparticles may avoid recognition by the ABC efflux pumps and endocytosis by ABC transporters, leading to increased intracellular accumulation of chemotherapeutic drugs (Fig. 1) (10,12,14).

3. Liposomes

Liposomes are preparations that utilize a phospholipid bilayer membrane vesicle to encapsulate drug molecules. The hydrophilic and hydrophobic bilayer cores entrap hydrophilic and lipophilic drugs, respectively. Liposomes have been demonstrated to prolong the blood-circulation time of drugs, to alter the pharmacokinetics and distribution of P-gp inhibitors in vivo, and to increase the drug concentration in the tumor cells, while reducing the impact on normal tissues, thus exerting toxicity to enhance the effects of chemotherapy (15-21). A study by Zhou et al (22), which investigated MDR reversal using doxorubicin (DOX) liposomes in vitro, demonstrated that DOX liposomes were mainly detected in the nucleus of human breast cancer P-gp overexpression cells (MCF-7/Adr) with an increased toxicity, and exhibited a stronger cellular retention capacity in human carcinoma KBv200 cells. Kang et al (23) used rhodamine (a P-gp substrate) to penetrate liposomes, and this combination resulted in increased liposome retention in the MCF-7/Adr cell line, which exhibits P-gp overexpression in vitro. Further assessment demonstrated that the incorporation of cholesterol and polyethyleneglycol-attached lipids was effective in further increasing the rhodamine retention in MCF-7/Pgp cells. More rigid liposomes are able to sequester rhodamine more efficiently, thereby inhibiting direct interactions of rhodamine with P-gp proteins. These studies indicated that by optimizing the composition of liposomes, reduction of P-gp-mediated MDR may be achieved.

4. Lipid nanoparticles

Lipid nanoparticles are a type of nanodrug delivery system that are assembled using natural or synthetic lipids, such as stearic acid, lecithin and triglycerides, as the matrix, to entrap anticancer drugs (particle size, 50-1,000 nm) in a lipid core (23,24). Lipid nanoparticles have various routes of administration, exhibit good biological compatibility and stability, and effectively control drug release to avoid degradation and leakage. Solid lipid nanoparticles (SLNs) and nanostructured
lipid carriers (NLCs) are the most common types, which have gained increasing attention as they represent promising drug carriers (25,26). One study showed that NLCs exhibit increased stability when compared with SLNs (24). Wong et al (27) showed that, compared with free doxorubicin, DOX-loaded SLNs exhibit a higher encapsulation efficiency, a faster release rate in vitro, and an enhanced uptake and retention capacity in human breast cancer cells (MDA435/LCC6/MDR1), resulting in significantly enhanced cytotoxicity. A novel polymer-lipid hybrid nanoparticle (PLN) system has also been developed (28). Prepared DOX-GG918-PLN and doxorubicin and mitomycin C co-loaded PLN carriers exhibited a good antitumor effect in vitro and in vivo, with significant reversal effects, which indicates that the carriers present a novel technique for improving the efficacy of local solid tumor chemotherapy (29-32). Liposomes alone exhibit no specific targeting, however, via the modification of nanodrug delivery systems using various ligands, including folic acid or anti-transferrin monoclonal antibodies, specific targeting may be obtained (33-35). Ligands with selective and specific affinities may be incorporated into the lipid bilayer of liposomes, which may then be identified by specific cells, yielding targeted nanoparticles (36,37).

5. Polymeric micelles

Polymeric micelles, which are a type of drug carrier with a hydrophobic core and hydrophilic polyethylene glycol (PEG) shell, present an ideal choice for the effective delivery of anticancer drugs (particle size, 10-100 nm) with poor solubility (38,39). Compared with the free drug, drug-loaded polymeric micelles, which demonstrate a higher stability and biocompatibility in vitro and in vivo, and a significantly increased blood circulation time, are transferred to the tumor site via active and passive targeting mechanisms. Passive targeting occurs via the enhanced permeability and retention effect, which causes drugs to be selectively accumulated and released at the tumor site. By modifying the surface of polymer micelles, drug accumulation by the tumor may be increased via the active targeting pathway. Therefore, polymeric micelles present an ideal carrier molecule for active or passive targeted drug delivery as they improve the therapeutic index while reducing toxic side effects (40-44). The use of drug-conjugated polymer micelles that exhibit simultaneous entrapment of two drugs and maintain antitumor activity has been reported (38). Currently, several types of polymer micelle transmission systems are being used to overcome MDR, and certain studies have demonstrated that a number of block copolymers may decrease the production of ATP in resistant cells, thus reducing the activity of P-gp (45-47). Saiyin et al (48) implemented the simultaneous entrapment of a chemotherapeutic drug and autophagy inhibitors, and engineered the sequential release of these drugs. The prioritized release of the autophagy inhibitors suppressed the phagocytosis of tumor cells, subsequently increasing sensitivity to the chemotherapeutic drug, which resulted in a synergistic effect. This combination provides a novel platform for chemotherapy. Yu et al (49) prepared docetaxel-loaded pH-responsive PEG-hyperbranched polyaclyhydrazone micelles, which exhibited increasing tumor toxicity in vitro; however, when combined with glucose, enhanced antitumor activity and lower systemic toxicity were observed. Therefore, these results indicate that polymeric micelles may be used for selective targeted drug delivery.

6. Combined treatment strategies based on nanodrug delivery systems

Enhancing the efficiency of drug delivery to tumor cells and preventing apoptosis by modulating intracellular signal transduction mechanisms presents an effective method to overcome MDR (50-52). The co-delivery of reversal agents and chemotherapy drugs by nanodrug delivery systems may regulate the expression of intracellular ABC transporter proteins and silence MDR genes (52-54), thereby affecting the efflux or apoptosis of tumor cells and reducing the toxicity of chemotherapy (55-57). In a study by Abouzeid et al (58), co-coated curcumin (a reversal agent) and paclitaxel-loaded PEG-phosphatidylethanolamine/vitamin E micelles were demonstrated to exhibit significantly increased toxicity in human ovarian carcinoma resistant cells (SK-OV-3/TR) in vitro and in vivo, with the synergistic antitumor effects observed in vivo being superior to those observed in vitro. Furthermore, Tang et al (59) reported that the co-delivery of DOX and a P-gp inhibitor (verapamil) using a reduction-sensitive liposome resulted in increased apoptosis induction and necrosis of MCF-7/Adr tumor cells.

7. Mesoporous silica nanoparticles

Recently, gene technology and nanobiomaterial vector delivery systems, such as silicon nanogene vectors as non-viral gene vectors, have gained increasing attention as a promising approach for tumor MDR reversal (60-63). Silicon nanodrug systems exhibit good biocompatibility and a non-cytotoxic surface that is easily modified. The main aims of the formed mesoporous silica nanodrug delivery systems (MSNs) are to control targeted-drug release and overcome MDR (64-66). With regard to MDR reversal, MSNs are considered to alter the original route of drug uptake, while avoiding identification, binding and efflux by ABC proteins. In addition, the different MSN pore sizes allow the effectively controlled release of intratumor drugs and accumulation (67-70). MSNs present an alternative method for the more efficient delivery of chemotherapy drugs and targeted gene therapy. Meng et al (70) revealed that coating P-gp-targeted siRNA with DOX using MSNs significantly increased the chemotherapeutic drug concentration within the cell nucleus of the squamous carcinoma resistant cell line, KB-V1, and promoted cell apoptosis and death. Notably, Zhang et al (71) also developed a polymer-lipid supported-MSN. This system exhibited targeted and controlled drug release in vitro and exhibited a significant effect in the treatment of breast cancer, with a low toxicity in vivo.

8. Conclusion

Cancer is a common disease that seriously affects human health and reversal of MDR in cancer has long been a topic of research. However, due to the complex and diverse resistance mechanisms of cancer, the limitation of biological activity and
totoxicity of MDR reversal agents, the existing reversal agents cannot meet the requirements of treatment. Compared with traditional anticancer drugs, nanodrug delivery systems show a clear advantage in terms of reversing MDR during the process of tumor therapy. Novel drug-loaded nanoparticle systems, such as the co-entrapped reversal agents and chemotherapy drugs and the co-loaded P-gp inhibitors and chemotherapy drugs, and the specific modification of nanoparticles may alter the transmission method and the targeting of drugs and antagonize the drug efflux by tumor cells. Thus, the accumulation of drug within the tumor cells may be improved. The good biocompatibility, high stability, drug release and targeting of nanodrug delivery systems overcome the shortcomings of the traditional drug delivery system, and show great promise in cancer MDR reversal. However, with the enhanced targeting, the tissue distribution of drugs has also changed and led to new adverse reactions; therefore, additional in vivo evaluation of safety and efficacy data are urgently required.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (grant nos. 81273707 and 81173215), the Ministry of Education in the New Century Excellent Talents (grant no. NECT-12-0677), the Natural Science Foundation of Ministry of Education in the New Century Excellent Talents Foundation of China (grant nos. 81273707 and 81173215), the Science Program of the Department Guangdong (grant nos. S2013010012880 and 2016A030311037), the Science and Technology Program of Guangzhou (grant no. 20144500005), the Science Program of the Department of Education of Guangdong (grant nos. 2013KJCX0021 and 2015KJHZ2012) and the Science and Technology Program of Guangzhou (grant no. 2015A050502027).

References


