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Mechanisms and applications of antitumor immunotherapy of responsive drug-loaded nanoparticles in breast cancer

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Abstract: During the chemotherapy of tumors, the cytotoxic effect of drugs is vital to kill tumor cells, and the delivery of a chemotherapeutic agent is of great importance for optimal therapeutic effects. The high *in vivo* clearance rate and low delivery efficiency of conventional chemotherapeutic agents affect the therapeutic effect. In recent years, the responsive drug delivery nanosystem has received increasing concern owing to its excellent biocompatibility, stable delivery performance, and controlled drug release strategies. To lucidly explain the cytocidal and immunotherapeutic effects of such responsive nanosystems in breast cancer, this review discusses the various stimuli and responses of drug-loaded liposomal nanosystems. The light/magnetic response of drug-loaded bionic membranes nanosystems and the heat/magnetic response of drug-loaded iron oxide nanosystems are also elaborated. Their cancer cell-killing efficacy and antitumor immunotherapeutic effects are also scrutinized.

Abbreviations

PEG	Polyethylene glycol
FA	Folic acid
HA	Hyaluronic acid
CIS	Cisplatin
EPI	Epirubicin
Hol	Honokiol
PTX	Paclitaxel
AND	Adenosine
oxHA	Oxidized HA
CD44	CD44-receptors
Cu^{2+}	Copper ions
TPGS	D-α-tocopheryl polyethylene glycol succinate
PBAE	A non-toxic degradable pH-sensitive polymer-poly (β-amino ester)
SS-PC	Disulfide phosphatidylcholine
EBP	endoglin-binding peptide
CHEMS	Cholesteryl hemisuccinate
IDO	Indoleamine 2,3-dioxygenase
DTX	Docetaxel
shRNA	Short hairpin RNA
Cys	Cystamine hydrochloride
Poly IC	Polycytidylic acid
SPIONs	Superparamagnetic iron oxide nanoparticles
DMSA	Dimercaptosuccinic acid
MNPs	Magnetic nanoparticles
PDC	Phosphatidylcholine
DOPE	1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine
DSPE	1,2-distearoyl-sn-glycero-3-phosphoethanolamine
DSPE	1,2-distearoyl-sn-glycero-3-phospho ethanol amine

Introduction

Breast cancer is a malignant tumor that seriously endangers human health. In 2020, 2261 thousand new cases of breast cancer and 685 thousand deaths from breast cancer in women were documented worldwide (Siegel *et al.*, 2021). Cancer immunotherapy is an anti-tumor strategy that activates the body's immune function to improve the recognition of tumor cells by the immune system. Conventional cancer immunotherapies in use include T-lymphocyte (T cell) activation of type 1 cytokines including interleukin 2 (IL-2) and interleukin 15 (IL-15), immune checkpoint inhibitors, and depletion of immunosuppressive cells. Research has illustrated that immunotherapy has some utility in clinical applications. However, the systemic

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TABEL 1

Mechanisms and applications of drug-loaded nanosystems

Type of nanoparticles	Composite	Drug	Application	Assay	Responsive strategy	References
Drug-loaded liposomes nanosystems	PEG and FA	CIS and EPI	Synergistic chemotherapy	*In vivo* and *in vitro* experiments	pH	Moammeri *et al.* (2022)
	PBAE and FA	Hol	Chemotherapy	*In vivo* and *in vitro* experiments	pH	Zhang *et al.* (2021a)
	TPGS, DOPE, HSPC, CHEMS, CHO and AND	PTX	Chemotherapy	*In vivo* and *in vitro* experiments	pH	Chaudhari *et al.* (2022)
	DOTAP, DOPE, CHO and PC	DTX and shRNA	Biotherapy and chemotherapy	*In vivo* and *in vitro* experiments	pH	Swami *et al.* (2021)
	DSPE, PEG and Cu^{2+}	PTX and DOX	Chemotherapy	*In vivo* and *in vitro* experiments	GSH	Yu *et al.* (2020)
	Porphyrin–phospholipid conjugate	IDO	Photoimmunotherapy	*In vivo* and *in vitro* experiments	GSH	Liu *et al.* (2019a)
	PDC, oxHA, Cys and CD44	DOX	Chemotherapy	*In vivo* and *in vitro* experiments	pH and GHS	Curcio *et al.* (2022)
Drug-loaded bionic membrane nanosystems	ICG, DCT, breast cancer membrane	poly(lactic-co-glycolic acid)	Phototherapy and Chemotherapy	*In vivo* and *in vitro* experiments	Photo-activation	Zhao *et al.* (2020)
	GTe, TM, BM	Tellurium	Radiotherapy and immunotherapy	*In vivo* and *in vitro* experiments	X-rays	Pan *et al.* (2022)
	Mimetic nanoparticles, IR780, PLGA	DOX	PTT	*In vivo* and *in vitro* experiments	Photoresponse	Pei *et al.* (2020)
	SPIO, CHINPs	HMME	PTT and SDT	*In vivo* and *in vitro* experiments	Laser and US	Lin *et al.* (2022)
	O2-PPSiI, ultrathin silica, PLGA, PFOB	PTx	PTT	*In vivo* and *in vitro* experiments	NIR	Zhang *et al.* (2022b)
	Biomimetic magnetic nanoparticles and magnetosome proteins	DOXO	Chemo-thermal therapy	*In vivo* and *in vitro* experiments	GMF and/or AMF	Oltolina *et al.* (2020)
Drug-loaded iron oxide nanosystems	Iron oxide and Silica-PEG	EBP, DOX and Poly IC	Chemotherapy and immunotherapy	*In vivo* experiments	pH	Mu *et al.* (2021)
	SPIONs and PEG	DOX	Chemotherapy	*In vitro* experiments	pH	Aghanejad *et al.* (2018)
	SPION and HA	DOX	Chemotherapy	*In vitro* experiments	Laser	Vyas *et al.* (2015)
	SPIONs, lauric acid and human serum albumin	paclitaxel	Chemotherapy	*In vivo* and *in vitro* experiments	Magnetic	Lugert *et al.* (2019)
	MNPs and DMSA	DOX	Magnetic hyperthermia	*In vivo* and *in vitro* experiments	Thermal	Piehler *et al.* (2020)

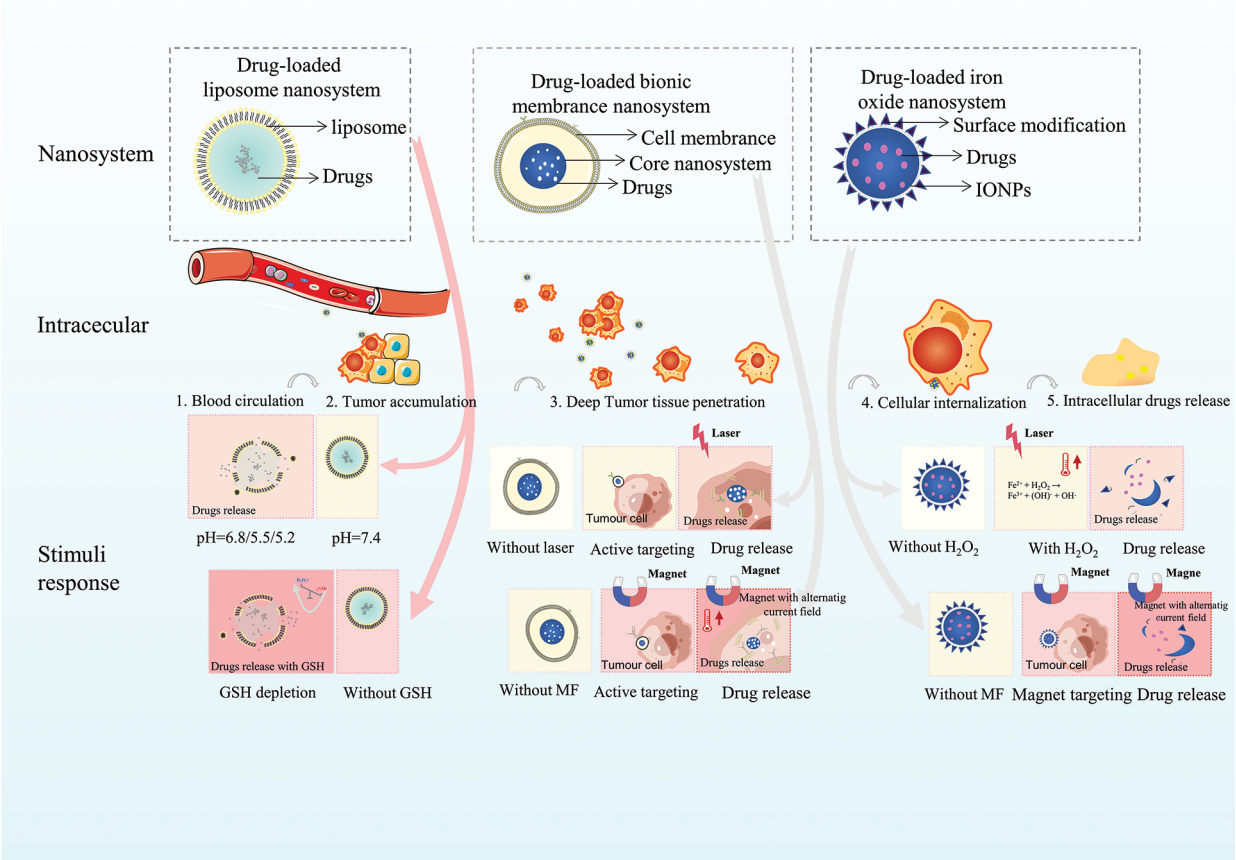

FIGURE 1. The stimuli and response mechanisms of drug-loaded nanosystems.

administration of immunotherapeutic agents can lead to their distribution in normal tissues as well, resulting in side effects on normal tissues. The non-specific off-target activation of the immune system also causes autoimmune-like damage to normal tissues. Theoretically, an ideal therapy probably should activate the local host immune response while selectively killing cancer cells.

The short circulation time, low targeting efficiency, poor tumor permeability, and uncontrolled drug release of conventional tumor-targeted drug delivery systems (DDS) limit their further clinical applications. The preparation of liposomal nanoparticles with the controlled release is one of the solutions. The excellent biocompatibility of liposomal drugs, the natural targeting advantages of bionic membranes with the advantages of liposomes, and the magnetic targeting advantages of iron oxide nanoparticles all provide new ideas for antitumor work with nanomaterials, as shown in Table 1. With different stimulus-response mechanisms, nanoparticle-based stimulus-responsive DDS can demonstrate more efficient trigger sensitivity and synergistic controlled release effects through rational "switch" design, effectively improving the side effects of antitumor therapy. As illustrated in Fig. 1, we present a review of liposomes, cell membrane biomimetic-modified nanoparticles, and iron oxide nanoparticles as cases of responsive nanoparticles which is indispensable in drug delivery and tumor therapy.

Drug-Loaded Liposome Nanosystems

Clinical experiments with drug-loaded liposomes

Liposomes are biofilm drug carriers with high biosafety, high bioavailability, high delivery potential, non-toxicity, and non-immunogenicity, and are considered to be efficient DDS (Shah *et al.*, 2020). The mobility and amphiphilic molecular properties of phospholipid bilayers empower liposomes with the ability to protect their contents and control the drug release, as well as enhance the solubility of water- and fat-soluble drugs (Inglut *et al.*, 2020; Witika *et al.*, 2020; Thi *et al.*, 2021). In 1995, Food and Drug Administration (FDA) approved the first liposomal adriamycin drug doxorubicin hydrochloride (Doxil) for clinical use. Doxil has shown excellent cancer inhibition in various solid tumors (Paridaens *et al.*, 2000). At present, the main liposomal adriamycin drugs clinically approved for breast cancer treatment are Doxil®, Lipodox®, Liposomal doxorubicin (Liposomal), and non-PEGylated Myocet®. In recent years, Chinese generic liposomal adriamycin molecules (such as Fudan Zhangjiang's "Ribodox", ShiyaoOuyi's "Domesol" and Changzhou Jinyuan's "Lixin") have also been approved for marketing. These FDA-approved liposomal adriamycin chemotherapy drugs are in different stages of breast cancer treatment clinical trials. A single polyglycolylated liposomal adriamycin has reached a Phase IV clinical trial (NCT00604968) and passed the efficacy and safety

evaluation for treatment in older women (Green *et al*., 2011). Long-circulating liposome Doxil is in phase III clinical trial (NCT00003782) and has demonstrated efficacy in patients with axillary lymph node metastases. Further, the combination of chemotherapeutic agents with different killing mechanisms (Doxorubicin, Cyclophosphamide, and Paclitaxel) has demonstrated better efficacy than single-agent chemotherapy strategies in a phase III clinical trial (NCT00003782) (Budd *et al*., 2015).

Mechanism of cell killing and immune action of drug-loaded liposomes

The above-mentioned drug-loaded liposomes have been well used in clinical applications. Researchers have further investigated the mechanism of drug-loaded liposomes, among which Doxil has been most intensively studied. Studies have shown that Doxil drives cell death mainly through oxidative stress, accumulation of damaged organelles, and mitochondrial dysfunction. For example, Doxil can mediate cell death by enhancing tumor protein 53 (P53) signaling, resulting in decreased levels of GATA binding protein 4 (GATA-4) expression and protein 53 (p300) degradation. Glutathione S-transferase P1 (GSTP1) can be utilized to promote cellular autophagy by blocking the phosphatidylinositol-3-kinase and the mammalian target of rapamycin (PI3K-Akt-mTOR) pathway signaling through interaction with phosphoinositide 3-kinase (PI3K), protein 110α (p110α). Additionally, the protein transferrin receptor (TNFR)-associated death protein can be activated by transferrin receptor 1 (TRFR1) through tumor necrosis factor-α (TNF-α), leading to necrotic vesicle formation and release of inflammatory factors to induce the cell death eventually (Chen *et al*., 2011; Effimia, 2021; Wang *et al*., 2021b).

Meanwhile, the mechanism of liposomal adriamycin-triggered antitumor immune action also has received attention. A study by Dastmalchi *et al*. (2020) found that some chemotherapeutic agents, including liposomal adriamycin, can mediate immunogenic cell death (ICD) at low doses. Besides, the chemotherapeutic agent can mediate danger signals release and trigger damage-associated molecular patterns (DAMPs), thus enhancing anti-tumor immune efficacy *in vivo* (Ding *et al*., 2021). Liposomal adriamycin could also trigger immunogenic effects by inducing membrane exposure of highly immunostimulatory DAMPs, allowing low amounts of iDAMP/PGE2 to be released into the tumor microenvironment (TME) (Nikolos *et al*., 2022). Although chemoimmunotherapy has shown some effectiveness, a possible side effect of drug resistance and systemic immunosuppression could also emerge (Tokumaru *et al*., 2020). Preclinical studies have indicated that biomaterial-based nanocarriers might enhance the immunogenicity of ICD and reduce side effects (Mishchenko *et al*., 2019). In a recent study, Kim *et al*. (2022) prepared DP-NPs liposomes with sustained release that induced ICD. In local immunotherapy experiments in mice with breast cancer, increased infiltration of CD4 and CD8 T cells in the target area and triggering of systemic T cell responses induced strong local and systemic anti-tumor immunity (Gao *et al*., 2021). Drug-loaded liposome systems can compensate for the low efficiency of conventional therapeutic regimens, such as the systemic administration of drugs that disrupt the homeostasis of the immune system at non-target sites and produce lethal toxic effects of systemic immune homeostasis (Jin *et al*., 2021).

Currently, nano-drug delivery carriers are mainly used for targeted delivery of immunogenic chemotherapeutic drugs of the immunomonoclonal class (anti-programmed death l (PD-1), anti-programmed death ligand 1 (PD-L1), anti-cluster of differentiation 47 (CD47) antibodies, etc.). For these, tumor antigens are released and the damage-associated molecular patterns (DAMPs) is triggered by targeting tumor cells ICD. Therefore, the anti-tumor immunity of natural killer (NK) cells was enhanced. Further, the activity of antigen-presenting cells and cytotoxic T cells was promoted, and the expression of immunosuppressive molecules was reduced in the tumor immune microenvironment. The cytotoxic T-cell production and antigen presentation were increased in secondary lymphoid organs in the peripheral immune system, thereby enhancing cancer immunity (Shi *et al*., 2019; Zhang *et al*., 2021b). Among the new immunotherapeutic strategies, liposome-based drug delivery systems are now commonly used for vaccination, tumor normalization, tumor modulation, tumor targeting, and combination therapy (Gu *et al*., 2020). In addition to immunotherapy, nanoplatforms can be combined with existing antitumor regimens including radiotherapy, phototherapy, or chemotherapy to improve clinical treatment effects (Raju *et al*., 2022). In short, with the targeting performance of the liposome DDS, it is not only favorable to the effective drug delivery in tumor tissues but also solves the insufficient recruitment of target dendritic cells (DCs) and the interference of immunosuppressive cells or factors in the TME, thereby reducing the possibility of tumor recurrence (Soliman *et al*., 2022). Therefore, the smarter drug-loaded liposome delivery system is the key to further enhancing the antitumor effect.

Therapeutic and immunotherapeutic effects of responsive drug-loaded liposomes

Responsive nanoliposomes are capable of stable delivery under normal physiological conditions and can be triggered by specific stimuli to undergo carrier disruption (swelling, surface charge reversal, chemical bond breakage, etc.), thereby prolonging blood circulation and enhancing tumor cell uptake (Li *et al*., 2022; Zhang *et al*., 2022a). Responsive drug-loaded liposomes have developed rapidly, among which Thermodox® temperature-sensitive liposomes have successfully been used for advanced clinical stages (like breast cancer stage III). Under the performance of temperature-responsive polymers, drug-loaded temperature-sensitive liposomes can maintain structural integrity at room temperature, while the structure disintegrates at high temperatures. Therefore, by virtue of the relationship between temperature and the structure of heat-sensitive liposomes, the manufactured drug-loaded heat-sensitive liposomes can control drug release (Yuba, 2020).

Currently, common responsive drug-loaded liposomes include both endogenous responses (TME responses such as pH responsiveness, enzyme responsiveness, hypoxia

response, and redox response) and exogenous responses (physical stimuli such as light heat, magnetic heat, ultrasound) (Sethuraman *et al.*, 2021). Endogenous mechanical stimuli (pressure, tension, shear) can lead to changes in the mechanical properties of the carrier, which in turn release the drug. The responsive nanoliposomes are subjected to specific conditions (such as acidic pH, high enzyme expression, and high redox) in the TME, and the carrier composition sends conformational changes or chemical changes that cause the removal of the outer protective layer of the carrier and the exposure of the functional components for controlled drug release. The rational design of the carrier "switch" can ensure the stable passage of drug molecules through the complex *in vivo* environment at the expected bioavailability while maximizing the controllability of drug release, tumor tissue specificity, and stimulus-response sensitivity under the premise of therapeutic safety.

Response mechanism and antitumor immunotherapy of pH-responsive drug-loaded liposomes

The tumor microacidic environment is related to tumorigenesis, progression, and development of drug resistance. The cells and tissues in tumor foci in the human body accumulate acidic metabolites in the tumor interstitium, resulting in a slightly acidic (pH = 6.5–7.2) overall environment in the tumor interstitium in contrast to normal tissue sites (pH = 7.4) (Stubbs *et al.*, 2000). Low pH and abnormal vascular systems can hinder the efficacy of drug therapy in solid tumors (Sharma *et al.*, 2006). Based on low pH, high redox, and higher levels of certain enzymes of the TME, pH-responsive liposome delivery carriers can be constructed by taking advantage of changes in polymorphic groups at different pH values (ionization, conformational changes, and solubility changes) or by introducing structures with acid-sensitive bonds such as hydrazone, imine, acyl hydrazone, and acetal/ketone bonds (Norioka *et al.*, 2017).

Stable delivery and controlled release of drugs enable pH-responsive liposomes to trigger local antitumor immune responses (Uthaman *et al.*, 2018). Accelerated drug release and tumor tissue permeation enrichment to promote drug uptake by tumor cells through five ways: sensitive chemical bond breaking, surface charge inversion, responsive removal of the outer protective layer of the carrier, exposure of functional components, and responsive changes in carrier morphology (Meng *et al.*, 2019). This strategy overcomes the deficiency of early or non-release of the drug while arriving target and can locally activate immunity and thus address the problem of a systemic toxic immune response. For example, liposomes constructed with pyridine betaine can reach the target area within 10 min and respond quickly to pH, thus releasing the drug for accumulation (Wang *et al.*, 2021a). Lipids with phosphatidylcholine membranes can undergo structural changes under acidic conditions in response to electrostatic and van der Waals interactions to release drugs (Omolo *et al.*, 2021). IN another study, de Oliveira Silva *et al.* (2019) constructed circulating pH-sensitive folate-coated doxorubicin-loaded liposomes, which increased the aggregation of drug carriers in the tumor mesenchyme through the enhanced permeability and retention (EPR) effect of liposomes, exocytosis, and active targeting ability of folate molecules. The low pH conditions in the TME could destabilize the hexagonal structure of 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) molecules and influence the cell membrane affinity. The endocytosis was enhanced to improve doxorubicin (DOX) uptake by cancer cells while also inducing p53-dependent apoptosis and autophagy under non-specific DNA damage and reactive oxygen species (ROS) generation, and enhancing the high immunogenicity in the TME to inhibit the depletion of immunosuppressive cells (regulatory T cells). All this mediated local antitumor immunity, enhanced the antitumor activity of drugs and avoided the occurrence of cardiotoxic side effects of systemic drug administration (Karanth and Murthy, 2007). A pH-sensitive targeted liposomal nanoparticle could improve the stability of the nanoparticle and prolong the circulation time *in vivo*, showing positive effects on the target tumor treatment (Zhang *et al.*, 2021a). Upregulation of the enzyme content in the TME and lowering the pH concurrently in tumor cells can use the design of a dual-response liposome delivery system. This can include pH-responsive and redox-responsive processes for intracellular internalization and intracellular drug release can lead to significantly higher toxic effects of drugs on breast cancer cells (Gao *et al.*, 2019). For example, the tumor suppression efficiency (~78.7%) of polymer-liposomes (LPDp) with the introduction of pH-responsive polymers was significantly enhanced ($p < 0.01$) antitumor effect than that of liposomes (LPp) containing PD-L1 inhibitors (~57.5%) and liposomes containing DOX (LD) in a single strategy (Liu *et al.*, 2019b).

Response mechanism and antitumor immunotherapy of GSH-responsive liposomes

Redox homeostasis is one of the necessary conditions to maintain homeostasis in the body. However, some cells in the TME can disrupt local homeostasis to increase local ROS production and glutathione tripeptide (glutamate, cysteine, glycine) or GSH levels (Mirhadi *et al.*, 2020). GSH is a tripeptide containing cysteine, which is an important intracellular reducing agent. The intracellular GSH concentration (0.5~10 mM) is higher than that in the extracellular fluid (2~20 μM). GSH and glutathione disulfide maintain the normal redox potential of cells (Santini *et al.*, 2000). Abnormal ROS production with high levels of GSH can be used to construct redox-responsive vectors, making the vectors highly redox-responsive and sensitive. High levels of GSH in tumor cells destabilize chemical bonds such as disulfide and diselenium bonds, and the high GSH concentration gradient difference in breast cancer tumor cells can be exploited to cause rapid cleavage of disulfide bonds in prodrugs by glutathione, leading to the release of active anticancer drugs (Kong *et al.*, 2016). Redox-responsive liposomes can solve the problem of drug resistance, reduce systemic immune side effects by improving local delivery efficiency, enter cells through passive diffusion of cell membranes, facilitate the cellular uptake of cell-penetrating peptides by endocytosis after completing the targeting step, and enhance

immunotherapeutic effects based on the TME using stimulus-response mechanisms to avoid endosomal escape (Naziris *et al.*, 2020). In a study, Luo *et al.* (2022) designed a fetal calf serum/calf serum (FCS/GCS) platform with high specificity and high efficiency tumor therapeutic nanoparticles using high intracellular GSH levels and hydrogen peroxide (H_2O_2) in tumors. Caspase activation mechanisms (pro-apoptotic factor cytochrome-C release, endoplasmic reticulum stress, etc.) can activate tumor necrosis factor receptor (TNFR) or Fas receptor to induce apoptosis and further trigger tumor antigen release while DAMP causes an increase in CD8 cells and cytotoxic T cells. The Fenton reaction is used to deplete GSH to produce large amounts of (•OH) to relieve the highly reductive immunosuppressive state of the TME, enhance the non-apoptotic regulatory cell death in the form of high iron levels, and enhance anti-tumor function (Pandrangi *et al.*, 2022).

Most of the currently clinically approved liposomes, including breast cancer treatments, are based on passive targeting strategies. Active targeting strategies are a viable option to address the limited phagocytosis and drug delivery of the endothelial system (Fraguas-Sánchez *et al.*, 2022). Small molecules, antibodies, peptides, and aptamers have been used as affinity molecules for liposomes to make progress in *in vivo* targeted delivery. Drug enrichment in the target region remains limited due to the complexity of the pathological environment, making active drug target development and clinical translation difficult (Liu *et al.*, 2021). In addition, although liposome synthesis has a certain degree of flexibility and freedom of design, the design of active targeting systems is complex. Further, the parameters of *in vitro* preparation do not meet the complex environment in the organism and are susceptible to instability (aggregation, fusion, precipitation, drug leakage) due to their composition, the loaded drug and the environment in which the carrier is located (Weber *et al.*, 2020; Ding *et al.*, 2022). Designing drug carrier systems with better homologous targeting ability, good immunogenicity, and high histocompatibility will be one of the directions to be tackled for future immunotherapy (Wang *et al.*, 2021b).

Nanobased formulations typically undergo a five-step cascade (Su *et al.*, 2017). For each step, the development of drug-carrying particles with the required specific nano-properties allows for responsive drug release and thus better adaptation to the complex environment and diverse biological barriers of tumor tissues, Liposomal systems are being used to carry drug nanoparticles or nucleic acids in new gene therapies (Ermilova and Swenson, 2020). For example, a new nanoparticle, low-density lipoprotein–N-succinyl chitosan–cystamine–urocanic acid (LDL-NSC-SS-UA) could carry both breast cancer resistance protein small interfering RNA (siRNA) and paclitaxel (PTX) for addressing breast cancer multi-drug resistance (Zhu *et al.*, 2017). The excellent biocompatibility of liposomal drugs, the advantages of natural targeting of bionanoplasmic membranes with the advantages of liposomes are promising. Additionally, magnetic targeting and inducing cell death via ferroptosis (iron) are advantages of iron oxide nanoparticles that provide new ideas for the anti-tumor immunization work with nanomaterials.

Drug-Loaded Bionic Membrane Nanosystems

Active targeting properties of drug-loaded bionic membrane nanosystems

In recent years, drug-loaded biomimetic membrane nanosystem has received the attention of researchers. On one hand, cell membranes of organic origin have low immunogenicity and excellent biocompatibility, which can effectively avoid the capture of nanocarriers by the monocyte-macrophage system and reticuloendothelial system, achieve long-lasting circulation in the body, and increase drug accumulation or inflammation. To assess the serum stability and half-life of blood circulation *in vivo*, a clearance half-life of 15.8 h was found for polyethylene glycolic nanoparticles and up to 39.6 h for nanoparticles (NPs) coated with erythrocyte membranes. On the other hand, specific targeting and homologous targeting capabilities can be obtained with the help of specific recognition units (proteins, polysaccharides, lipids, etc.) on the cell membrane. Currently, the main bionic membranes are erythrocyte membranes, exosome membranes, macrophage membranes, and tumor cell membranes. The nanoparticles modified with bionic membranes also showed cell targeting. Such cell membrane-encapsulated nanoparticles were composed of natural cell membranes with flexible biological properties and functionally integrated nanosystems which are indispensable in biomedical fields. The chemotaxis of some functional cells in the blood and the active recruitment of leukocytes such as neutrophils, and macrophages, allow carriers based on these cell membrane bionics to actively target inflammation and related diseases to bridge the active targeting shortcomings of liposomal drug carriers. For example, bionanoparticles modified with macrophage membranes could exhibit excellent diagnostic and therapeutic effects and drug delivery properties (good tumor targeting, biocompatibility, prolonged *in vivo* circulation time, and stable liposome structure) (Liang *et al.*, 2020). The use of exosomes, which are cell-derived vesicles has many advantages. Since they originate from their parental cells, they have an innate homing ability due to the presence of homologous surface adhesion proteins, mRNA, lipid molecules, DNA. Further, the expression of the surface transmembrane protein CD47 on the membrane facilitates the avoidance of immune clearance by the mononuclear phagocytic system, prolongs the circulation time of nanomaterials *in vivo*, and facilitates systemic delivery and targeting (Chen *et al.*, 2016; Ai *et al.*, 2018; Cheng *et al.*, 2021). A novel platelet mimetic dosage form prepared using platelet-loaded photothermal nanoparticles with immune agonists could ameliorate the uneven distribution of agents in phototherapy by exploiting the adhesion mechanisms of platelets. Thermal injury induced further post-injury which led to feedback-based additional platelet recruitment and improved the targeting capacity of the delivery system, thus enabling efficient combined tumor photothermal-immunotherapy in animal experiments (Lv *et al.*, 2021).

Active targeting has also been shown to improve the distribution of NPs within target tissues. The use of targeting peptides overexpressed on breast cancer cells resulted in enhanced penetration and uniform distribution

of NPs in a breast cancer mice model (Du *et al.*, 2019). Once the NPs reach the tumor target, to the sufficient release of the drug to achieve the anti-tumor effect is another problem to be solved. Therefore, bio-nanoparticles are being designed to respond to the stimulation of the TME or intracellular signals to achieve rapid and accurate release of anti-tumor drugs at the target site or focal site at high doses. This can enhance their accumulation, thus improving the therapeutic effect of cancer. Common ways in which nanomedicines respond include the organism's environmental factors (such as pH and redox reactions) and external physical stimuli (such as light and heat).

Mechanism of cell killing and immune action of drug-loaded bionic membrane nanosystems

The immune system can recognize and remove cancer cells from the TME. However, cancer cells can survive in various stages of antitumor immune response by suppressing the immune system so that the immune system cannot identify and kill cells, which is called immune escape. Tumor cells may employ multiple immune escape approaches or immunosuppressive mechanisms, such as defection of immune cells, loss or downregulation of MHC expression, and upregulation of various suppressor molecules, including PD-L1, CD47, NK cell ligand, and T cell depletion, ultimately leading to rapid tumor growth (Ahmad *et al.*, 2004; Sade-Feldman *et al.*, 2017; Adams *et al.*, 2015; Liu *et al.*, 2015; Vodnala *et al.*, 2019).

Suppressed immune response in breast cancer patients is not only due to the lack of cytotoxic T cell-associated antigens and helper T cells in the body but also due to the relatively high titer of soluble immunosuppressive molecules produced by tumor cells, resulting in immune tolerance. PD-1 and PD-L1 are involved in the formation of a TME that inhibits the activation of T-cells and the reduction of cytokine production, thereby mediating negative immune regulation. This prompts tumor cells to evade surveillance and killing by the immune system by sending "Don't find me" signals, and upregulating tumor activity (Konishi *et al.*, 2004; Arasanz *et al.*, 2017). In conclusion, inhibition of PD-1 or PD-L1, thereby enhancing the endogenous anti-tumor immune effect and reducing tumor infiltration and metastasis is important for breast cancer immunotherapy.

A bionic membrane-modified nano-DDS carries immunomodulatory drugs into the body disguised as endogenous substances while retaining the corresponding functions and surface physicochemical properties of the original cell membrane structure. This can avoid immunological recognition such as reducing the uptake of the reticuloendothelial system, improving the anti-immune clearance ability, thus escaping immune clearance and prolonging the circulation time in the organism. It can help the specific targeting and homologous targeting ability with the specific recognition units (proteins, polysaccharides, lipids, etc.) on the bionic membrane, and targeted delivery to the drug target area to regulate immune function (Vijayan *et al.*, 2018; Xie *et al.*, 2019). Tumor cells can induce effector cytotoxic T cell deactivation or apoptosis by transducing "Don't find me" signals by the high expression of PD-L1 molecules. Bionic membrane-encapsulated NPs target PD-1/PD-L1 inhibitors through active or passive targeting and release PD-L1 inhibitors to block PD-L1 inhibitory signals. This promotes the reactivation of immune responses, upregulates T cell growth and proliferation, enhances T cell recognition of tumors, and thereby reduces tumor load for immunotherapy of breast cancer (Sangro *et al.*, 2021). PD-L1 signaling blockade associated with fibrinogen-like protein 1 (FGL1) gene silencing was found to have a highly synergistic therapeutic effect on breast cancer. FGL1 is overproduced by tumor cells and is critical for the negative regulation of T-cell function, and plasma concentrations of FGL1 are associated with prognosis and chemoresistance. The antitumor assay showed that a hybrid Met-loaded bionic membrane camouflaged Poly (lactic-co-glycolic acid) NP delivery system could effectively alleviate tumor hypoxia and induce M1-type differentiation of tumor-associated macrophages, thereby improving the tumor immunosuppressive microenvironment (Gong *et al.*, 2021).

By transmitting the "Don't eat me" signal, tumor cells can avoid macrophage phagocytosis through the expression of CD47. CD47 can bind to inhibitory immune receptors and send a "Don't eat me" signal to the innate immune system, which is the main intrinsic immune escape mechanism of tumor cells. CD47 expressed on cells binds to inhibitory immune receptors on macrophages, which activates tyrosine phosphorylase. This thereby inhibits macrophage phagocytosis of target cells and leads to immune evasion of tumors. CD47 is gradually down-regulated in the process of red blood cell senescence, which eventually leads to phagocytosis and clearance of red blood cells by macrophages (Oldenborg *et al.*, 2000). The CD47 expression of tumor cells is on average about 3-fold higher than normal cell levels. Besides, the anti-CD47 antibody is also known as a "universal antibody" that is expected to be effective against all tumors. The anti-CD47 antibody attaches to the antigen CD47 and blocks it by attaching to the natural receptor, thus blocking the "Don't eat me" signaling pathway and inducing phagocytosis of tumor cells by macrophages. Thereafter, macrophages present tumor cell antigens to adaptive immune cells hence acting as antigen-presenting cells.

Mechanisms of action and immunotherapeutic effects of responsive drug-loaded bionic membrane nanosystems: response mechanism of photoresponsive bionic membrane nanosystems and anti-tumor immunotherapy

Unlike active drug targeting strategies based on pathophysiology, photo-responsive nanodrug release systems use near-infrared light at a wavelength range of 700–1000 nm to irradiate the target area. This is independent of the heterogeneity of cells, tissue types, and the TME to exhibit more direct and controlled targeting. They are triggered by remote photo-stimuli that are absorbed by photo-responsive molecules on the nanodrug, which subsequently absorb the light and converts it into heat or reactive oxygen clusters inducing the release of the drug

(Yang *et al.*, 2017). For example, the total drug release of a nanodrug in a normal environment without 980 nm laser irradiation is less than 14%, while the release of drug is up to 75% in 16 h after 10 min of irradiation of the nanodrug using a 980 nm laser. The photo-responsive nanodrug release system not only has the tunability of external stimulation but also the modulation of the power and duration of light stimulation, which can regulate the degree of ROS production or temperature change. Not only that, the repetitive cycle of local photo-stimulation replaces the repetitive administration of drugs. For example, Shim *et al.* (2017) constructed a nano DDS triggered by long-range near-infrared light stimulation, where the light stimulus would be absorbed by light-responsive molecules or three-dimensional nanostructures.

The release mechanism of photothermal therapy in responsive drug-loaded bio-nanostructured nanosystems is based on the absorption of light energy and its conversion to thermal energy by the light-absorbing component of the photo-responsive molecular structure. This rise in the local temperature led to a phase transition of the thermosensitive lipid component of the bio-nanostructured membrane that affects the release of the drug, enhancing the spatial and temporal controllability of drug release (Zhang *et al.*, 2011). Drug release further induces ICD to mediate antitumor immunity further, dead cells can secrete DAMPs that can promote significant DC maturation and the activation of specific effector T cells can eliminate tumor cells (Krysko *et al.*, 2012; Kroemer *et al.*, 2013). In a study, Pei *et al.* (2020) showed that the photothermal conversion efficiency of the NPs were constant after covering the bionic film coating and accelerated the release rate of the drug after laser irradiation of the NPs reaching the target region. The drug could be released in a targeted way, thus eliminating mouse 4T1 breast cancer cells. The drug release mechanism of photodynamic therapy with a responsive drug-loaded bionic membrane nanosystem can selectively enrich the drug-loaded bionic membrane nanosystem carrying photosensitizer in tumor tissues by the targeting advantage of the bionic membrane. After laser-triggered treatment in the target area, the nanosystem can convert oxygen into cell-killing ROS and induce tumor cell necrosis and apoptosis. It can also seal tumor blood vessels and cause vascular damage through oxidative damage to the surrounding organelles and biomolecules, thus realizing the anti-tumor effect in the target area. Thus, photo-switching systems have been employed to make endosomal drug escape active, adjust the chemical and biological drugs release, and control drug release. This strategy would hopefully overcome the limitations of physiological DDS and has important implications for phototherapy-based remote control of drug applications.

Mechanisms of action and immunotherapeutic effects of responsive drug-loaded bionic membrane nanosystems: response mechanism of magnetically responsive bionic membrane nanosystems and anti-tumor immunotherapy

As a novel targeted drug delivery method, a magnetically manipulated targeted system is based on the principle that magnetic nanocarriers can be magnetically resonantly contrasted under strong magnetic fields (MFs). This can generate high heat under alternating high-frequency MFs, and achieve controlled motion under simple low-frequency MF manipulation.

Magnetically responsive nanodrug release systems use MFs as a response stimulus for nanomaterials. The advantage of MFs is their unique properties: they can mediate the targeting of NPs by a constant MF, can heat NPs *in vivo* by an alternating MF, or combine both to mediate the magnetic response of nanomaterials synergistically. Magnetic nanocarriers can be injected intravenously into the body, modified by bionic membranes to obtain an active targeting effect, and pooled to the tumor site to inhibit tumor growth in combination with magnetic heat or controlled drug release, or both (Sergio *et al.*, 2015).

When placed in an alternating MF, magnetic nanoparticles can absorb energy and convert magnetic energy into heat release due to hysteresis loss or Nier relaxation. Therefore, magnetic nanoparticles are widely used to generate high heat locally in tumors for thermally responsive drug release. The most typical application is to use magnetic nanoparticles as the core, and the outer layer is covered with temperature-sensitive lipids or polymers. Here, the magnetic core generates hyperthermia with the existing alternating MF, and the temperature-sensitive nanoparticle shell undergoes a conformational transition. The drug is encapsulated in the nanoparticle core when no exogenous MF is present, and the superparamagnetic nanoparticles are magnetized when an exogenous MF is applied. Thus, they are mutually compressed to release the encapsulated drug and trigger the rapid drug release (Qin *et al.*, 2009). In one report, Zhang *et al.* (2017) coated superparamagnetic and magnetically responsive magnetic nanoclusters (MNC) with azide (N3)-modified leukocyte membrane fragments and obtained artificial antigen-presenting cells by the click reaction. This enabled the magnetically responsive nanodrugs to avoid immune clearance with the addition of a bionic membrane. Further effective guidance to the tumor tissue was done under the visual control of MF and magnetic resonance imaging, followed by synergistic cytotoxic effects of magnetic nanoparticles in combination with thermal therapy. Xuan *et al.* (2018) developed a magnetic mesoporous silica nanoparticle (MMSN) covered with red blood cell (RBC) membrane, which effectively integrated immune adjuvant, photosensitizer delivery and MF-assisted targeted photodynamic therapy. The RBC-based nanoparticle could avoid immune clearance and obtain MF-induced tumor hyperaccumulation in *in vivo* experiments. When light irradiation was applied, single-linear oxygen loaded with dextran B rapidly generated RBC@MMSNs and led to tumor tissue necrosis. Another strategy controls the drug release rate by controlling the duration of the alternating MF and adjusting the rate of contraction of the temperature-sensitive shell pore size. Satarkar and Zach Hilt (2008) demonstrated the feasibility of triggering drug release when magnetically induced temperatures rise.

In magnetic responsiveness-mediated enhanced nanodrug transport, a research team constructed a liposome connected to magnetic nanostrands, which are linked by

DNA and loaded with the drug in the liposome. When the magnetic composite nanocarrier reached a specific site, the magnetic nanostrands oscillated upon application of a radiofrequency field, thereby disrupting the liposome structure and releasing the drug rapidly in large quantities (Peiris *et al.*, 2012). When an MF is coupled to magnetic nanoparticles, the MF can be manipulated to initiate signaling pathways. For example, Cho *et al.* (2012) developed magnetic nanoparticle magnetic switches capable of initiating apoptotic cells. The magnetic switch was made of a zinc-doped structure, iron oxide magnetic nanoparticles. By controlling the magnetic switch using a remote and noninvasive MF signaling approach, an MF was applied to accumulate nanoparticles to bind DR4s while in its operation. This promoted the apoptotic signaling pathway and caused apoptosis of tumor cells for therapeutic effects. However, there are limitations in MF-mediated targeting, as the MF strength shows a little effect with tissue depth, the magnetic nanocarriers cannot be manipulated at the deep tissues due to their small size and weak magnetic response. Thus, magnetic targeting is limited to the surface or outside of the body. The extracorporeal circulation magnetic manipulation targeting delivery system directs blood flow outside the body and reduces the distance between the magnetic nanoparticles and MF, which favors achieving magnetic manipulation. Therefore, researchers have shifted their research on magnetic nanoparticles toward iron oxide nanoparticle systems and further investigate their anti-tumor immune effects.

Drug-Loaded Iron Oxide Nanosystems

Iron oxide nanoparticles (IONPs) are a series of iron oxide nanomaterials such as iron oxides and hydroxyl oxides (Xu *et al.*, 2012), mainly FeO, Fe_2O_3, and Fe_3O_4. Among them, Fe_3O_4 nanoparticles have been approved by the FDA for clinical treatment in iron deficiency anemia (Soetaert *et al.*, 2020), as they increase the hemoglobin content making them the first generation of nanomaterials to be used in the clinic (Frtús *et al.*, 2020). On the one hand, Fe_3O_4 nanoparticles are a cure for iron deficiency anemia. On the other hand, Fe_3O_4 nanoparticles are prominently effective in the treatment of tumors. Recent publications explained that IONPs not only produce thermal effects through the Fenton reaction and laser irradiation but also participate in immune regulation through the ferroptosis pathway and act on tumor-associated immune cells. This brings new opportunities to further promote the research of IONPs in clinical practice.

Mechanism of cell killing and immune action of drug-loaded iron oxide nanosystems

Ferroptosis is an interesting mode of cell death caused by the massive accumulation of regulated iron ion-dependent forms of lipid ROS (Dixon *et al.*, 2012). It regulates tumor development through mechanisms such as lipid peroxidation, iron metabolism, and amino acid metabolism (Jiang *et al.*, 2021). Ferroptosis can drive cell death through pathways that promote the Fenton reaction, GSH synthesis, and polyunsaturated fatty acid metabolism (Dolma *et al.*, 2003). In one study, ferumoxytol iron oxide nanoparticles were used to induce chemokine-mediated recruitment of monocytes into breast cancer cells. They polarized to an anti-inflammatory M2 phenotype, and subsequently induced to a pro-inflammatory M1 phenotype, which could trigger apoptosis via the Fenton response pathway (Zanganeh *et al.*, 2016). Triple-negative breast cancer was reported to be more sensitive to ferroptosis due to its iron-rich death gene profile (Verma *et al.*, 2020). Therefore, immunotherapy has become a popular therapy for malignancy treatment in recent years.

Immune cells, a key to immunotherapy, can participate in their mediated anti-tumor immunity through ferroptosis. Among them, CD8+ T cells can enhance the sensitivity of breast cancer to ferroptosis by releasing interferon gamma (IFNγ) to promote T cell-mediated antitumor immunity (Wang *et al.*, 2019). In addition to conventional therapies, immunotherapy combined with ferroptosis can also achieve good performance in breast cancer treatment. Mimetic Fe_3O_4 magnetic vesicles (Pa-M/Ti-NC) camouflaged by the leukocyte membrane could create an immunogenic microenvironment as a basis to increase the intracellular H_2O_2 content. This could acquire a large amount of Fe^{2+} by reduction to promote the ferroptosis of tumor cells (Zhang *et al.*, 2019), thus achieving the anti-tumor ferroptosis synergistic immunotherapy.

T cells are significant mediators of antitumor immunity, and ferroptosis is involved in the killing process against tumors. Thus, regulating the ferroptosis pathway contributes to enhancing the antitumor effects of immunotherapy. Mechanistically, immunotherapy-activated CD8+ T cells downregulated the expression of Xc-, SLC3A2, and SLC7A11, by secreting IFNγ, thereby achieving reduced uptake of cystine by tumor cells to induce lipid peroxidation and ferroptosis in tumor cells (Wang *et al.*, 2019). In contrast, a bionic magnetic nanoplatform (Fe_3O_4SAS@PLT) constructed by Jiang *et al.* (2020) could not only induce an effective immune response by inhibiting System xc-effective triggering of cystine into cells to synthesize GSH for ferroptosis of tumor cells, and also induce an effective immune response. In summary, the ferroptosis pathway in breast cancer cells is regulated by T cells and is involved in T cell-mediated antitumor immunity. Hence, targeting the ferroptosis pathway might be a promising approach for future tumor therapy. Tumor cells undergoing ferroptosis can release a variety of immunostimulatory signals (Tang *et al.*, 2021) that can activate DCs and macrophages (Xu *et al.*, 2021). Moreover, these signals can also accelerate the maturation of DCs and increase the phagocytosis of ferroptosis-induced dead cancer cells by macrophages. Luo *et al.* (2021) identified an important phagocytic signal, 1-steaoryl-2-15-HpETE-sn-glycero-3-PE, on ferroptosis-induced dead cells, which could enhance the phagocytic efficacy of macrophages (Luo *et al.*, 2021). To summarize, ferroptosis-induced cancer cells can enhance phagocytosis by releasing immunostimulatory signals to promote immune cell maturation and identify tumor cells (Lei *et al.*, 2022).

Mechanism of action and immunotherapeutic effects of responsive drug-loaded iron oxide nanosystems: response mechanism of thermally responsive iron oxide nanosystems and antitumor immunotherapy

Although ferroptosis is widely used as a new approach to cell death mode in cancer therapy, the cell death immunogenicity during ferroptosis still needs to be improved. Based on the fact that temperature modulation of antioxidants can also make tumors more sensitive to ferroptosis through its pathway, this approach can achieve better therapeutic effects. For example, Xie *et al.* (2021) designed a co-encapsulated system (GBP@Fe_3O_4) of targeted peptide modified, liquid 1H-perfluoropentane (1H-PFP) and Fe_3O_4 nanoparticles. They proposed a new strategy of thermally triggered tumor-specific ferroptosis, which allows Fe_3O_4 to generate strong ROS through the Fenton reaction in a moderately hot (45°C) environment to amplify oxidative damage, thus inducing tumor ferroptosis and achieving sufficient anti-tumor effects. This exogenous heat-triggered ferroptosis-based strategy has been successfully implemented on kidney cancer and breast cancer cell lines (Xie *et al.*, 2021). Thus, such a treatment method is proposed as a new idea for cancer treatment. To extend the *in vivo* circulation time of Fe_3O_4 nanomicrospheres, wrapping them with erythrocyte membranes could effectively promote the enrichment of the composite microspheres, significantly enhancing the photothermal therapy effect in the animal model (Peng *et al.*, 2017). Another popular method for treating malignancies is chemo-dynamic therapy (CDT) based on the Fenton reaction. A novel therapeutic nanomedicine called PTCGNPs was reacted with H_2O_2 to synthesize ROS through an iron-based Fenton reaction, resulting in a chemical/chemical kinetic combination (Ren *et al.*, 2020). Single thermos-responsive type can be commonly used as a stand-alone carrier for controlled drug release. However, multiple stimuli-responsive drug carriers possess better specificity and flexibility. Another research team proposed a pH/thermosensitive dual-responsive nanotherapeutic system with excellent delivery capability. A pH/thermosensitive gel containing IONPs and adriamycin (Doxorubicin, Dox) was to produce local thermal therapy which accelerated drug release that irreversibly damaged the tumor, making tumor cells more sensitive to chemotherapy. Such research for increasing drug delivery and strengthening tumor combination therapy has gained increasing attention (Liu *et al.*, 2022). In another study, Zhu *et al.* (2020) used an external heat source (near-infrared light, NIR) to load Comprisil A4 (Azo-CA4) into upconversion nanoparticles (UCNPs) for enhancing the release of chemicals from nanoparticles. AzoCA4-treated cells displayed isomerization following NIR light exposure led to microtubule breaking in UCNPs, releasing Azo-CA4 and enabling its function. A combination of NIR and UV conversion could also cause the reduction of Fe^{3+} to Fe^{2+} in UCNPs, which increased lipid peroxidation and caused ferroptosis in tumor cells, thus emerging as a synergistic anti-tumor approach.

Mechanism of action and immunotherapeutic effects of responsive drug-loaded iron oxide nanosystems: response mechanism of magnetically responsive iron oxide nanosystems and anti-tumor immunotherapy

The magnetic responsive DDS is a novel DDS designed on the basis of characteristics and "magnetic responsiveness" of the tumor tissue microenvironment and cell structure. The magnetically responsive nanosystem delivers the exogenous drug to a predetermined location, where the drug it carries is enriched to reduce its toxic side effects on healthy tissues. This helps achieve efficient transport and reduce toxicity, with the significant advantage of fast response time compared to other stimulus-responsive systems.

Using superparamagnetic Fe_3O_4 as a magnetically responsive drug carrier has advantages of low cytotoxicity, easy formation of superparamagnetic properties, and good stability (Zheng *et al.*, 2018). A research team developed bovine serum albumin (Fe_3O_4/BSA) particles loaded with iron oxide nanoparticles that could internalize bone marrow mesenchymal stem cells (MSCs), thereby significantly reducing the release rate of MSCs in a static MF. The uptake of Fe_3O_4/BSA particles significantly increased the osteogenic differentiation of MSCs under constant static MF conditions, suggesting that magnetically manipulated stem cells induced differentiation (Jiang *et al.*, 2016). The magnetic control method has free release control of nanomedicine, improves drug release, and increases mechanical lethality against tumors. In contrast to the pH and redox stimulation triggering drug release, magnetic control achieves external stimulation. With further study, magnetic control can achieve external and internal sensitive responses to tumor treatment.

To decrease drug resistance, Yao *et al.* (2020) used $Zn_{0.2}Fe_{2.8}O_4$ magnetic nanoparticles with a strong magnetic response type and the anticancer drug adriamycin (DOX), co-carried in poly (lactic acid)-glycolic acid copolymer. The release of the chemical agent within it through the action of an external MF, resulted in a dual magnetic-chemical combination killing effect on tumor cells.

Conclusion

Nanomedicines are usually effective in the body through five processes: blood circulation, tumor accumulation, deep tumor tissue penetration, cellular internalization, and intracellular drug release. Therefore, based on these processes, the development of drug-loaded responsive nanoparticles can adapt to the complex environment and diverse biological barriers of tumor tissues to accomplish drug release efficiency. However, there are still unresolved challenges in this field, such as the effectiveness of active targeting of drug-loaded liposomal nanoparticles, which is still limited by the complexity of *in vivo* pathophysiology. Whether the interaction with the immune system after membrane modification by bionic membrane-loaded nanoparticles induces or exacerbates inflammation, which leads to the release of pathological inflammatory mediators is also not known. The less studied ferroptosis of drug-

loaded iron oxide nanoparticles in targeting immune cells still needs further exploration.

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