Reversion of Multidrug Resistance in Tumor By Biocompatible Nanomaterials

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Abstract: In this review we have focused on the utilization of the biocompatible nanomaterials to reverse multidrug resistance (MDR), a major clinical obstacle in cancer therapeutics. Based on the comprehension of the mechanism of MDR and common reversal methods, the strategies and key properties of anti-MDR nanomaterials are explored and described to show how these features could provide the potential therapeutic effects that are not achievable with other modalities. The use of biocompatible nanoparticles with different designs and therapeutic approaches to reverse the MDR of cancer chemotherapeutics offers promising opportunities to benefit patients in the future.

Keywords: Biocompatible nanomaterials, multidrug resistance, tumor therapeutics, reversal MDR agents, nanotechnology, cancers.

INTRODUCTION

Tumor seriously threatens human's health. Although much effort has been extended to the efficient cancer therapies, the multidrug resistance (MDR) is still a major obstacle in cancer chemotherapeutic treatments. It is now known that the MDR of tumor cells could considerably reduce the effectiveness of cytotoxic chemotherapies and almost 90% of the cancer therapy failures are relevant to the problems caused by the MDR [1,2]. Different factors, such as drug efflux related proteins, alteration of specific enzyme systems for drug metabolism, reduction of apoptotic activity, transcription factors, all lead to the MDR. As far as the mechanism of drug efflux related proteins is concerned, the drug-resistance related proteins on the cell membrane may pump out the drug molecules from the drug-resistance tumor cells, which will cause the low drug concentration inside cancer cells. Besides, as a result of drug resistance, anticancer drugs can be enzymatically inactivated or the drug activity can be prevented by mutation. These effects may cause the intracellular drug concentration to be lower than the effective concentration or make the drug lose its function in cancer therapy [3].

Recent studies indicate that some proteins, such as P-glycoprotein (P-gp) and other MDR associated proteins could play crucial roles in the relative effects in mediating the drug uptake or absorption to cancer cells [4,5]. Among them, P-gp is one of the superfamilies of ATP-dependent membrane transport proteins, which mainly contributes to the drug resistance of the related cancers [6]. It was reported that P-gp could recognize the xenobiotics inner leaflet of plasma membrane and then flip the molecules to the outer leaflet [7]. Moreover, P-gp may also interact directly with the hydrophobic substrates and pump the relative reagents out of the tumor cells [8]. So, the diversity of tumors and MDR pumps suggests a need for clinically approved MDR modulators (also called chemosensitizers) or inhibitors.

Fortunately, with the advancement of nanotechnology, nanomaterials have sparked a considerable interest in diagnostic and therapeutic of tumor, especially in overcoming the MDR. Research in nanomedicine has not only become a frontier movement but is also a revolutionizing cancer therapeutic. Recently, the applications of drug coated polymer nanospheres and nanoparticles to inhibit the related drug resistance have attracted much attention, achievements of which have been gained *in vitro* and previous clinic. Recent reports illustrate that some drug coated polymer nanospheres and nanoparticles could increase the delivery of the anticancer drug [9-11]. What's more, new strategies to inhibit the MDR of the targeted tumor cells have explored, through which the synergistic enhanced effect of drug uptake of the drug resistance leukemia K562 cells by combining the unique properties of tetraheptylammonium capped Fe_3O_4 magnetic nanoparticles with the accumulation of anticancer drug daunorubicin was realized [12,13]. The rationale behind application of nanoparticles with different designs and therapeutic approaches is to increase the intracellular drug concentration by the synergistic effect of anticancer agents with relevant nanoparticles. The presence of these biocompatible nanomaterials could facilitate the drug accumulation inside tumor cells, and enhance the efficient utilization of anticancer drug on target tumor cells and tissues. So, biocompatible nanomaterials could play a remarkable impact on the approach to overcome MDR. While a large number of researches [9-11] and reviews [14,15] about biocompatible nanomaterials as drug delivery carriers have been published, the purpose of this review is focused on the novel nanotech-

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nological strategies to reverse the MDR of cancer chemotherapy.

1. MECHANISMS OF DRUG RESISTANCE IN TUMORS

As known, chemotherapy is still a major form of treatment for cancer. Although there has been tremendous progress in the treatment of cancer, treatment failure is still frequently encountered, due to the lack of clinical procedures for overcoming the resistance of cancer cells to a multitude of chemotherapeutic and biological agents that limits the efficacy of cancer therapeutics, known as MDR. MDR in cancer refers to a state of resistance against structurally and functionally unrelated drugs. As illustrated in Table **1**, the MDR mechanisms can have different origins, including drug efflux related proteins, alteration of specific enzyme systems for drug metabolism, reduction of apoptotic activity, transcription factors, and others.

1.1. Proteins Related with the Drug Efflux

A basic mechanism of MDR is a procedure mediated by the ATP-binding cassette transporters. The ATP-Binding cassette transporters are known to contribute to the MDR including P-gp, multi-drug resistance associated protein (MRP), breast cancer resistance protein, etc. In addition, lung resistance protein, another drug efflux protein relevant to the MDR, is not involved in the family of ATP-binding cassette transporters.

P-gp is an expression of MDR gene 1 and is a 170-kDa membrane-associated glycoprotein that functions as a transporter or efflux pump to remove drug out of cells. P-gp effluxes a broad spectrum of substrates, including several hydrophobic or amphipathic cytotoxic anticancer agents such as vinca alkaloids, taxanes, anthracyclines, topotecan, dactinomycin, and mitomycin-C out of the cells [16], thus rendering chemotherapy is ineffective. MDR mediated by P-gp is a major form. Many subtypes of MRP, such as MRP 1-5, MRP 7-8, correlate with MDR in cancer. Among them MRP 1 is the most significant. The mechanism of MRP resulting in MDR is similar to P-gp [17-20]. Although breast cancer resistance protein, like P-gp and MRP, belongs to the family of ATP-Binding Cassette transporters, it is academically called a half transporter, since it only owns one ATP-binding structural domain and one hydrophobicity membrane spanning domain, quite different from those of the P-gp and MRP. Breast cancer resistance protein also depends on the energy provided by ATP to efflux the drug out of the target cells and lead to the MDR [21].

Another family of proteins, classified as the non-ATP-binding cassette transporter, for example, the lung resistance protein, is a kind of the major vault transporter protein that effluxes drug, which may also induce MDR. It makes the drug away from target through changing the drug disposition from nucleus to endochylema. The drugs here include the famous cisplatin, carboplatin, alkylating agent, which cannot be mediated by P-glycoprotein and MRP [22].

1.2. MDR Mediated by Enzyme

The variation of enzyme in nucleus and cytoplasm may induce MDR, such as glutathione S-transferase, Topoisomerase Ⅱ, protein kinase C, *et al.* The reaction between the electrophilic drug and glutathione can be catalyzed by glutathione S-transferase, which will increase the water solubility of the drug to facilitate the elimination of the drug out of

Table 1. Mechanisms of MDR in Tumors

Mechanisms	Functional Molecules	
drug efflux related proteins	ATP-Binding Cassette transporters	P–glycoprotein
		multi-drug resistance associated protein
		breast cancer resistance protein
	non-ATP-Binding Cassette transporters	lung resistance protein
mediated by enzyme	Glutathione S-transferase	
	Topoisomerase Ⅱ	
	protein kinase C	
reduction of apoptotic activity	*Bcl-2*	
	mutation *p53*	
	cmy-c	
transcription factor	nuclear factor κB	
	hypoxia inducible factor – 1	
other mechanisms	DNA methylation, microenvironment resistance, *et al.*	

body, resulting in the MDR [23,24]. The low expression of TopoisomeraseⅡ, as a target of many drugs that participates in the DNA unwinding, repair and transcription, will decrease the sensitivity of drug to tumor, and thus increase resistance [25]. Protein kinase C plays an important role in cellular signal transduction and correlates with the function of P-gp. The drug efflux pump ability of P-gp is enhanced by protein kinase C, which promotes the phosphorylation of P-gp in the MDR tumor cell [26].

1.3. Reduction of Apoptotic Activity

As the chemotherapeutic agents usually aim to induce apoptosis, the relationship between apoptosis and MDR has become an attractive topic in the recent years. The overexpression of apoptosis inhibiting gene, such as Bcl-2 and mutation p53 can lead to an occurrence of MDR [27].

1.4. Transcription Factors and Other Mechanisms

Studies have discovered that the abnormal expression of nuclear factor B [28], hypoxia- inducible factor-1 occurs in MDR tumors [29]. The other mechanisms, such as DNA methylation, microenvironment resistance, etc., also contribute to MDR [30-33].

Although these categories represent distinct mechanisms, the MDR phenotype is usually the synergistic result of a combination of MDR mechanisms, for example, the simultaneous inhibition of apoptosis and an increase of the efflux. Many of the mechanisms of MDR have been validated, but, as discoveries in cellular physiology progress, new factors that contribute to MDR may likely emerge.

2. REVERSAL OF MULTI-DRUG RESISTANCE

As illuminated above, MDR is a major reason of treatment failure and relapsing of cancers. We should perform clinical strategy to overcome it by searching for reversal agent, which is an emergent request in tumor chemotherapeutics. It is of great significance to reverse MDR and enhance sensitivity in tumor therapy. Reversal of MDR means all or partial restoration of tumor cells to drug sensitivity. Corresponding to the mechanism of MDR, reversal agents to reverse MDR are evolved all over the world, as summarized in Table **2**.

2.1. By Chemical Agents

A number of compounds that inhibit P-gp activities have been identified or synthesized to specifically overcome the MDR. Three generations of them, including calcium channel blocker, calmodulin inhibitor, ciclosporin, antiarrhythic drugs, and so on, apparently restore the sensitivity of the drug-resistant tumor cells to the chemotherapeutic treatment by inhibiting P-gp-mediated cellular effluxing of the cytotoxic drugs. However, the results have been disappointing, because the earlier chemosensitizers, such as verapamil and ciclosporin-A led to significant toxicities and pharmacokinetic interactions due to their low potencies and poor specificity for the drug efflux transporters [34]. So, the clinical use of them to overcome MDR is limited due to the serious adverse effects of these compounds. Although novel agents are more potent and specific, they can also affect the pharmacokinetics of the cytotoxic agents concurrently administered. In addition, none of these inhibitors are completely effective for the treatment of solid tumors, possibly due to the complicated mechanisms of resistance as previously discussed.

2.2. By Immunology

1) Antibody

The use of monoclonal antibodies directed to tumor-associated antigens is considered vital for specific targeting of MDR human cancer cells. Lots of antibodies can be utilized and performed to overcome MDR. Hanibuchi *et al*. suggested that the mouse-human chimeric KM966 (anti-GM2 monoclonal antibody) targets the GM2 antigen, and

Table 2. Reversal Agents Corresponding to the Mechanism of MDR

Mechanisms	Reversal Agent	
Chemical agents	first generation	ciclosporin, verapamil, quinidin
	second generation	PSC833, dextrorotatory verapamil
	third generation	tariquidar, zosuquidar, laniquidar
immunology	antibody	
	immunocyte	
	cytokine	
gene technology	antisense oligomerization deoxyribonucleic acid	
	ribozyme	
	RNA interference	
	antisense RNA	
traditional Chinese medicine	tetrandrine	
nanotechnology	biocompatible nanomaterials	

might be useful for the immunological circumvention of multiple-organ metastases of refractory small cell lung cancer [35].

2) Immunocyte

The cell immunity is an essential part of tumor immunity. P-gp promotes the killing ability mediated by natural killer cell, cytotoxicity T lymphocyte, lymphokine-activated killer. So these immunocytes can reverse the MDR in tumor [36,37].

3) Cytokine

A few of cytokines, such as TNF, INF, IL-2, decrease the expression of P-gp, and increase the sensitivity of tumor cell to doxorubicin (Dox) and vinblastine. The death-inducing cytokine TRAIL is a promising agent for anticancer therapy since it preferentially kills cancer versus normal cells; however, some cancer cells are TRAIL resistant. Park *et al*. [38] reported that P-gp could enhance TRAIL-triggered apoptosis in multidrug resistant cancer cells by its interaction with the death receptor DR5. They reveal that TRAIL treatment preferentially causes apoptosis in P-gp-overexpressing MDR cells, and suggests that the significant clinical implications for the use of TRAIL in treating neoplasms have failed chemotherapy.

2.3. By Gene Technology

With the rapid advancements in human genomics and cancer genetics in recent years, gene therapy is growing a promising strategy for cancer management. It is proposed to be used alone or in combination with cytotoxic drug treatment to overcome the MDR. The following methods can be adopted: antisense oligomerization DNA for reversing MDR, ribozyme for reversing MDR, RNA interference, and antisense RNA technology [39].

2.4. By Traditional Chinese Medicine

For example, tetrandrine (TET), a kind of calcium channel blocker, is a benzylisoquinoline alkaloid isolated from the Chinese herb "Hanfangji" (Radix of *Stephania tetrandra*) that has also been shown to be a potent inhibitor of P-gp drug efflux *in vitro* [40]. TET exhibited strong activity to reverse drug resistance to daunorubicin, vinblastine and Dox in leukemia cells.

2.5. By Biocompatible Nanomaterials

Biocompatible nanomaterials, as a class of potential and promising therapeutics for cancers, may provide a useful alternative to inhibit the MDR. These contents will be the focus and will be reviewed in the following section in details.

3. KEY PROPERTIES OF ANTI-MDR NANOMATERIALS

3.1. Sizes of Nanoparticles

It is generally thought that the effective size of nanoparticles involved in the therapeutics for cancer should be in the range of 10–100 nm [41-43]. Thus, well-designed nanoparticles in the 10–100 nm size range with a surface charge either slightly positive or slightly negative should own the accessibility to and within disseminated tumors when dosed into the circulatory system.

3.2. Surface Properties of Nanoparticles

Compared with larger particles, nanoparticles have higher surface-to-volume ratios thus the control of their surface properties is crucial to their behavior *in vivo*. The large surface area allows nanoparticles to be held in suspension as well as surface adsorption.

The ultimate fate of nanoparticles within the body can be determined by the interactions of nanoparticles with their local environment, which depends on a combination of size and surface properties. Altering parameters such as conformation and charge also have profound effects on how any kind of nanoparticle behaves in a biological environment. If the surface charge becomes larger (either positive or negative), macrophage scavenging system works and can lead to the greater clearance by the reticuloendothelial system. The superplasticity versatility of nanoparticles along with appropriate surface chemistry, including optical properties, changes in solubility, catalytic activity, heat capacity, and magnetic properties (such as superparamagnetism for magnetic nanoparticles), contributes to their usefulness in tumor. Upon understanding the size and surface requirements for reaching specified sites within the body, localization of nanoparticles to these sites can be accomplished [44,45].

4. APPLICATION OF NANOMATERIALS TO REVERSE MULTIDRUG RESISTANCE

4.1. Biocompatible Nanomaterial as Drug Carrier

The clinical use of reversal agent to overcome MDR is limited due to the serious adverse effects. Nanotechnology offers an unprecedented opportunity in the rational delivery of drugs and overcoming MDR. A significant strategy suggested for delivery of anticancer drugs, with the aim of reversing MDR, is to load the drug with colloidal carriers such as biocompatible nanoparticles. The advantages of nanoparticles stem from their size and surface properties. Nanoparticles, sufficiently large to accommodate multiple types of molecules, are beneficial to the drugs/genes delivery to tumors. Nanoparticle therapeutics for cancer is comprised of therapeutic entities, such as small-molecule drugs, peptides, proteins and nucleic acids, and components that assemble with the carried entities, such as lipids and polymers particles. Such nanoparticles can enhance anticancer effects compared with the therapeutic entities that they contain [46,47]. Now, some polymer nanospheres and nanoparticles have been introduced such as drug delivery systems to enhance the related drug delivery efficiency to cancer cells, and reports have shown that some drug-coated polymer could increase the anticancer drug delivery [48,49]. This is owing to active cellular uptake and more specific targeting to tumor tissues *via* improved pharmacokinetics and pharmacodynamics, as well as active intracellular delivery.

The cure efficiency of cancer chemotherapy depends not only on the anticancer drug itself but also on how it is delivered to its targets [50]. Nanoparticles are sufficiently large to contain multiple targeting ligands that can allow multivalent binding to cell-surface receptors. At addition of targeting

ligands that provide specific nanoparticle–cell surface interactions can play a vital role in the ultimate location of the nanoparticles. The relative applications of nanoparticles provide opportunities in drug delivery systems for achieving drug targeting and controlled drug release [51,52]. For example, nanoparticles can be targeted to cancer cells if their surfaces contain moieties such as small molecules, peptides, proteins or antibodies. These moieties can bind with cancer cell surface receptor proteins, such as transferrin receptors, that are known to be overexpressed on a wide range of cancer cells. These targeting ligands enable nanoparticles to bind to cell-surface receptors and enter cells by receptor-mediated endocytosis [53]. Potentially, combined with nanospheres or nanoparticles, the capability of anticancer drugs against biotransformation and rapid clearance from the body could be promoted, which could further afford the proper biodistribution of anticancer drugs to target tumor cells and tissues [54,55]. As illustrated above, nanoparticles of different sizes and surfaces have a different ability to enter target cells. Small-sized nanoparticles are more readily to enter the cells or be phagocytosed by the cells than larger sized ones [56]. Thus the relative efficiency of the drug delivery systems composed of drug-nanoparticle conjugates will be critically dependent upon the nanoparticle surface chemistry and size of the functionalized nanoparticles.

Further investigations showed that the MDR cancer cells both accumulated and retained nanoparticles-loaded Dox at substantially higher levels than Dox solution alone and inhibited MDR [57]. Co-therapy in overcoming tumor MDR with biocompatible nanomaterial was examined too. Combined polyalkylcyanoacrylate nanoparticles formulation of cyclosporin A and Dox were prepared and evaluated in an attempt to show improved growth inhibition efficacy in resistant cell culture line. The result showed the synergistic effect achieved by combining the chemo-sensitizing compound cyclosporin A, with an effective cytotoxic drug like doxorubicin [58]. In Yadav's study, poly(ethylene oxide)-modified poly(beta-aminoester) and PEO-modified poly(epsilon-caprolactone) nanoparticles were formulated to efficiently encapsulate MDR-1 silencing siRNA and paclitaxel (PTX), respectively. Combination of MDR-1 gene silencing and nanoparticle-mediated delivery significantly influenced the cytotoxic activity of PTX in multidrug resistant $SKOV3_{TR}$ cells, similar to what was observed in drug sensitive SKOV3 cells. They speculate that the enhancement in cytotoxicity was due to an increased intracellular drug accumulation upon MDR-1 gene silencing leading to an apoptotic cell-kill effect [59].

In the meantime, the anticancer drugs could be readily modified on the nanoparticles covalently or through electrostatic interaction to afford the sustained drug release and enhance the drug accumulation inside cell lines [60-63].

On the basis of the above consideration, the biocompatible magnetic nanoparticles like Fe_3O_4, which are feasible to produce, characterize and easily functionalize, may offer an exciting opportunity toward developing strategy for effective cancer diagnosis and therapy. It is observed that the superparamagnetic particles like magnetite could be utilized in tissue specific release of therapeutic agents and magnetic field assisted radionuclide therapy. Some progress has been made in this field. A novel strategy to inhibit the MDR of the targeted tumor cells by combining the unique properties of tetraheptylammonium capped Fe_3O_4 magnetic nanoparticle with the drug accumulation of daunorubicin has been explored [12,13]. The unique property of the magnetic nanoparticles and the interaction between the magnetic nanoparticles Fe_3O_4 and biologically active molecules on the membrane of leukemia cell lines may contribute to their beneficial effect on cellular uptake. This observation demonstrates the remarkable synergistic effect of these functionalized nanoparticles on drug uptake in drug sensitive and drug resistance leukemia cancer cells and their potential valuable applications as anti-MDR agents. Fig. (**1**) illustrates the possible process of drug accumulation of the drug resistant tumor cells and the synergistic effect of magnetic nanoparticles Fe_3O_4 on the relative drug uptake of daunorubicin in the drug resistant leukemia K562 cells. It is reasonable that the competitive binding of the Fe_3O_4 nanoparticles to the overexpression P-gp on the membrane of the drug resistant leukemia K562 cells may make it possible for the accumulation of anticancer drug daunorubicin in target tumor cells and thus reach an effective drug concentration, suggesting that Fe_3O_4 nanoparticles could play as a promising inhibitor of P-gp to reverse the relative drug resistance. Since Fe_3O_4 nanoparticles could be fixed at the ailing area by using external magnetic field during the tumor treatments, it is believed that the unique properties of Fe_3O_4 magnetic nanoparticles could be very useful in the future clinic tumor target treatments.

Alternative strategies for overcoming drug resistance could be based on systems that allow selective drug accumulation in tumor tissues, tumor cells or even compartments of tumor cells without increased systemic toxicity. This might be provided by nanoparticle-based drugs because they can readily enter cells by endocytosis. Other biocompatible nanomaterials were also reported to efficiently enhance the accumulation and utilization of anticancer drugs on target cancer cells through the combination of drug molecules with Au or CdS nanoparticles [64,65]. These nanoparticles can readily bind with daunorubicin on the external membrane of the targeted cells and facilitate the uptake of anticancer drug in the human leukemia K562 cells (see an example in Fig. (**2**)). Thus, the competitive binding of the relevant nanoparticles with accompanying anticancer drug to some components in the membrane of leukemia K562 cells could efficiently prevent the drug release by the cancer cells and inhibit the possible MDR of the drug-resistant leukemia cells, which could be further utilized to improve the future drug delivery efficiency in respective tumor chemotherapies.

Meanwhile, Chen *et al*. [66] recently reported the synergistic effect of the combination of multi-nanoparticles, i.e., different nanoparticles like nano Fe_3O_4 and Au nanoparticles, which could be combined to reverse the drug resistance of K562/A02 cells. The results of cytotoxic effect, RT-PCR, flow cytometry and confocal fluorescence microscopy indicated that the magnetic nanoparticles Fe_3O_4 and Au can efficiently facilitate the anticancer drug to reverse the drug resistance of cancer cells.

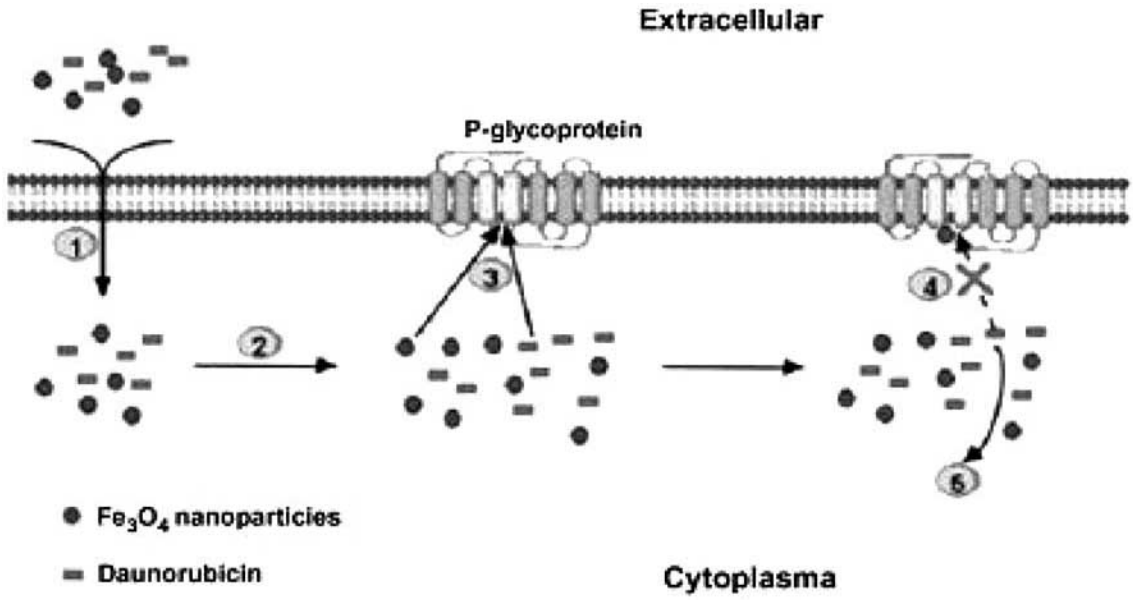

Fig. (1). Schematic drawing of the possible process for the enhanced synergistic effect of Fe_3O_4 nanoparticles to the drug accumulation of daunorubicin in the drug resistant leukemia K562 cells. (1) the Fe_3O_4 nanoparticles and daunorubicin diffuse from extracellular to cytoplasma, (2) the Fe_3O_4 nanoparticles and daunorubicin move to the P-gp, (3) the competive interaction of the Fe_3O_4 nanoparticles and daunorubicin with P-gp, (4) and (5) the binding of Fe_3O_4 nanoparticles with P-gp blocked the recognition of P-gp to daunorubicin and that make more the daunorubicin molecules could move to the nucleus. Reprinted from with permission reference [12].

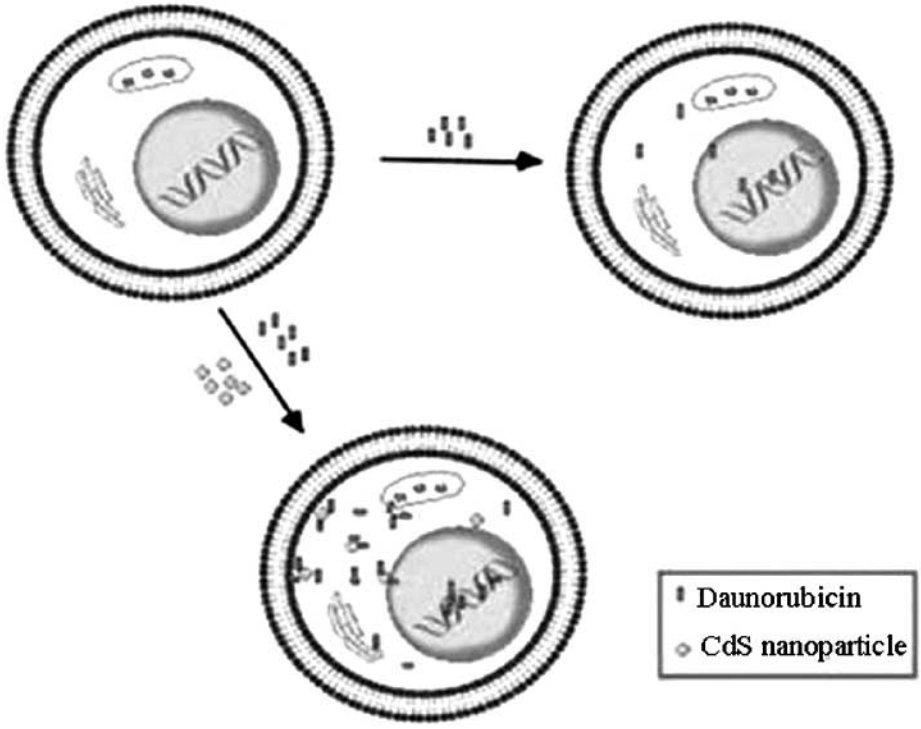

Fig. (2). Schematic drawing of the synergistic effect of CdS nanoparticles on daunorubicin uptake of leukemia K562 cells. Reprinted with permission from reference [65].

4.2. Enhancement of Drug Delivery by Multifunctional Nanoparticles

With advancement in material design, there is an opportunity to develop multifunctional nanosystems with thermal, sound, and light energies. The influence of nano-TiO_2 and UV illumination on the drug resistance of target cancer cells has been explored [67]. The observation demonstrates that nano-TiO_2 can significantly enhance the drug uptake in the drug-resistant leukemia cancer cells. Besides, the nano-TiO_2 under UV irradiation accompanied with daunorubicin could provoke some considerable changes of the cell membrane of

the target leukemia cells, which indicate that nano-TiO_2 could not only increase the drug accumulation in target cancer cells, but also act as an effective anti-MDR agent to inhibit the relative drug resistance.

Some researchers have combined the ultrasound means with nanoparticle systems to achieve tumor-specific drug release [68]. Rapoport *et al.* used various concentrations of Dox and Pluronic P 105 micelles, with the aid of ultrasound to evaluate the efficiency in multidrug resistance and drug sensitive ovarian cancer cell lines. The results showed that the highest cell-kill percentage (lowest IC_{50}) was achieved with the Dox loaded Pluronic P 105 micelles under the ultrasound exposure [69]. A similar study of micellar encapsulated Dox combined with ultrasound demonstrated the frequency dependent enhancement for both WT and MDR ovarian carcinoma cell lines [70]. Thus the combination of the focused ultrasound and drug loaded nanoparticles may become a promising technique to overcome MDR.

4.3. Evaluation of the Reversing of MDR *In Vivo*

It is significant to evaluate the reversion of MDR in tumor by biocompatible nanomaterials with animal models *in vivo* and clinical trials. Pluronic block copolymers are a novel class of polymeric inhibitors of P-gp that sensitize MDR tumors to Dox, paclitaxel, vinblastine, and other anticancer agents *in vitro* and *in vivo* [71-73]. In a typical experiment [74], female BDF1 mice inoculated introperitoneal with P388 cells were treated every 3rd day with (i) PBS (control), (ii) 0.02% P85 (P85), (iii) Dox 2.5mg/kg bodyweight (Dox) or (iv) Dox 2.5mg/kg body weight with 0.02% P85 (Dox/P85). Mann–Whitney non-parametric statistical test used for pair wise comparison showed that Dox/P85 and Dox treatments increased the animal lifespan over PBS control. Furthermore, Dox/P85 treatment increased the animal lifespan over Dox while no effect on the lifespan was observed for P85 and PBS control, and appeared to suppress development of resistance *in vivo*. PEGylated nanostructured lipid carriers (PEG-NLCs) also showed enhanced cellular uptake by human lung adenocarcinoma epithelial A549 cells. *In vivo* experiments indicated that PEG-NLCs loaded with 10-hydroxycamptothecin (HCPT) have superior efficacy against A549 lung cancer compared with HCPT solution [75].

In addition, the promising nanomedicine-based loader polymeric micelles have been evaluated in several clinical trials as carriers for anticancer drugs [76,77]. There are several anticancer agent-incorporated micelle carrier systems under clinical evaluation. Phase 1 studies of a cis-diamminedichloroplatinum incorporated micelle, Nc-6004, and an sN-38 incorporated micelle, NK012, are now underway. A phase 2 study of a PTX incorporated micelle, NK105, against stomach cancer is also underway [78].

5. ACHIEVEMENTS AND FUTURE CHALLENGES

Nanotechnology-based therapeutics may provide a useful alternative to reverse MDR. Now the results from the researches using cell culture systems or animal models are already fuelling the enthusiasm for this type of therapeutic modality. Especially, it is suggested that the efficacy would be improved, the pump-mediated MDR might be overcome and the side effects could be significantly reduced without the emergence of new ones. Although there are numerous positive features of biocompatible nanomaterial based therapeutics for cancer, there are also some issues of concern. The size and surface properties of nanoparticles can endow them the access to some special locations that are not available to larger particles. Since the appropriate size can provide useful features (i.e., larger payloads and accommodation of multiple targeting ligands), and surface properties also affect the biodistribution through mechanisms such as nonspecific binding to proteins in the blood, removal by macrophages and local disturbances in barriers that would otherwise limit their access, the relevant approach should improve further to obtain the optimal properties. In addition, the clinical tests of pharmacokinetics, biodistribution, and toxicity have not been extensively evaluated.

CONCLUSION

The unique properties of nanomaterials can be exploited in designing different platforms for the reversing of MDR involved in the treatment of cancer. Although compared with many other reversal agents the history of utilizing biocompatible nanocomposites is relatively short, this strategy could offer promising opportunities in the future biomedical applications. The use of safe and effective biocompatible nanomaterials promises to alleviate many of the challenges in clinical cancer therapy to benefit patients in the future.

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ABBREVIATIONS

MDR	=	multidrug resistance
P-gp	=	P-glycoprotein
MRP	=	multidrug resistance associated protein
Dox	=	doxorubicin
TET	=	tetrandrine
PTX	=	paclitaxel
PEG-NLCs	=	PEGylated nanostructured lipid carriers
HCPT	=	10-hydroxycamptothecin

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