NANOPARTICLES – BASED DRUG DELIVERY IN CANCER THERAPY : A REVIEW

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Abstract

Nanotechnology has been extensively studied and exploited for cancer treatment as nanoparticles can play a significant role as a drug delivery system. Compared to conventional drugs, nanoparticle-based drug delivery has specific advantages, such as improved stability and biocompatibility, enhanced permeability and retention effect, and precise targeting. The application and development of hybrid nanoparticles, which incorporates the combined properties of different nanoparticles, has led this type of drug-carrier system to the next level. In addition, nanoparticle-based drug delivery systems have been shown to play a role in overcoming cancer-related drug resistance. The mechanisms of cancer drug resistance include overexpression of drug efflux transporters, defective apoptotic pathways, and hypoxic environment. Nanoparticles targeting these mechanisms can lead to an improvement in the reversal of multidrug resistance. Furthermore, as more tumor drug resistance mechanisms are revealed, nanoparticles are increasingly being developed to target these mechanisms. Moreover, scientists have recently started to investigate the role of nanoparticles in immunotherapy, which plays a more important role in cancer treatment. In this review, we discuss the roles of nanoparticles and hybrid nanoparticles for drug delivery in chemotherapy, targeted therapy, and immunotherapy and describe the targeting mechanism of nanoparticle-based drug delivery as well as its function on reversing drug resistance.

INTRODUCTION

Finding new and innovative treatments for cancer is a major problem across the world. With an increase in the number of methods that can treat cancer and the concept of an individualized treatment, the therapeutic efficacy of some malignant tumors has greatly improved. Chemotherapy is a conventional and widely used cancer treatment method. While chemotherapy works through a number of different mechanisms, its major function includes indiscriminately killing vigorously growing cells, including tumor and normal cells, which causes some serious side effects including bone marrow suppression, hair loss, and gastrointestinal reactions. Therefore, developing drugs that more accurately target tumor cells, instead of normal cells, has been the purpose of a large proportion of cancer-related research in the past few decades. Although the emergence of targeted therapy has made great progress in precision therapy, there are still many unavoidable adverse effects, and the development of drug resistance has always been a problem. Currently, cancer remains the second leading cause of death, and current therapies for many cancers are inadequate. Hence, increasingly more studies are seeking precise therapy of cancer and solutions for drug resistance.

Over the last few decades, nanotechnology has been increasingly used in medicine, including applications for diagnosis, treatment, and tumor targeting in a safer and more effective manner. Nanoparticle (NP)-based drug delivery systems have shown many advantages in cancer treatment, such as good pharmacokinetics, precise targeting of tumor cells, reduction of side effects, and drug resistance . NPs used in drug delivery systems are usually designed or chosen based on their size and characteristics according to the pathophysiology of the tumors. Mechanically, nano-carriers in cancer therapy target to tumor cells through the carrier effect of NPs and the positioning effect of the targeting substance after being absorbed. Next, they release the drugs to tumor cells in order to induce killing. Drugs located on the inside of the nano-carriers include traditional chemotherapy agents and nucleic acids, indicating that they can play a role in both cytotoxic and gene therapy .

NPs IN CANCER THERAPY

The NPs used in medical treatment usually have specific sizes, shapes, and surface characteristics as these three aspects have a major influence on the efficiency of the nano-drug delivery and thus control therapeutic efficacy . NPs with a diameter range of 10 to 100 nm are generally considered suitable for cancer therapy, as they can effectively deliver drugs and achieve enhanced permeability and retention (EPR) effect. Smaller particles can easily leak from the normal vasculature (less than 1–2 nm) to damage normal cells and can be easily filtered by kidneys (less than 10 nm in diameter), while particles that are larger than 100 nm are likely to be cleared from circulation by phagocytes. Moreover, the surface characteristics of NPs can influence their bioavailability and half-life. For instance, NPs that are coated with hydrophilic materials such as polyethylene glycol (PEG) lessen the opsonization and therefore avoid clearance by the immune system. Therefore, NPs are generally modified to become hydrophilic, which increases the time period of drugs in circulation and enhances their penetration and accumulation in tumors. Collectively, the various characteristics of NPs determine their therapeutic effect in cancer management. Different types of NPs for cancer therapy are shown in

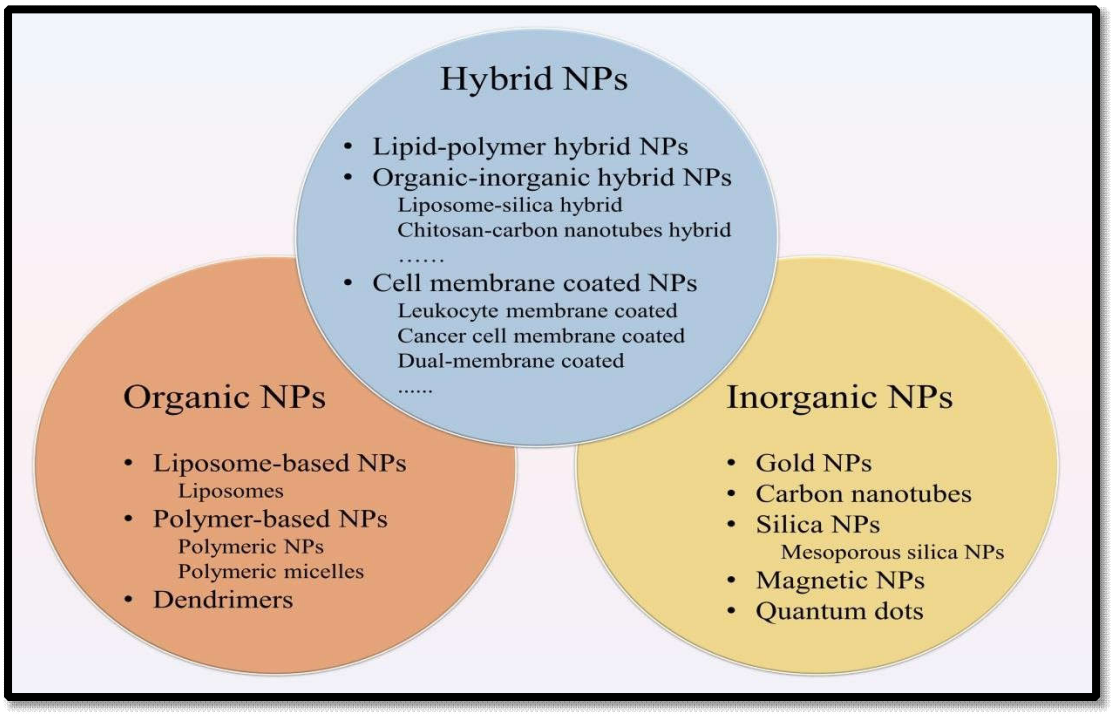


Figure 1 and the following text will describe their respective advantages in tumor treatment.

ORGANIC NPs

Organic NPs have been widely explored for decades and contain many types of materials.

Liposome, the first nano-scale drug approved for clinical application, consists of an outer lipid layer and a core entrapping either hydrophobic or hydrophilic drug. Liposomes can carry out many functions by modifying the lipid layer structure, including imitating the biophysical characteristics (e.g., mobility and deformation) of living cells, which can help achieve the purpose of more effective therapeutic drug delivery. With decades of research, the development of liposomes has gone through several generations. With regard to cancer therapy, liposomes provide a good platform for in vivo delivery of many anti-tumor drugs, such as doxorubicin and paclitaxel, among other chemotherapeutic agents, as well as nucleic acids.

INORGANIC NPs

Inorganic NPs have the advantages of a higher surface area to volume ratio. They have a wide and easily modified surface conjugation chemistry and facile preparation, although this usually occurs at the expense of poorer biocompatibility and biodegradability. The inorganic NPs that have been studied include gold NPs (AuNPs), carbon nanotubes (CNTs), quantum dots, magnetic NPs (MNPs), and silica NPs (SNPs). AuNPs are the most widely studied inorganic NPs, and mixed monolayer protected clusters based on the gold core are considered to be a promising candidate in the drug delivery system. The gold core is inert and non-toxic, and surface-functionalized AuNPs have been proven to enhance drug accumulation in tumors as well as to overcome the drug resistance. Moreover, AuNPs are thought to be involved in multimodal cancer treatment including gene therapy, photothermal therapy and immunotherapy.

HYBRID NPs

As both organic and inorganic NPs have their own advantages and disadvantages, combining the two in a single hybrid drug delivery system endows the multifunctional carrier with better biological properties that can enhance treatment efficacy as well as reduce drug resistance.

Lipid-polymer hybrid NPs, which consist of an inner polymeric core and a lipid shell, have been demonstrated to be a promising drug delivery platform in the treatment of pancreatic cancer, breast cancer, and metastatic prostate cancer. This type of hybrid NPs combines the high biocompatibility of lipids with the structural integrity provided by polymer NPs, and are therefore capable of encapsulating both hydrophilic and hydrophobic drugs in order to achieve a better therapeutic effect . Meanwhile, this system can be effectively internalized by cancer cells and avoids fast clearance by the reticuloendothelial system.

The combination of organic and inorganic hybrid nano- materials is a common method of NP design. For example, a liposome-silica hybrid (LSH) nanoparticle consists of a silica core and a surrounding lipid bilayer and has been synthesized and shown to be valid in delivering drugs to kill prostate and breast cancer cells. The LSH nanoparticle has also been reported to offer a platform for the synergistic delivery of gemcitabine and paclitaxel to pancreatic cancer in a mouse model of the disease created an advanced nano-in-micro platform by assembling the porous silicon NPs and giant liposomes onto a microfluidic chip, and co-delivery of synthesized DNA nanostructures and drugs in this platform was proven to significantly enhance cell death of doxorubicin-resistant breast cancer cells. Furthermore, CNTs and the chitosan hybrid NP used in the vectorization of methotrexate to lung cancer cells tend to increase anticancer activity while reducing drug toxicity on normal cells. Moreover, half-shells of metal multilayers (such as manganese and gold) and PLGA hybrid NPs have the potential of combining targeted drug delivery and hyperthermia, which can enhance the destruction of tumor cells.

MECHANISMS OF TARGETING

Targeting of cancer cells specifically is a vital characteristic of nano-carriers for drug delivery, as it enhances the therapeutic efficacy while protecting normal cells from cytotoxicity. Numerous studies have been carried out to explore the targeting design of NP-based drugs. In order to better address the challenges of tumor targeting and the nano-carrier system design, it is crucial to first understand tumor biology and the interaction between nano-carriers and tumor cells. The targeting mechanisms can be broadly divided into two categories, passive targeting and active targeting (**Figure 2**).

PASSIVE TARGETING

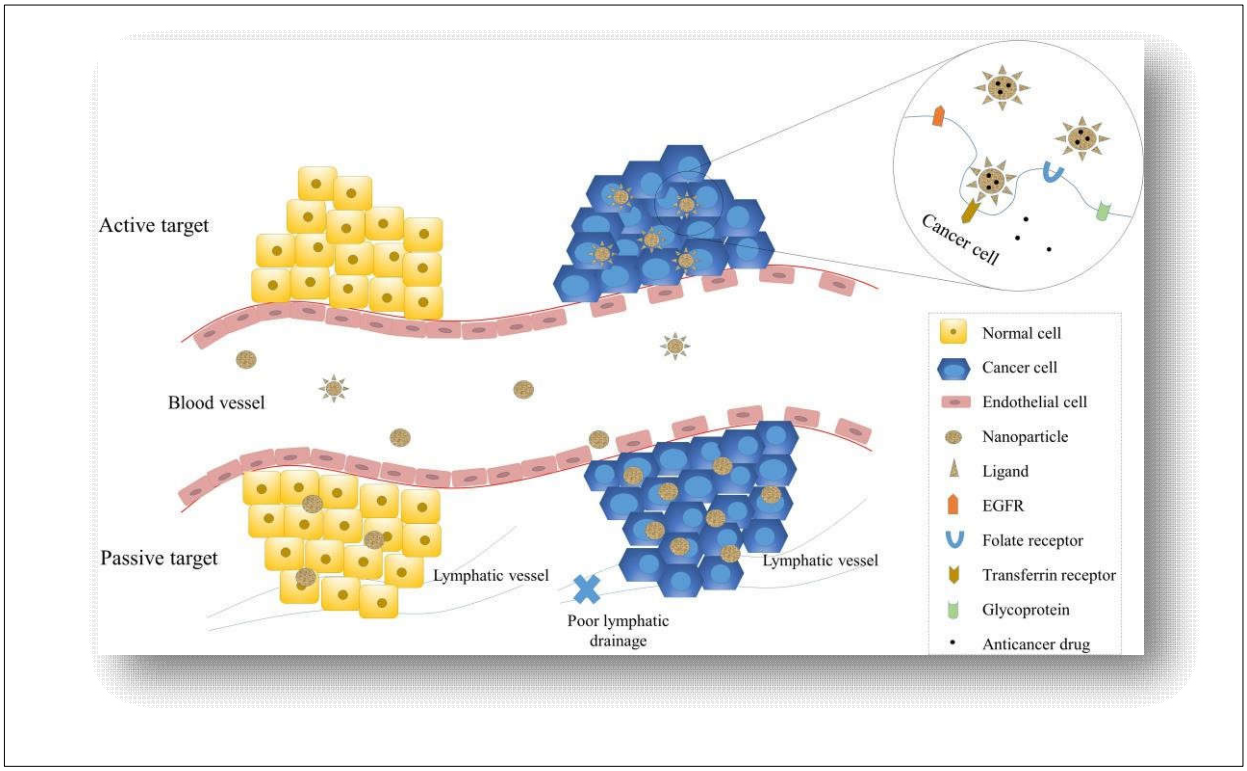
Passive targeting is designed to utilize the different characteristics of tumor and normal tissue. In passive targeting, the drugs are successfully delivered to the target site in order to play a therapeutic role. High proliferation of cancer cells induces neovascularization, and large pores in the vascular wall led to a worsening permselectivity of tumor vessels compared to normal vessels. The rapid and defective angiogenesis enables macromolecules, including NPs, to leak from blood vessels that supply the tumor and accumulate within tumor tissue. Meanwhile, the poor lymphatic drainage associated with cancer increases the retention of NPs, allowing the nano- carriers to release their contents to tumor cells. These processes cause the EPR effect, one of the driving forces of passive targeting. The EPR effect is influenced by the size of NPs, as many studies have demonstrated that smaller NPs have better penetrability but do not leak into normal vessels. On the other hand, larger particles are more likely to be cleared by the immune system.

ACTIVE TARGETING

Active targeting specifically targets cancer cells through direct interactions between ligands and receptors. The ligands on the surface of NPs are selected to target the molecules that are overexpressed on the surface of cancer cells, which allows them to distinguish targeted cells from healthy cells. The interaction between ligands on NPs and the receptors on the surface of cancer cells induces receptor-mediated endocytosis, which allows internalized NPs to successfully release therapeutic drugs. Therefore, active targeting is particularly suitable for macromolecular drug delivery, such as proteins and siRNAs. The types of targeting moieties include monoclonal antibodies, peptides, amino acids, vitamins, and carbohydrates. These ligands specifically bind to receptors on targeted cells, and the widely investigated receptors include transferrin receptor, folate receptor, glycoproteins, and the epidermal growth factor receptor (EGFR).

Targeting to Cancer Cells

Transferrin, a type of serum glycoprotein, functions to transport iron into cells. Transferrin receptors are overexpressed in most solid tumor cells and are expressed at low levels in normal cells. Thus, transferrin-conjugated NPs are used as an active targeting method to deliver drugs for cancer treatment. Compared to unmodified NPs, transferrin-modified NPs have been shown to exhibit higher cellular uptake efficiency and enhanced intracellular delivery of drugs. Moreover, evidence indicates that transferrin conjugated polymeric NPs play a significant role in overcoming drug-resistant chemotherapy.



Targeting to Endothelium

Some NPs do not directly target cancer cells but instead have an effect on angiogenesis, which is another method of cancer treatment. The interaction between vascular endothelial growth factor (VEGF) and VEGF receptors (VEGFRs) plays an essential role in vascularization. Additionally, targeting VEGFR-2 and VEGFR-3, two major VEGF receptors,simultaneously by liposomes has been shown to enhance therapeutic efficacy.

MECHANISMS OF NPS IN OVERCOMING DRUG RESISTANCE

Drug resistance is still a major problem in cancer treatment, despite the fact that methods of cancer therapy are increasing. Multidrug resistance leads to a failure of various types of cancer treatments, leading to cancer progression and poor prognosis. The mechanisms of tumor drug resistance include cellular and physiological factors, such as overexpression of ATP binding cassette (ABC) transporters (e.g., effiux transporter), defective apoptotic machineries, interstitial fluid pressure, and acidic and hypoxic tumor microenvironment. Nanotechnology applied to drug delivery for cancer treatment has been shown to play a significant role in overcoming drug resistance (**Table 1**).

TARGETING EFFLUX TRANSPORTERS

Effiux transporters belong to a family of ABC transporters that have been proven to play essential roles in drug resistance. Effiux transporters reduce intercellular drug concentration by pumping the drug out of the cell, leading to a failure of treatment. Among them, P-glycoprotein (P-gp), one of the most widely investigated effiux transporters, is overexpressed in several drug- resistant tumors. In addition, high expression of P-gp has been associated with poor treatment-response in many tumors, such as breast and ovarian cancer . A myriad of studies have demonstrated that

some chemotherapeutics-loaded NPs can bypass the exposure of anti- tumor drugs to effiux transporters, since NPs largely enter the cell through endocytosis instead of diffusion and release the drug at a perinuclear site within the cell, away from cell membranes and effiux pumps. The nanoparticle- based drug delivery system can modify the control of drug release. For example, several researches have utilized low pH level and redox as triggers for drug release in NPs. Furthermore, NPs, such as polymers, also act as MDR modulators. For instance, micelles based on amphiphilic deblock polymer of N-(2hydroxypropyl) meth acrylamide (HPMA) and poly (propylene oxide) block (PPO) are able to inhibit P-gp.

Targeted pathway	Mechanisms (in addition to antitumor efficiency)	Drugs	References
Efflux transporters	Bypass efflux transporters	NP itself	(Murakami et al., 2011)
	Inhibit efflux transporters	COX-2 inhibitors	(Zhang S. et al., 2019)
		P-gp-targeted siRNA	(Patil et al., 2010; Navarro et al., 2012)
		miRNA-495	(He et al., 2019)
Apoptosis	Inhibit anti-apoptosis pathway	Bcl-2-targeted siRNA	(Wang et al., 2006; Saad et al., 2008; Chen et al., 2009; Choi et al., 2019)
		NF-κB inhibitors (pyrrolidine Di thiocarbamate/curcumin)	(Fan et al., 2010; Misra and Sahoo, 2011; Zhao et al., 2019)
	Activate pro-apoptosis pathway	Ceramide	(Devalapally et al., 2007; van Vlerkenet al., 2010)
		p53 gene therapy	(Prabha and Labhasetwar, 2004; Choiet al., 2008)
Efflux transporters and apoptosis	Inhibit efflux transporter expression meanwhile promoting apoptosis through down-regulationof Bcl-2 and NF-κB expression	Bcl-2 convertor gene-loaded NPs	(Cheng et al., 2018)
		Resveratrol	(Zhao et al., 2016; Singh et al., 2018)
	Inhibit efflux transporters and promoteapoptosis by inducing mitochondrial outermembrane permeabilization	Mitochondria-targeted NPs	(Wang et al., 2020)
Hypoxia	Silence the HIF-1α gene	HIF-1α siRNA	(Zhao et al., 2015; Luan et al., 2018; Hajizadeh et al., 2020)
	Inhibit the function of HIF-1α	HIF-1α inhibitors	(Reddy et al., 2011)
	Indirectly downregulate HIF-1α expression	Inhibitors of the PI3K/Akt/mtor pathway	(Zhang et al., 2018)
		HSP90 inhibitors	(Long et al., 2018)

Abbreviations: Bcl-2 = B cell lymphoma-2; COX-2 = cyclooxygenase 2; HIF-1α = hypoxia-inducible factor 1α; HSP90 = heat shock protein 90; NF-κB = nuclear factor kappa B; NPs = nanoparticles; P-gp = P-glycoprotein; PI3K = phosphoinositol-3-kinase; siRNA = small interfering RNA.

more effective platform to deliver ceramide into cancer cells that carry p53 missense mutations, an important cancer phenomenon . As p53 plays a significant role in apoptosis, reinstating p53 function or other tumor suppressors is considered a potential way to overcome drug resistance in cancer. Therefore, p53 gene therapy utilizing a nanoparticle-based delivery system has been further researched. Transfecting the p53 gene by cationic solid lipid NPs and PLGA has been reported in lung and breast cancer cells, respectively. These results show the effective induction of apoptosis and inhibition of tumor growth.

Furthermore, some NP-based drug delivery systems function by inhibiting effiux pumps, as well as promoting apoptosis. utilized an amphiphilic cationic NP complex encapsulating paclitaxel and

the Bcl-2 convertor gene in order to inhibit drug-resistant liver cancer cell growth. Findings from the study showed that this NP complex impaired P-gp-induced drug effiux and the activation of apoptosis. This work is a pioneer study that was able to successfully overcome both pump- and non-pump-mediated drug resistance. In addition, co-delivery of doxorubicin and resveratrol in NPs have shown significant cytotoxicity on doxorubicin- resistant breast cancer cells by inducing apoptosis throughthe down-regulation of Bcl-2 and NF-κB expression, as wellas through the inhibition of effiux transporter expression. Similarly, another study demonstratedthe effectiveness of folic acid-conjugated planetary ball-milled NPs that were encapsulated with resveratrol and docetaxel for the treatment of multidrug-resistant prostate cancer. Results indicated that the expression of anti-apoptotic genes was down- regulated, while the ABC-transporter markers were inhibited. Moreover, mitochondria targeted NPs also showed an effect on both effiux transporters and apoptotic pathway.

TARGETING HYPOXIA

Hypoxia is another factor that contributes to multidrug resistance. Due to irregular blood vessels, as well as the increased oxygen demand of rapidly proliferating cancer cells, some cancer cells are often in a hypoxic state. Hypoxia induces the drug resistance of tumors in many ways. For instance, slowly dividing cells in hypoxic regions can escape from cytotoxic chemotherapeutics such as alkylating agents and antibiotics. Additionally, hypoxia produces a gradient ofoxygen within the tumor, thereby increasing tumor heterogeneity and promoting a more aggressive phenotype. Besides, hypoxia has also been proven to mediate the overexpression of drug effiux proteins. During the process, hypoxia-inducible factor 1α (HIF1α) plays an essential role, and overexpression of HIF-1α has been observed in many human cancers. Therefore, targeting HIF-1α is another treatment method for overcoming drug resistance.

There is also an extensive study on the application of NPs in the treatment of hypoxia. Silencing the HIF-1α gene is one of the ways to inhibit hypoxic environment. Several studies have reported the effectiveness of nano systems containing HIF-1α siRNA to overcome drug resistance in cancer HIF-1α inhibitors have also shown therapeutic efficacy in reducing hypoxia-mediated drug resistance inaddition to directly inhibiting the function of HIF-1, indirect inhibition of HIF-1 signaling has also been previously considered. For example, the PI3K/Akt/mTOR pathway can regulate the expression of HIF-1α, and the inhibition of this pathway down-regulates HIF-1α expression, thereby enhancing the sensitivityof MDR cells to cancer treatment.

In this process, NPs, such as PLGA-PEG and PEGylated and nonPEGylated liposomes, can offer better platforms to achieve combination therapy. In addition, heat shock protein 90 (HSP90) is required for HIF-1 transcriptional activity, andinhibition of HSP90 can also down-regulate HIF-1α expression. The HSP90 inhibitor in 17AAG-loaded NPs hasbeen shown to dramatically improve bladder cancer treatment.

THE ROLE OF NPS IN CANCER IMMUNOTHERAPY

The development of immunotherapy has brought cancer treatment into a new era. NPs not only play an important role in delivery chemotherapy but have also shown great potential for applications in immunotherapy. Cancer immunotherapy is mainly achieved by activating the antitumor immune response. NP-associated immunotherapy includes nano vaccines, artificial antigen-presenting cells (aAPCs), and targeting of the immunosuppressed tumor microenvironment (TME).

Nano vaccines deliver tumor-associated antigens (TAAs) and adjuvants to APCs, such as dendritic cells (DCs). Additionally, NPs can be used as adjuvants themselves to increase APC antigen presentation and promote DC maturation, leading to the activation of the anti-tumor function of cytotoxic T cells. NPs, such as liposomes, gold NPs, PLGA NPs, micelles, and dendrimers all have the capability of cytoplasmic delivery of TAAs into DCs, thus enhancing the immune response against tumor cells. Among different types of NPs, inorganic NPs such as mesoporous silica and polymers such asacetylated dextran (AcDEX) have been shown to function as an adjuvant in immunotherapy, leading to a stimulation of the immune response. Unlike nano vaccines, artificial APCs function with MHC-antigen complexes and co- stimulatory molecules that directly bind to T cell receptors (TCRs) and co-stimulatory receptors on T cells, respectively, resulting in T cell activation. Targeting the immunosuppressive TME is mainly achieved by targeting tumor-associated macrophages (TAMs), myeloid derived suppressor cells (MDSCs), and regulatory T cells (Tregs), all of which are important cell types in the TME. Furthermore, in order to minimize interactions with the reticuloendothelial system, NPs are usually modified with PEG.

CONCLUSION AND FUTURE PERSPECTIVES

Nanotechnology applied to cancer therapy has led to a new era of cancer treatment. Various types of NPs, including organic and inorganic NPs, have already been widely used in the clinical treatment of several cancer types. Compared to traditional drugs, NP-based drug delivery systems are associated with improved pharmacokinetics, biocompatibility, tumor targeting, and stability, while simultaneously playing a significant role in reducing systemic toxicity and overcoming drug resistance. These advantages enable NP-based drugs to be widely applied to chemotherapy, targeted therapy, radiotherapy, hyperthermia, and gene therapy.

Moreover, nanocarrier delivery systems provide improved platforms for combination therapy, which helps overcome mechanisms of drug resistance, including effiux transporter overexpression, defective apoptotic pathway, and hypoxia tumor microenvironment. According to different mechanisms of MDR, NPs that are loaded with varieties of targeting agents combined with cytotoxic agents can achieve the reversal of drug resistance.

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