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Review article

Nanoliposomes for doxorubicin delivery: Reversing drug resistance, stimuli-responsive carriers and clinical translation

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ABSTRACT

Cancer is still a major threat to human life that is characterized by abnormal proliferation and metastasis of cancer cells. Chemotherapy is procedure of using anti-cancer drugs for preventing dissemination and proliferation of tumor cells to kill them in improving survival rate and prognosis of patients. Chemotherapy has been a common conventional therapy for cancer, and it can be used along with surgical resection in cancer patients. However, drug resistance has led to chemotherapy failure in patients, especially in advanced and metastatic stages. Therefore, nano-scale delivery systems have been developed for reversing drug resistance and potentiating efficacy of chemotherapy agents. Liposomes are spherical vesicles with low particle size and high biocompatibility that have been used for drug delivery in cancer suppression. Liposomes can increase internalization of doxorubicin (DOX) as an anti-cancer drug in tumor cells to boost its cytotoxicity. Furthermore, co-delivery of DOX with other anti-tumor drugs or gene therapy can lead to synergistic cancer therapy. pH-, redox-, light- and multi-sensitive liposomes have been designed for precise delivery of DOX in cancer suppression. Modification of liposomes with ligands such as hyaluronic acid that binds to CD44 receptor, enhances selectivity towards cancer cells. Furthermore, DOX-loaded liposomes mainly internalize in cancer cells via endocytosis that is dependent on different factors such as particle size, zeta potential and other physico-chemical properties.

1. Introduction

The number of cancer-related deaths in 2020 (10 million) demonstrates that cancer is still a major cause of death [1]. The most common and malignant cancers have been categorized in both males and females, but overall, lung cancer, breast cancer and colorectal

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cancers are among the most common and malignant tumors in both sexes. The currently available treatments for cancer in pre-clinical and clinical settings are gene therapy, surgery, hormone therapy, radiation therapy and the most common one is chemotherapy [2–5]. In spite of significant progresses in discovery of anti-cancer drugs for purpose of cancer chemotherapy, cancer recurrence and poor prognosis are observed in patients receiving chemotherapy. The cancer cells owing to their unique characteristics such as proliferation and metastasis can mediate resistance to chemotherapy. Based on estimates, up to 80–90% of cancer-related deaths result from drug resistance and strategies should be chosen in reversing such condition [6]. Overall, chemo-resistance development can be explored in two cases including intrinsic and acquired drug resistance. In intrinsic drug resistance, cancer cells demonstrate mutations that can establish their colony and abnormally proliferate lacking response to anti-cancer activity of chemotherapeutic agents. However, if cancer cells develop resistance upon exposure to chemotherapeutic agents, it is called acquired drug resistance [7]. Doxorubicin (DOX) is an anti-cancer drug with cancer suppression ability via topoisomerase activity inhibition and reactive oxygen species (ROS) generation. However, hyperactivity of drug efflux pumps such as P-glycoprotein, activation of oncogenic pathways and others have been implicated in development of DOX resistance in cancer cells [8]. The exact mechanism responsible for DOX resistance in cancer is not been determined; however as it was mentioned, a combination of underlying mechanisms can lead to drug resistance [9–15]. The lncRNA SAMMSON has been implicated in DOX resistance in breast cancer. Silencing SAMMSON alleviates DOX resistance and promotes oxidative metabolism [16]. Down-regulation of BCKDK is associated with protein translation inhibition in breast cancer and enhanced sensitivity to DOX chemotherapy [17]. Down-regulation of CXCR4 suppresses PI3K/Akt/mTOR axis in triggering autophagic cell death and sensitizing osteosarcoma cells to DOX chemotherapy [18]. For reversing DOX resistance, several strategies have been taken. One of them is co-application of DOX with other anti-cancer agents. For instance, resveratrol stimulates apoptosis and increases sensitivity of tumor cells to DOX chemotherapy. Lercanidipine and amlodipine as calcium channel inhibitors are capable of suppressing ERK/MAPK and TGF-β pathways in re-sensitizing gastric tumor cells to DOX chemotherapy [20]. Another approach in gene therapy in mediating DOX sensitivity [21,22]. Noteworthy, recent studies have focused on application of nanocarriers for DOX delivery and increasing its accumulation at cancer cells [23–25]. The scope of current review is to understand potential of liposomes in delivery of DOX in cancer therapy. This article will cover how application of liposomes can increase potential of DOX in cancer suppression and liposomal nanostructures are beneficial in preventing drug resistance. Moreover, it is discussed that liposomes can deliver DOX with other anti-tumor drugs and even genes. The surface modification of liposomes for increasing their selectivity and their application in phototherapy for synergistic chemo-/photo-therapy is discussed. Moreover, the stimuli-responsive liposomes for site-specific delivery of DOX are shown. DOX is commonly used in cancer therapy and DOX-loaded liposomal nanostructures can be used for targeted treatment of human cancers.

2. Liposomes: Basics and biomedical application

Nanotechnology is defined as a field dealing with synthesis of materials at nanoscale and advent of nanotechnology provided a milestone progress in drug delivery [26]. The use of nanotechnology allows for efficient, precise and specific delivery of drugs to improve their accumulation at unreachable physiological destinations. Multiple kinds of nanocarriers have been developed with purpose of drug delivery that have their own characteristics in terms of size, stability and biocompatibility. Drug loading and encapsulation efficiency are different among nano-scale delivery systems and clinical application of delivery systems depends on their safety profile [27]. The closed spherical vesicles with a lipid bilayer membrane surrounding an aqueous core are known as liposomes [28]. The diameter of liposomes is at length of 400 nm to 2.5 mm and their particle size can be different with average range of 1–100 nm. The unique properties (physical and chemical characteristics) of liposomes have made them appropriate options for purpose of drug delivery. Overall, several reasons are followed by using liposomes for drug delivery purposes. The first and most important reason is increasing targeting ability for enhancing accumulation of favorable drugs at desirable site and preventing accumulation in unwanted tissues that is of importance for minimizing adverse impacts. The second reason can be improving solubility of drugs to accelerate parenteral drug administration. Reducing clearance of drugs and providing sustained release of drug at desirable site. Furthermore, liposomes can promote stability of drugs and facilitate their penetration via barriers such as blood-brain barrier and blood-cochlear barrier [29–32]. Therefore, it is highly suggested to use liposomes for purpose of drug delivery. The liposome discovery was first performed by Alec Bangham approximately 4 decades ago and after that, their use in various fields, especially biomedical application was followed. Although liposomes are recommended for purpose of drug delivery, one of their limitations is fast limitation that can be overcome using PEGylation. Furthermore, surface modification with targeting agents such as antibodies, peptides and polymers such as hyaluronic acid can promote targeting ability of liposomes [33–37]. Fig. 1 provides an overview of liposome structure and its biomedical application.

Recently, liposomes have been employed as ideal nano-scale delivery systems for cancer diagnosis and therapy [15,38–41]. The hybrid nanovesicles comprised of exosomes and liposomes with thermosensitive property have been developed for suppressing CD47 and mediating a combination of photothermal therapy and immunotherapy [42]. The combination therapy with liposomes is of importance for purpose of cancer therapy. Furthermore, liposomes can internalize in tumor cells via endocytosis [43]. Owing to long-term circulating feature of liposomes, they have been widely used for delivery of anti-cancer drugs. Oridonin-loaded liposomes are able to suppress colon cancer proliferation and they have high encapsulation efficiency (85.79%) [44]. The targeting efficiency of liposomes can be improved via surface modification; a strategy that has been followed by a recent experiment via modifying liposomes with cRGD to increase their attachment into endothelial cells. Furthermore, liposomes can be designed in a way to release cargo in response to temperature to suppress tumor proliferation [45]. Interestingly, liposomes have been employed for delivery of both synthetic molecules and phytochemicals in cancer therapy [46–48]. The stimuli-responsive liposomes, especially pH-sensitive liposomes are of interest for site-specific release of cargo in cancer suppression [49]. In addition to drugs, liposomes can be used for delivery of genetic tools in effective cancer therapy [50–57]. The following sections emphasize on use of liposomes for DOX delivery in cancer therapy and improving its accumulation at tumor site (Table 1).

3. Liposomes for DOX delivery

3.1. Co-delivery with drugs

After the development of drug resistance in procedure of cancer therapy, some thoughts have been created to re-sensitize tumor cells. Majority of chemotherapeutic agents induce apoptosis, cell cycle arrest and DNA damage for purpose of tumor suppression. However, tumor cells exert compensatory mechanisms in preventing chemotherapy-mediated suppression. For instance, in case of apoptosis, tumor cells increase expression level of anti-apoptotic factors such as Bcl-2 to prevent apoptosis and mediate drug resistance. In case of cell cycle arrest and DNA damage, they activate repair mechanisms. Therefore, chemotherapeutic agents such as DOX are not always that much effective that they appear to be at first point due to intrinsic resistance mechanisms. In this case, several underlying solutions can be considered that one of

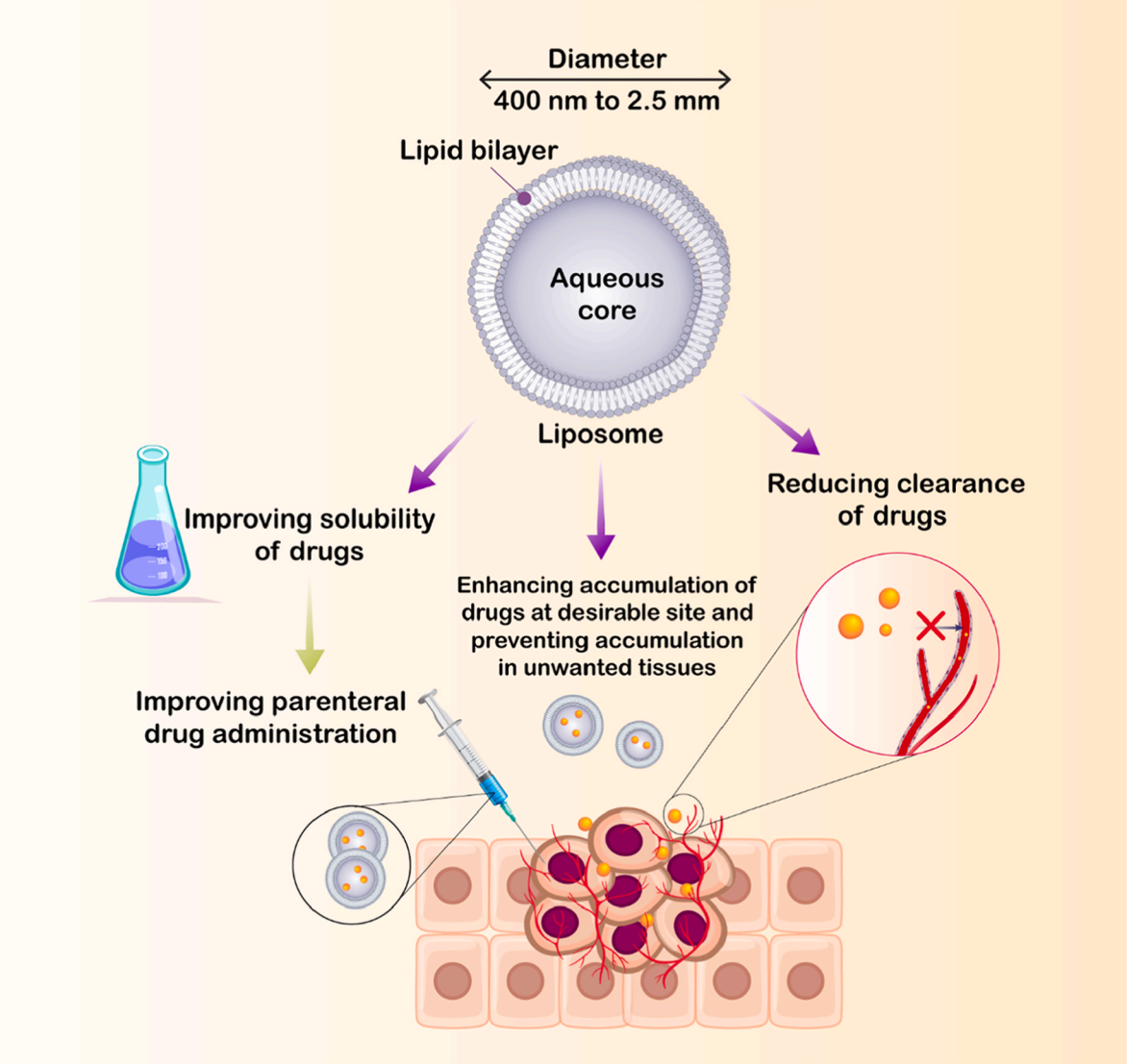

Fig. 1. Liposome structure and its biomedical application.

them is co-application of other anti-cancer agents. For instance, if apoptosis inhibition or DNA damage repair are responsible for development of drug resistance, other anti-cancer agents can be used to target other pathways in triggering apoptosis and DNA damage (in condition that there is no multidrug resistance) to increase sensitivity to chemotherapy [9,10,83–87]. Various kinds of small molecules and plant derived-natural products have been employed for purpose of chemosensitivity and they have demonstrated promising results [88–91]. However, there is another problem and is poor bioavailability of both drugs for synergistic cancer chemotherapy that is due to presence of biological barriers [92,93]. This drawback is more obvious in vivo compared to in vitro and in animal models, synergistic cancer therapy with co-application of two anti-cancer agents shows low efficacy. For this purpose, it is highly recommended to develop nanoplatforms for co-delivery of drugs and improving their bioavailability and therapeutic index [94–98]. The current section focuses on the role of liposomes for co-delivery of DOX with other drugs in cancer chemotherapy.

Schisandrin B (Sch B) is a potent anti-cancer agent for tumor suppression and it is a modulator of molecular pathways. Sch B is capable of impairing progression of tumor cells and induces apoptosis via PI3K/Akt signaling inhibition [99]. Sch B impairs cancer metastasis via EMT inhibition and it reduces stemness of tumor cells [100]. The interesting point is capacity of Sch B in cancer chemotherapy; so that it can increase ability of paclitaxel in suppressing proliferation and metastasis of cervical cancer cells to boost paclitaxel chemotherapy [101]. In a recent experiment, liposomes have been prepared for co-delivery of DOX and Sch B to mediate synergistic impact and there has been focus on molecular mechanisms affected in cancer therapy. The co-delivery of DOX and Sch B exerts inhibitory impact on metastasis of lung tumor cells. This combination delivery by liposomes is beneficial in EMT inhibition via down-regulation of vimentin and also, inhibition of VEGF and MMP-9 [102]. The combination delivery can be also beneficial in affecting viability and proliferation rate of tumor cells. In a recent attempt, liposomes were employed for co-delivery of DOX and glucoevatromonoside derivative in breast cancer therapy. The prepared co-loaded drug liposomes had particle size of 193.9 and 200.4 nm, zeta potential of −2.2 and −2.4 mV, and high entrapment efficiency. This co-delivery of drugs by liposomes led to induction of apoptosis and G2/M cell cycle arrest in decreasing progression of breast tumor cells [103]. These two studies highlight the fact that both inhibition of proliferation and invasion of tumor cells by co-delivery can be advantageous in increasing drug sensitivity.

Long-term and multiple uses of chemotherapy drugs can lead to development of drug resistance in cancer due to overexpression of P-gp that can also mediate multidrug resistance (MDR) [104]. Increasing evidence has focused on application of P-gp inhibitors in cancer

Table 1
An overview of liposomes employed for DOX delivery in cancer suppression.

Nanovehicle	Cargo	Cancer type	Remark	Ref
Chondroitin sulfate-modified liposomes	Doxorubicin Retinoic acid	Breast cancer	Good serum stability 98.7% encapsulation efficiency Anti-metastatic activity	[58]
RSPO-conjugated liposomes	Doxorubicin	Lung cancer	Stimulation of tumor tissue necrosis Growth inhibition	[59]
Cetuximab-coated thermosensitive liposomes	Doxorubicin	Breast cancer	High stability and particle size of 120 nm High cellular uptake due to modification with cetuximab Combination of phototherapy and chemotherapy	[60]
Heat-triggered liposomes	Doxorubicin	Prostate cancer	Preventing off-targeting Suppressing tumor growth	[61]
rBC2LCN lectin-modified liposomes	Doxorubicin	Pancreatic cancer	High cytotoxicity and decreasing tumor weight in vivo Reducing side effects	[62]
MR-labelled liposomes	Doxorubicin	Breast cancer	Ultrasound-mediated DOX release in breast cancer in mice	[63]
Cell-penetrating peptide-modified pH-sensitive liposomes	Doxorubicin	Breast cancer	Prolonged blood circulation time High selectivity and specificity towards tumor cells Increased accumulation of DOX at tumor site	[64]
Phosphatidylcholine-based liposomes	Doxorubicin	Breast cancer	High encapsulation efficiency (more than 80%) Drug release over 48 h Sustained release and high cytotoxicity on tumor cells	[65]
Magnetic resonance activatable thermosensitive liposomes	Doxorubicin	Breast cancer	200 nm in size and 68% drug release Decreased viability of tumor cells Minimal homolytic potential	[66]
Chlorotoxin peptide-modified liposomes	Doxorubicin	Glioblastoma	Growth inhibition 100–150 nm particle size High entrapment efficiency	[67]
pH-sensitive liposomes	Doxorubicin	Cervical cancer	Delivery of DOX to cancer cells and providing nuclear accumulation Apoptosis induction via caspase-3 overexpression	[68]
pH-sensitive liposomes	Doxorubicin Tariquidar	Ovarian cancer	High stability at pH 7.4 and drug release at acidic pH Targeted delivery of drugs to cancer cells	[69]
MT1-MMP-activated liposomes	Doxorubicin	Pancreatic cancer	Increased tumor blood perfusion to enhance accumulation of DOX at tumor site Good distribution of DOX at tumor tissue Heat-triggered release of DOX	[70]
Heparin-modified bone-targeting liposomes	Doxorubicin	Breast cancer	Alendronate functions as a bone-targeting agent Anti-metastatic ability	[71]
Liposomes	Doxorubicin	Lung cancer	102–120 nm of particle size High drug release of 98% after 45 h High cellular uptake due to modification with GE11 protein	[72]
Transferrin- and octaarginine-modified liposomes	Doxorubicin	Ovarian cancer	High cytoplasmic accumulation of DOX Providing nuclear delivery Internalization in cancer cells via receptor-mediated endocytosis and macropinocytosis	[73]
Live macrophage-delivered liposomes	Doxorubicin	Breast cancer	Increased DOX accumulation at tumor site Deeper penetration Improving survival rate of mice	[74]
Alpha-tocopheryl succinate-modified liposomes	Doxorubicin	Breast cancer	pH-sensitive release of DOX High encapsulation efficiency and biocompatibility Promising anti-cancer activity	[75]
Stearylamine-bearing liposomes	Doxorubicin	Melanoma	Inducing anti-tumor immunity and preventing metastasis in animal model	[76]
Magnetic liposomes	Doxorubicin	Hepatocellular carcinoma	Decreasing viability of tumor cells up to 80% Anti-proliferation activity	[77]
Temperature-sensitive liposomes	Doxorubicin	Colon cancer	High nuclear localization of DOX Induction of pro-inflammatory cytokine storm Triggering M1 polarization of macrophages	[78]
Temperature-sensitive liposomes	Doxorubicin	Prostate and colorectal cancers	High uptake and release of DOX in tumor cells Sustained release Enhanced anti-cancer activity	[79]
Thermosensitive liposomes	Doxorubicin	Ovarian cancer	High drug release and cytotoxicity on tumor cells	[80]
Polyelectrolyte/Gold nanoparticles incorporating liposomes	Doxorubicin	Cervical cancer	Release of DOX lacking changes in structure of liposome or tubule and cytotoxicity on cancer cells	[81]
Liposomes	Doxorubicin Simvastatin	Colon cancer	Great anti-proliferative activity	[82]

chemotherapy and suppressing MDR [105]. The most important problem in use of chemotherapy drug and P-gp inhibitor is that they are effective in reversing MDR at high concentration levels, therefore resulting in adverse impacts in vivo [105]. It is also worth mentioning that some cancer types such as breast cancer are not negative for P-gp and demonstrate low expression level of P-gp during initial steps of chemotherapy [106,107]. Based on these discussions, it is suggested to use nanoparticles for co-delivery of DOX and P-gp inhibition in breast cancer therapy. In an effort, liposomes with high size uniformity and entrapment efficiency were developed for release of DOX and P-gp inhibitor in breast cancer therapy. Co-delivery of cyclosporine A (CsA) and DOX by liposomes led to a significant reduction in their side impacts and by increasing their internalization in cancer cells, a remarkable increase was observed in anti-cancer activity and tumor suppression [108]. Some of the natural products have demonstrated ability in reducing expression and activity of P-gp that is beneficial in reversing drug resistance during DOX chemotherapy. Quercetin is a phytochemical that can prevent nuclear translocation of YB-1 and decreases P-gp expression in reversing MDR [109]. Quercetin prevents signal transduction from nucleotide-binding domain to transmembrane domain to

avoid activity of P-gp [110]. In an experiment, PEGylated liposomes were prepared for co-delivery of DOX and quercetin as P-gp modulator. This combination delivery diminished tumor growth and volume and it caused high decrease in proliferation rate of cancer cells. This strategy is beneficial in suppressing drug resistance [111].

Curcumin is another anti-cancer agent that its combination with resveratrol can suppress PI3K signaling in preventing drug resistance [112,113]. Different kinds of nanostructures have been developed for delivery of curcumin and DOX in cancer therapy. MnO_2-shelled DOX/curcumin-loaded nanoformulations can induce anti-tumor immunity and suppress carcinogenesis in colorectal cancer therapy [114]. For reversing MDR in esophageal cancer, PEGylated cancer cell membrane-coated nanostructures have been employed for co-delivery of curcumin and DOX with capacity of impairing tumor growth [115]. Tuftsin-bearing liposomes have been synthesized for encapsulation of DOX and curcumin in cervical cancer suppression. This combination and delivery by liposomes can result in significant reduction in growth and volume of tumor in vitro and in vivo. The histopathological analysis revealed capacity of this combination in cancer therapy lacking side effects on other organs of body [116]. One of the ways for improving blood circulation time of liposomes is to provide their PEGylation. PEGylated liposomes are favored for co-delivery of curcumin and DOX in colon cancer therapy. DOX and curcumin delivery by PEGylated liposomes suppressed tumor progression in vivo and they suppressed angiogenesis and migration of colon cancer cells. Furthermore, drug-loaded PEGylated liposomes induced apoptosis and prevented resistance to cell death [117]. Two important factors result in increased anti-cancer activity of DOX and curcumin upon delivery by liposomes including long circulation in blood and increased internalization in cancer cells [118]. Based on these studies, liposomes are able to effectively deliver DOX along with other anti-cancer agents for increasing cytotoxicity and appropriate tumor suppression (Fig. 2) [118–127]. Table 2 provides a summary of co-delivery of DOX with anti-cancer drugs by liposomes in cancer therapy.

3.2. Co-delivery with genes

Three major arms for treatment of cancer include surgery, chemotherapy and radiotherapy. The most traditional strategy in cancer treatment is surgical resection and it is used for eliminating primary or secondary metastatic cancers. Robotic and laparoscopic technologies have been employed for improving morbidity and mortality after surgery. However, tumor recurrence and relapse can commonly occurs after surgery [144,145]. Irradiation is another approach in treatment of cancer that involves inducing DNA damage in tumor cells and upon application of high doses, it can cause cell death and inhibits tumor growth. However, it can lead to some unexpected and undesirable adverse impacts [3,146,147]. Due to aforementioned drawbacks, chemotherapy has been used in cancer treatment, although it has faced drug resistance and side effects that can be improved using nanocarriers. Gene therapy is a new emerging approach in cancer therapy that includes insertion of exogenous nucleic acids into target cells for therapeutic purposes [148]. Gene therapy has also its own problems such as degradation in blood circulation, low accumulation at tumor site and off-targeting feature [86,149,150]. The current section focuses on the use of liposomes for co-delivery of liposomes and genetic tools in cancer chemotherapy.

microRNAs (miRNAs) are one of the most well-known regulators of molecular pathways in cells and they are produced primarily in nucleus and then with help of exportin-5, they are transferred into cytoplasm to be embedded in RISC complex, leading to generation of a mature and functional miRNA that can reduce expression of target gene via binding to 3′-UTR and preventing mRNA translation [151]. Dysregulation of miRNAs can cause significant alterations in biological mechanisms in cells and is associated with cancer initiation and development [152]. miRNAs can be considered as promising target in cancer chemotherapy and reversing drug resistance [153–156]. In an effort, liposomes have been used for co-delivery of miR-375 and DOX in HCC suppression. This nanoplatform provides co-delivery of gene and DOX in HCC suppression that follows two important results including preventing drug resistance and increasing cytotoxicity. miR-375 released from liposomes can induce apoptosis and cell cycle arrest at G2/M phase that subsequently, increases DOX sensitivity of HCC cells [157]. Therefore, it is highly suggested to deliver tumor-suppressor miRNAs for improving DOX's cytotoxicity on tumor cells. It has been reported that co-delivery of miR-101 and DOX is beneficial in HCC suppression, as miR-101 diminishes growth and metastasis of HCC cells and then, cytotoxicity of DOX against tumor cells increases [158].

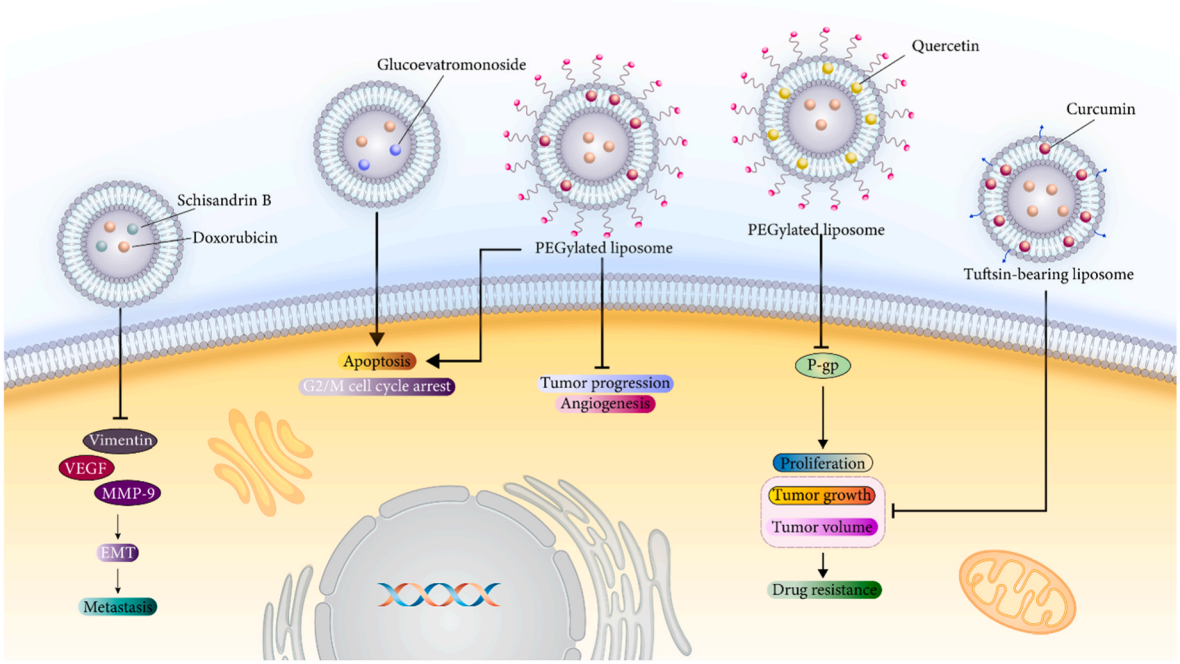

Fig. 2. Liposomes in co-drug delivery.

Table 2
Liposomal nanocarriers for co-delivery of drugs in cancer therapy.

Drugs	Zeta potential (mV) Particle size (nm) Encapsulation efficiency (%)	Remarks	Refs
Doxorubicin Verapamil	118.1 nm up to 95%	Increased cytotoxicity of anti-tumor drugs against prostate cancer	[128]
Gemcitabine Doxorubicin	Up to 75.5 nm −26.3 mV	Embedding anti-cancer agent in lipid bilayer of liposomes Intravenous administration of liposomes Suppressing tumor growth Exerting long-term immune response	[129]
Doxorubicin	130 nm	Herceptin conjugation of liposomes for increasing their selectivity towards cancer cells	[130]
Simvastatin	Up to 80%	Inhibiting prostate cancer progression in vitro and in vivo Decreasing tumor growth up to 80%	
Paclitaxel Doxorubicin	112.4 and 128.5 nm −21 mV Up to 98%	Increased blood circulation time and internalization in cancer cells High anti-cancer activity Decreasing toxicity on organs and improving biocompatibility	[131]
Doxorubicin	Up to 122 nm	Disulfiram prevents P-gp activity and mediates its degradation to increase internalization of DOX	[132]
Disulfiram	−7.9, −8.6 and −8.9 mV	Suppressing tumor progression synergistically	
Doxorubicin Biochanin A	125 nm −19.5 mV 70%	Reversing drug resistance and impairing tumor progression	[133]
Doxorubicin Dihydroaretmisinin	158.8 nm −15.8 mV Up to 95%	Decreasing IC_{50} value Tumor inhibition up to 88.59% Preferential nuclear accumulation of anti-cancer agents	[134]
Paclitaxel	244.4 nm	Long circulation in bloodstream	[135]
Doxorubicin	74.1 and 89.6%	High cytotoxicity and suppressing tumor progression	
Doxorubicin Astragaloside IV	109 and 130.7 nm −15.9 and −16.2 mV Up to 98%	Modification with folate ligand and octa-arginine polypeptide in increasing selectivity of liposomes towards breast tumor cells Inhibiting cancer proliferation Reversing drug resistance	[136]
Doxorubicin Irinotecan	–	No adverse effect Positive impact on relapsed or refractory pediatric WT	[137]
Doxorubicin chloroquine	132 nm More than 90%	Cytotoxicity on drug resistant-breast cancer cells	[138]
Doxorubicin Paclitaxel	262 nm −6.2 mV	High tumor suppression Improved biocompatibility	[139]
Doxorubicin Curcumin	170 nm −50 mV Up to 90%	Inhibition of angiogenesis and invasion Apoptosis induction Increased cytotoxicity on colon cancer cells	[117]
Doxorubicin Itraconazol	133.3 and 146.4 nm −2.5 and −2.7 mV	Suppressing tumor growth Increasing drug accumulation Decreasing tumor weight and volume	[140]
Doxorubicin Curcumin	161, 180 and 182 nm Up to −42 mV Up to 87%	Inhibition of inflammation and angiogenesis Down-regulation of NF-kB Colon cancer suppression	[141]
Doxorubicin	120 nm	Increased tumor distribution	[142]
Irinotecan	−15 mV	High anti-tumor activity in vivo	
Doxorubicin Curcumin	190–230 nm 2–4 mV	Suppressing tumor growth and increased accumulation at tumor site	[143]

STAB1 is one of the targets in cancer therapy and its down-regulation by miR-1224 suppresses gastric cancer progression [159]. SATB1 can be used as a biomarker and its overexpression provides unfavorable prognosis in colon cancer [160]. In an experiment, co-delivery of DOX with SATB1-shRNA has been performed to impair gastric cancer progression. The thermosensitive magnetic liposomes increase DOX and DOX internalization that is of importance in suppressing gastric cancer progression in vitro and in vivo [161]. This study revealed that liposomes can be employed for delivery of shRNA as a promising genetic tool in increasing DOX's cytotoxicity against cancer cells. Similar to shRNA, small interfering RNA (siRNA) is beneficial in cancer therapy and it is widely used for purpose of cancer proliferation and invasion suppression. Furthermore, siRNA use can avoid drug resistance that is an increasing challenge in recent years. The reason of using nanocarriers for siRNA delivery is that tumor cells and tissues can create barrier known as blood-tumor barrier that prevents accumulation at tumor site. Furthermore, cell membrane has a negative charge and it is a little hard for siRNA with negative charge to appropriately penetrate through cell membrane. Besides, there are enzymes in bloodstream called RNase enzymes that can degrade siRNA and decrease its potential in cancer therapy [86,162–167]. In respect to potential of liposomes in drug and gene delivery, Yang and colleagues have developed liposomal nanocarriers for co-delivery of Bmi-1-siRNA and DOX in cancer therapy. Tumor growth undergoes inhibition by this co-delivery and it is beneficial in impairing tumor progression as well as increasing cytotoxicity of DOX against cancer cells [168]. Based on these studies, liposomes are ideal candidates in gene delivery and enhancing DOX sensitivity of tumor cells. However, number of experiments about gene delivery is lower compared to drug delivery, urging more studies in this field. Furthermore, it is suggested to use liposomes for delivery of DOX, with genes and drugs (triple delivery) to understand how this kind of delivery is beneficial in impairing tumor progression, especially in vivo (Fig. 3).

4. Surface modification

It is quite obvious that use of liposomes can promote internalization of DOX in cancer cells. This leads to two important results including A) enhanced cytotoxicity of anti-cancer drugs, and B) preventing drug resistance. The conventional liposomes can increase blood circulation time of DOX and improve its bioavailability. All of these benefits have resulted in special attention towards use of liposomes for purpose of cancer therapy and DOX delivery. However, it has been reported that conventional and unmodified liposomes can undergo some changes to increase their targatibility that is of importance in cancer suppression. For this purpose, biologists have worked on recognition of receptors

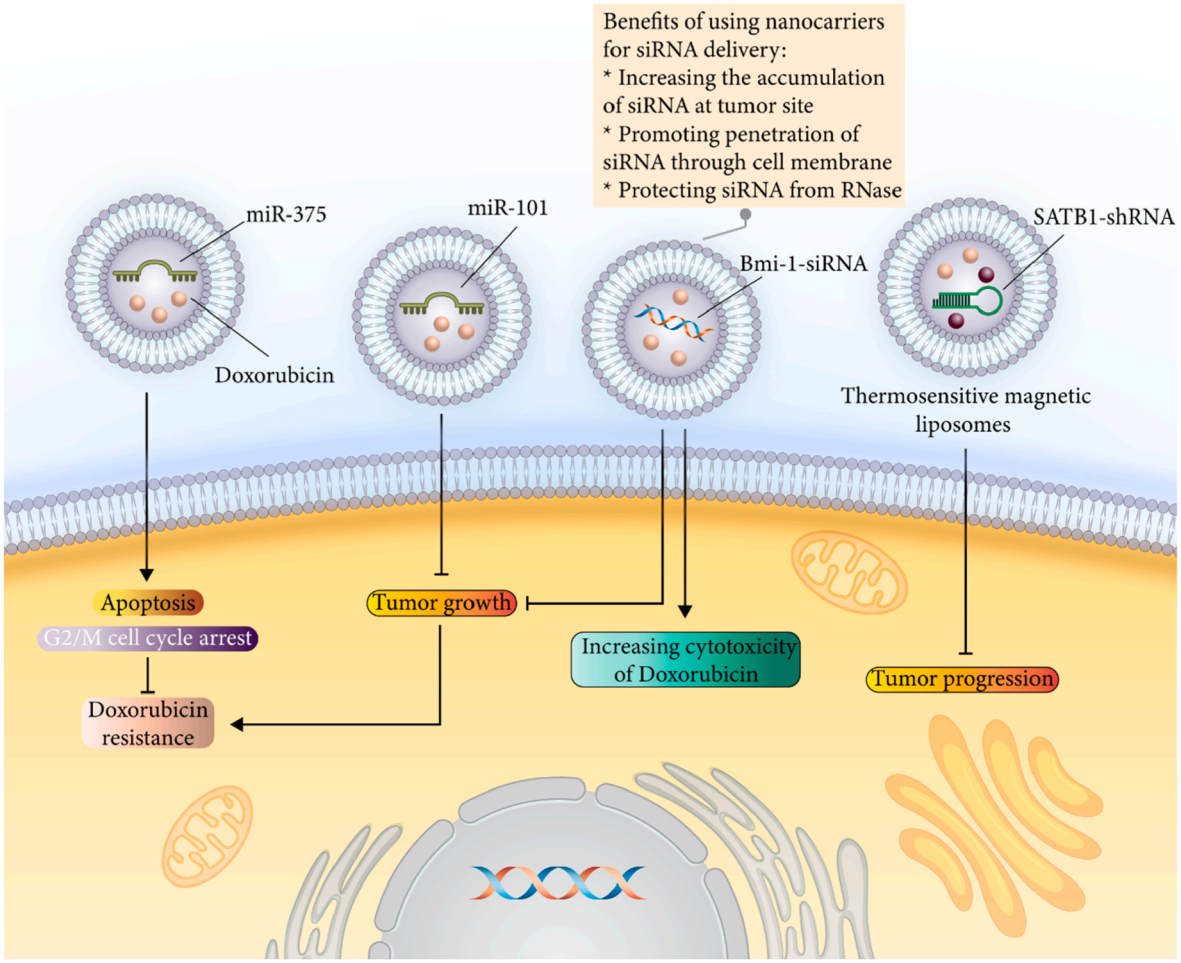

Fig. 3. Liposomes in delivery of genes and DOX.

overexpressing on the surface of cancer cells. Then, a corresponding ligand can be attached to surface of liposomes to enhance their targeting efficiency [169–171]. Transferrin (Tf) is an important agent for purpose of drug delivery, as it can mediate endocytic uptake of nanoparticles by transferrin receptor (TfR) [172]. The overexpression of TfR has been in a number of tissues in body, especially those that demonstrate high turnover rate of cells. In tumor cells, there is a positive association between expression level of TfR and proliferation rate [173]. Owing to overexpression of TfR on cancer cells, it is used for purpose of cancer therapy and a number of small molecules targeting TfR have been developed [174,175]. Tf-modified liposomes have been designed for DOX delivery. Film dispersion and ammonium sulfate gradient method were used for preparation of liposomes and then, Tf was conjugated to surface of liposomes via amide bound with DSPE-PEG(2000)-COOH. The Tf modification increases internalization of DOX in HepG2 cells and it improves tissue distribution in animal model. Tf-modified liposomes effectively delivered DOX to tumor site and reduced DOX concentration in organs of body such as heart and kidney [176]. Dual modification can also be performed in increasing selectivity and specificity of liposomes in drug delivery. Folate receptors (FRs) are one of the proteins that their function in cells, has been studied with details due to specific role of folic acid in DNA synthesis and supporting growth rate of cancer cells. Normal tissues demonstrate low expression level of FR, while expression level of this receptor significantly increases in tumor cells to internalize folate for cancer proliferation [177–179]. The modification of nanoparticles with folic acid has been of importance in providing targeted drug delivery [180]. In an effort, dual modification of liposomes with Tf and folic acid has been performed. Dual modification of PEGylated liposomes with Tf and folic acid resulted in 7-fold enhancement in cellular association of nanostructures. Compared to non-targeted nanoparticles, dual-modified DOX-loaded liposomes demonstrated higher cytotoxicity and they suppressed tumor growth in vivo up to 79% [181]. Furthermore, it is possible to develop derivatives of these ligands to increase their specificity. For instance, an experiment has developed a folate derivative, known as folate-polyethylene glycol-cholesterol hemisuccinate (F-PEG-CHEMS) for modification of DOX-loaded liposomes. The liposomes had particle size of 120 nm with high colloidal stability, and were synthesized using polycarbonate membrane extrusion. The KB cells overexpressing FR demonstrated high interaction with liposomes and nanostructures easily internalized in tumor cells. They showed high circulation time, showing they are promising factor for DOX delivery in cancer suppression [182].

TAT peptide has been used for translocating cell membranes and increasing intracellular delivery of cargoes [183–185]. Due to positive charge of TAT peptide, it can be easily internalized in cancer cells [184,186,187]. However, non-specificity is one of the drawbacks of TAT peptide, limiting its application in drug delivery [188]. Therefore, cleavable and non-cleavable PEGs are used to shield it [189–191]. In an effort, folate and TAT co-modified liposomes were constructed using pH gradient method and post-insertion method. The particle size of nanoparticles was up to 148 nm, zeta potential of −11.7 mV and entrapment efficiency of 92.8%. The TAT peptide with cationic charge was fully shielded in liposomes. The DOX-loaded dual-modified liposomes were internalized in cancer cells and suppressed tumor progression. Furthermore, they demonstrated high accumulation rate at tumor tissue in vivo [192]. Due to easy surface modification of liposomes, various

studies have focused on attaching ligands on the surface of liposomes for targeted drug delivery. Neurophilin-1 (NRP-1) undergoes upregulation in glioblastoma cells and tumor endothelium [193]. NRP-1 is involved in oncogenic functions in cells such as angiogenesis, invasion and vascular permeability [193,194]. The expression level of NRP-1 enhances in positive association with glioblastoma malignancy. Therefore, it is of importance to develop peptides targeting NRP-1. RGERPPR is a specific peptide designed for targeting NRP-1 and it can also penetration into tumor vessels and stroma [195–198]. The peptide-modified liposomes have been used for DOX delivery in glioblastoma suppression. The RGERPPR peptide-functionalized liposomes demonstrated particle size of 90 nm with narrow size distributions. They enhanced internalization in tumor cells and improved survival rate of mice in vivo [199]. These studies highlight the fact that liposomal nanocarriers are ideal candidates in DOX delivery and cancer suppression. However, there is another way to increase their specificity towards tumor cells. The most effective way is performing surface modification and the first step is understanding which receptors show overexpression in cancer cells. Then, corresponding ligands can be conjugated to surface of liposomes in attachment to receptors overexpressed on surface of cancer cells and increasing cellular uptake (Table 3 and Fig. 4) [200–206].

5. Phototherapy combination

One of the new emerging strategies for cancer treatment is phototherapy that is divided into two categories including photodynamic therapy (PDT) and phototherapy therapy (PTT). The aim of phototherapy is to induce cell death in cancer cells either by increasing ROS generation or triggering hyperthermia. The nanotechnology-based phototherapy can be used for tumor ablation and in recent years due to development of drug resistance, a number of researchers have focused on combination of phototherapy and chemotherapy in cancer suppression [221–224]. Different kinds of nanostructures have been used for phototherapy of cancer. Triphenylamine-perylene diimide conjugate-based organic nanostructures have been employed to provide photothermal conversion upon exposure to NIR irradiation and by increasing ROS generation, they mediate tumor ablation [225]. For developing nanostructures for purpose of phototherapy, a special attention should be directed towards biocompatibility [226]. Notably, always NIR irradiation is not necessary for phototherapy. It has been reported that hyperthermia can mediate release of IR780 from virus-like particles to mediate cancer phototherapy [227]. The development of nanostructures for purpose of phototherapy depends on use a photosensitizer in nanoparticles that can be activated upon irradiation, leading to PDT or PTT for purpose of tumor ablation [228–231]. The current section focuses on the role of liposomes for purpose of phototherapy and increasing potential of DOX in cancer suppression.

In an experiment, thermosensitive liposomes were decorated with graphene oxide (GO) for purpose of photo-chemotherapy. The attachment of GO to surface of cationic DOX-loaded liposomes was performed via conjugation to poly (L-lysine). The resulting nanocarriers demonstrated particle size of 267.9 nm, zeta potential of +43.9 mV and encapsulation efficiency of 86.4%. The structure of GO attached to liposome surface was layer-by-layer allowing gel-to-liquid phase transition in response to NIR laser irradiation. These nanostructures can mediate both phototherapy and chemotherapy in ablating breast tumor cells [232]. In previous sections, it was discussed that use of P-gp inhibitors can significantly increase potential of DOX in cancer suppression. Notably, combination of DOX, P-gp inhibitor and PDT can exert synergistic cancer suppression. A recent experiment has developed

Table 3
The surface modified liposomes for targeted delivery of DOX.

Cargo	Ligand and surface modification	Cancer type	Remark	Ref
Doxorubicin	Anti-MUC1/CD44 dual-aptamer	Breast cancer	Increased cellular uptake Cytotoxicity on cancer stem cells Inhibiting metastasis in nude mice	[207]
Doxorubicin	epigallocatechin-3-O-gallate (EGCG) and polyethyleneglycol (PEG) modification	Myeloma Melanoma Leukemia	Upregulation of caspase-3 and -8 to induce apoptosis	[208]
Doxorubicin	Sigma-2	Prostate cancer	Modification of liposomes increased their internalization in DU-145 cells	[209]
Doxorubicin	Lactoferrin	Hepatocellular carcinoma	100 nm in particle size and encapsulation efficiency of 97% High cellular uptake and cytotoxicity	[210]
Doxorubicin	EGFR	Breast cancer	Attachment to cancer cells overexpressing EGFR receptor High stability in serum Cargo release upon hyperthermia High cytotoxicity on cancer cells	[211]
Doxorubicin	Anti-MT1-MMP antibody	Fibrosarcoma	Increase in cellular uptake and administration to mice resulted in tumor growth inhibition	[212]
Doxorubicin	TAT peptide and transferrin	Glioma	Targeting endothelial and tumor monolayer cells High tumor distribution Increased survival time of xenografts	[213]
Doxorubicin	NGR ligand	Breast cancer	90 nm in particle size and zeta potential of 95% Specific targeting of tumor cells and enhanced internalization in cancer cells	[214]
Doxorubicin	TAT peptide and angiopep-2	Glioma	Penetrating from cell membrane via an unsaturated pathway Crossing over BBB High stability and cellular uptake	[215]
Doxorubicin	D-mannose and L-fructose	Sarcoma	Modification of PEGylated liposomes increase tumor tissue distribution of DOX and mediate exhaustion of tumor-associated macrophages	[216]
Paclitaxel Doxorubicin	Transferrin and TAT peptide	Melanoma	Apoptosis induction Increased cytotoxicity against cancer cells Co-encapsulation of paclitaxel and DOX	[217]
Doxorubicin	AG73 peptide	Colon cancer	Good biodistribution and high cytotoxicity	[218]
Doxorubicin	PHSCNK	Breast cancer	100 nm particle size Negative charge High cytotoxicity and cellular uptake	[219]
Doxorubicin Paclitaxel	TAT peptide and transferrin	Glioma	More efficiently in tumor suppression in combination therapy compared to monotherapy Increased cellular uptake Passing through endothelial monolayer and penetration into deep parts of tumor spheroids	[220]

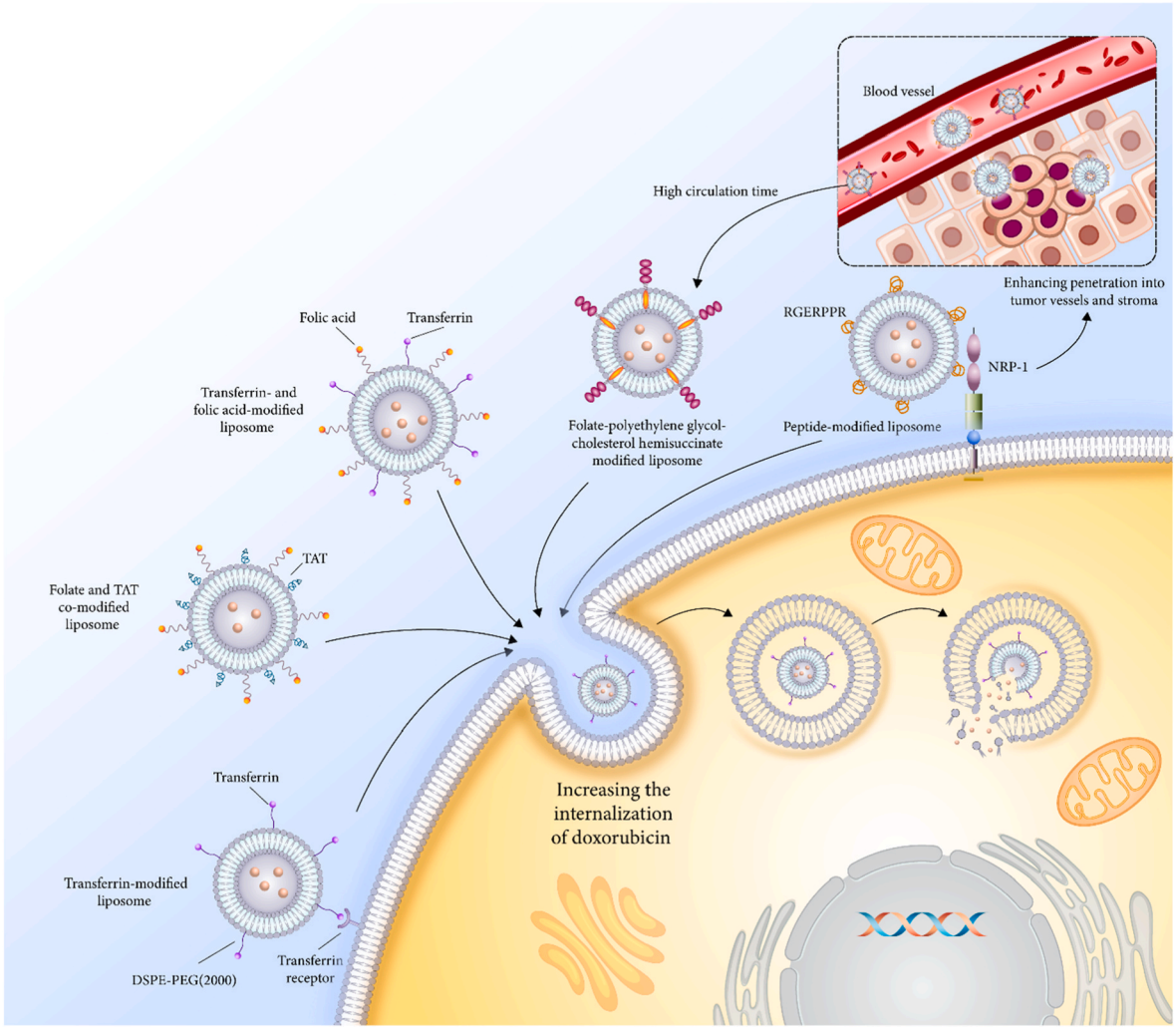

Fig. 4. Surface-modified liposomes in DOX delivery.

PEGylated liposomes for purpose of delivery of DOX, quinine as P-gp inhibitor and indocyanine green (ICG) for PDT. The liposomes were remotely co-loaded with DOX and quinine, and ICG was adsorbed to nanocarriers. Co-delivery of DOX and quinine by liposomes led to effective suppression of tumor growth. Notably, addition of PDT to this co-delivery boosted anti-cancer activity [233]. The phototherapy can be exploited in a way to increase nuclear accumulation of DOX and provide synergistic treatment. A good example of such technique is to add or dope protoporphyrin IX (PpIX) into lipid bilayer of liposomes. When DOX-loaded liposomes reach cancer cells, due to presence of PpIX, they demonstrate high affinity for merging with membrane and increasing cellular uptake of DOX. Upon mild laser irradiation, the activity of drug efflux transporters such as P-gp is impaired and they mediate nuclear delivery of DOX that is of importance in effective suppression of lung cancer [234].

Recently, magnetic nanostructures have been commonly used due to their potential for imaging, diagnosis and treatment [235–237]. Magnetic nanostructures are future and appropriate materials for hyperthermia and imaging. The exposure of magnetic nanostructure to magnetic field results in heat production [238,239]. In an experiment, photosensitive magnetic liposomes have been designed for DOX delivery in cancer suppression. The *m*-THPC as photosensitizer and DOX as anti-cancer drug have been loaded in hydrophobic bilayer of liposomes and resulting magnetic nanocarriers demonstrated particle size of 10, 22 and 30 nm, while liposomes had particle size of 40, 70 and 110 nm. The superparamagnetic nanostructures were loaded in core of liposomes and their heating efficiency synergized with DOX in cancer suppression [240]. Although chemotherapy or PDT alone is beneficial in cancer ablation, it has been reported their combination exerts synergistic impact and using liposomes enables increased accumulation at tumor site [241]. In respect to increased efficacy in killing tumor cells upon combination of chemotherapy and phototherapy [242–244], the chance of tumor recurrence due to presence of cancer cell population available after therapy decreases. Therefore, it is highly suggested to use nanoparticles for combination of chemo (DOX)-phototherapy (Fig. 5) [245–247].

6. Stimuli-responsive carriers

6.1. *pH-sensitive*

Recently, much attention has been directed towards using multifunctional and stimuli-responsive nanocarriers for DOX [248–252]. Tumor microenvironment (TME) has been composed of extracellular matrix and stromal cells such as fibroblasts, immune-inflammatory cells, and endothelial cells that are associated with tumor progression and metastasis upon interacting with cancer cells [253,254]. The biological properties of TME are determined via different factors including tissue acidosis, hypoxia, proteases, immune reactions and abnormal vessel structures, among others [255–257]. The metabolic plasticity of tumor cells is vital for reshaping TME that is vital for their adaptation to oxygen and nutrient supply [258]. TME is different from normal tissue and has

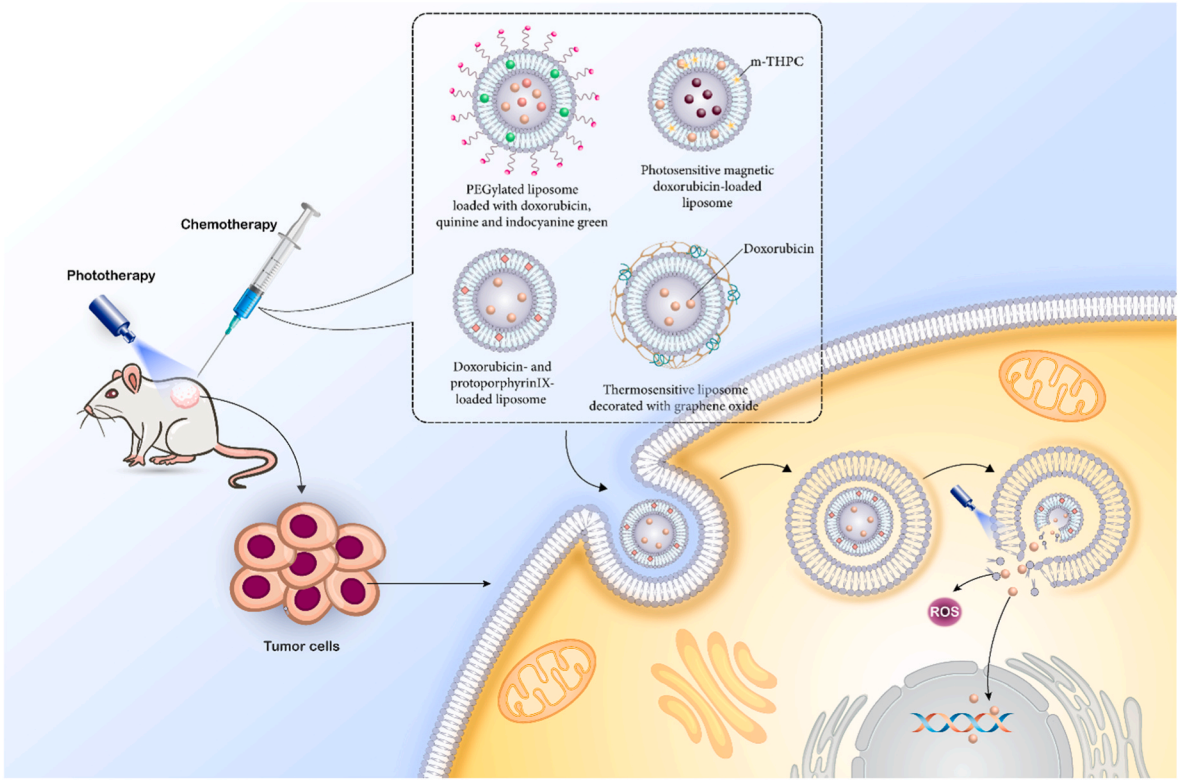

Fig. 5. Liposomes in combination of chemotherapy and phototherapy.

lower pH. In recent years, low pH level of TME has been considered as a promising factor for effective drug delivery in cancer suppression [259]. pH-sensitive liposomes can be used for stimulation of anti-tumor immunity [260]. Besides, co-delivery of curcumin and gemcitabine via pH-sensitive liposomes has been beneficial in promoting drug internalization in cancer cells and impairing tumor progression [261]. This section focuses on the role of pH-sensitive liposomes for DOX delivery.

In a recent experiment, pH-sensitive liposomes were developed for delivery of DOX in glioma treatment. Glucose and triphenylphosphonium (TPP) were as targeting agents for preparation of liposomes to appropriately deliver DOX and lonidamine as chemotherapeutic sensitizer in glioma suppression. The pH-sensitive liposomes can penetrate into blood-brain barrier (BBB) and reach cancer cells. These pH-sensitive liposomes are beneficial in improving pharmacokinetic features and increasing ability in tumor recognition. Besides, cargo-loaded pH-sensitive liposomes can induce apoptosis and significantly suppress growth and metastasis of glioma, while they reduce adverse impacts on normal tissues. Furthermore, pH-sensitive liposomes suppress lung metastasis in animal models and improve their survival time [262]. In recent years, nucleolin has been considered as a promising target for therapeutic approaches [263,264]. This nucleolar protein exerts various biological functions in cells including regulating metabolism, cell cycle progression, nucleolus structure and microtubule nucleation [265–267]. The overexpression of nucleolin has been shown in different cancers and it is responsible for unfavorable prognosis [268–272]. Nucleolin can increase progression of cancer cells via triggering metastasis and angiogenesis [273]. An interesting experiment has evaluated expression level of nuceolin in cancer cells and its impact on the internalization of liposomes. This experiment revealed that F3-peptide-targeted liposomes can deliver DOX to cancer cells and expression level of nucleolin in tumor cells is not a restriction factor. In order to use nucleolin in future studies for development of targeted nano-scale delivery systems, a special attention should be directed towards structural nucleolin homology (higher than 84%) among species [274].

Although liposomes have been promising carriers for DOX in cancer therapy, there are some restrictions that should be considered by studies. One of the limitations of liposomes their uptake by mononuclear phagocyte system [258] and another one is difficulty in predicting liposome extravasation. Stability and circulation time in bloodstream are other drawbacks of liposomes that should be considered. One of the most common and well-known ways to improve liposome characteristics such as improving bloodstream circulation, stability and decreasing uptake by MPS is to perform PEGylation [275–279]. An interesting study has evaluated impact of PEGylation on anti-tumor activity of pH-sensitive DOX-loaded liposomes. In this experiment, two different kinds of liposomes including PEGylated and non-PEGylated were prepared. Based on TEM images, no different was observed in morphology or size of liposomes. Both kinds of liposomes had diameter of 140 nm and zeta potential close to neutrality, and their entrapment efficiency was higher than 90%. Interestingly, non-PEGylated DOX-loaded pH-sensitive liposomes had higher internalization in cancer cells compared to PEGylated liposomes, showing that PEGylation diminishes accumulation of nanoparticles at tumor site. In animal models (in vivo), non-PEGylated liposomes caused more decrease in tumor growth, up to 60% that was higher compared to PEGylated liposomes. Therefore, it is recommended to do not PEGylate DOX-loaded pH-sensitive liposomes for purpose of cancer therapy [280]. The benefit of using pH-sensitive liposomes is that they can release DOX at pH similar to TME that is 6.5 compared to normal and physiological pH that is 7.4 [281].

6.2. *Redox-responsive*

Another feature of TME is glutathione level that has been also exploited in development of nano-scale delivery systems. Aerobic cells generate reactive oxygen species (ROS) that is beneficial for vital pathway and mechanisms responsible for cell survival. The levels of antioxidants in cancer cells is higher compared to ROS and if ROS production increases, it can cause cell death [282–284]. A recent experiment has developed redox-sensitive liposomes containing DOX and salinomycin (Sal) for treatment of liver cancer. Two types of CD133-and

EpCAM-targeted peptides were used to design Y-shaped CEP ligands that were attached to surface of liposomes. These liposomes selectively targeted liver cancer stem cells. The liposomes underwent endocytosis to enter into cytoplasm of liver cancer cells and high concentration level of glutathione (GSH) led to release of cargo due to breaking disulfide bonds. Then, release of DOX and Sal occurs to suppress tumor proliferation [285]. In another experiment, redox-responsive liposomes were modified with glucose and triphenylphosphonium (TPP) and then, loaded with DOX and lonidamine (LND). These two anti-cancer agents exert synergistic impact in cancer suppression. These liposomes increase internalization of drugs at tumor cells and provide their mitochondrial uptake. They provide lysosomal escape and suppress growth rate of cancer cells, while triggering apoptosis. The redox-sensitive liposomes increased ROS generation and decreased ATP generation to mediate mitochondrial dysfunction in favor of cancer suppression [286]. Noteworthy, GSH levels are higher in cells compared to extracellular matrix, and cancer cells have higher levels of GSH compared to normal cells [287–290]. Redox-sensitive liposomes are promising factors for purpose of cancer therapy and suppressing progression of various cancers. The redox-sensitive DOX-loaded liposomes had particle size of −26.07 mV and they increased internalization of drugs at tumor cells that are beneficial in cancer therapy. These nanocarriers suppressed tumor growth in vivo and increased survival of animal models. They released cargo in response to redox status and their modification with hyaluronic acid was performed to increase their selectivity towards osteosarcoma cells overexpressing CD44 [291].

6.3. Light- and thermo-responsive

Although previous sections have focused on the pH and ROS as factors to develop multifunctional liposomes for purpose of DOX delivery in cancer suppression, there is another kind of smart liposomes that more control is placed on them and are known as light-responsive liposomes that are based on exogenous stimuli. During development of liposomes for DOX delivery, it should be noted that use of cholesterol and PEGylation are vital for DOX loading, but they lead to slowed light-triggered release of drug. It has been shown that presence of DOX in liposomes can increase its bloodstream circulation and stability. The liposomes were injected into animal models via intravenous route and upon near infrared irradiation (NIR), a significant increase in DOX release, up to 7-fold increase in DOX concentration was observed [292]. In order to create photoactivable liposomes, it is necessary to load photosensitizers in liposomes [293]. Furthermore, light-responsive liposomes not only release DOX in response to exogenous stimulus, but also are beneficial in providing photo-chemotherapy [294] that was discussed in previous section. Porphyrin-phospholipid (PoP) is commonly used for generation of self-assembled nanoparticles and are promising for precise cargo release and theranostic purposes [292, 295–300]. It has been reported that introduction of low amount of Pop such as 2 mol% to prepared liposomes does not affect their blood circulation time and can enhance phototherapeutic potential because of light-mediated drug release and vasculature permeabilization [292]. Since liposomes have demonstrated good potential in improving vascular permeabilization in DOX-mediated chemotherapy [301], more studies related to light-responsive liposomes for this purpose should be peformed. Light-responsive liposomes with small amounts of unsaturated and PoPs have been used for DOX delivery. In physiological conditions, liposomes demonstrate high stability lacking cargo release, but exposure to light leads to drug release at a minute. With low concentration levels of PoP, rapid laser-mediated drug release occurs. Furthermore, NIR irradiation results in oxidation of DOPC and cholesterol to mediate drug release. Addition of scavenger or antioxidant results in lack of cargo release at the presence of light, showing that oxidation of lipids is necessary for DOX release under irradiation. In vivo experiment on xenograft mice demonstrated that DOX-loaded liposomes can suppress tumor growth efficiently [302].

6.4. Multi-responsive

For more precise delivery of DOX by liposomes in cancer therapy, multi-responsive liposomes have been developed. In a recent effort, liposomes that are sensitive to both redox and light have been designed for DOX delivery. Compared to conventional liposomes, these nanoformulations demonstrated higher biocompatibility on normal cells and in another hand, they had higher cytotoxicity on cancer cells. They were internalized in cancer cells via endocytosis and upon irradiation, high amount of ROS was produced that suppressed tumor growth up to 93.5%. Upon vein injection of DOX-loaded multifunctional liposomes, they preferentially accumulated at tumor site and reached to tumor site upon 24 h. Upon irradiation and drug release, tumor growth inhibition occurred by 94.9% [303]. In another experiment, pH-temperature dual sensitive liposomes were developed for DOX delivery. It is obvious that TME has lower pH compared to normal tissue, and rapid metabolism of cancer cells can result in hyperthermia that is of importance for development pH- and temperature-sensitive liposomes. The prepared liposomes were stabilized by cholesterol and DPPC and then, were conjugated to NH_2-PEGylated gold nanoparticles. The final nanostructures demonstrated particle size of 415–650 nm and zeta potential of −23 mV that is attributed to phosphate groups of DG-CDP. The nanoparticles showed encapsulation efficiency of 78% and they released DOX in response of pH and temperature at TME that is beneficial in cancer therapy (Fig. 6) [251]. Table 4 provides a summary of stimuli-responsive liposomes for DOX delivery in cancer therapy.

7. Internalization mechanism

In section 4, it was discussed that surface modification of liposomes is of importance in increasing their internalization in cancer cells and promotes tumor tissue distribution of DOX in elevating its cytotoxicity [307–309]. Now, this question comes into mind that how nanostructures can internalize into tumor cells? how surface modification of liposomes with ligands can affect their internalization pathway? This section focuses on the internalization mechanism of DOX-loaded liposomes that is a continuation of section 4. Overall, nanostructures can enter into cells via different pathways based on the particle size and surface treatment. The structures with micrometer size can enter into cells via phagocytosis or macropinocytosis [310–313]. During phagocytosis, cup-shaped membrane protrusions are formed that are vital for surrounding the particles. The particles taken up by protrusions determine their shape and size. Overall, dead cells, cell debris and pathogens are taken up by phagocytosis. As an actin-regulated mechanism, macropinocytosis surrounds extracellular fluid and can take particles via plasma membrane ruffling, forming organelles known as macropinosomes [311]. Actin assembly is of importance for phagocytosis and macropinocytosis, since these two pathways are involved in uptake of particles with micrometer size [313,314]. The particles with nanometer size are taken up by cells via a pathway known as endocytosis that includes clathrin-, caveolae- and receptor-mediated endocytosis. In clathrin-mediated endocytosis, coated pits are developed on the cytoplasmic part of cell membrane. Viruses mainly use clathrin-mediated endocytosis for entering into cells [315,316]. In caveolae-mediated endocytosis, hairpin-like caveolin coats are generated on the cytoplasmic part of cell membrane with diameter of 50–80 nm [317,318]. Biochemical and complicated signaling pathways participate in caveolin- and clathrin-mediated endocytosis [319]. Noteworthy, conjugation of receptors on the surface of nanostructures leads to their internalization in cells via receptor-mediated endocytosis [320]. Fig. 7 provides a schematic representation of pathways related to internalization of particles with different sizes in cells.

It has been reported that DOX-loaded liposomes can internalize into cancer cells via endocytosis that increases accumulation of DOX at nucleus [321]. Although PEGylation of liposomes has been shown to increase blood circulation time, this function may lead to lack of

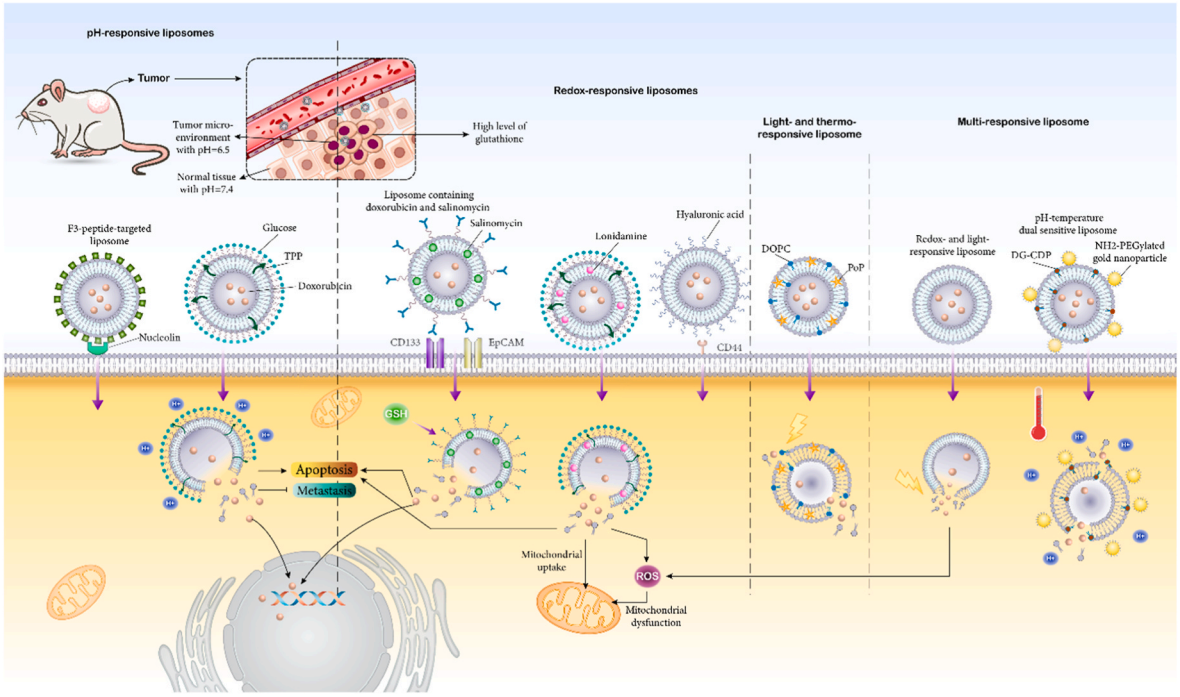

Fig. 6. Stimuli-responsive liposomes in DOX delivery.

Table 4
Stimuli-responsive liposomes for cancer therapy via DOX delivery.

Stimulus	Cargo	Cancer type	Remark	Ref
ROS- and light-responsive	Doxorubicin	Breast cancer	DOX release in response to redox and light Drug release at tumor site	[303]
Light responsive	Doxorubicin	Pancreatic cancer	Increased accumulation of drug at tumor site upon intravenous administration Combination of chemotherapy and phototherapy	[292]
Light responsive	Doxorubicin	Breast cancer	Encapsulation efficiency of 90% Magnetic resonance imaging and phototherapy Combination with chemotherapy in suppressing tumor growth	[294]
Light responsive	Doxorubicin	Pancreatic cancer	High stability Drug release upon NIR irradiation Light-triggered drug release due to oxidation of DPPC and cholesterol Inhibiting tumor growth in xenograft model	[302]
Light responsive	Doxorubicin Chlorin e6	Colon cancer	Internalization in cytoplasmic area Light irradiation led to accumulation of DOX at nucleus High cytotoxicity on cancer cells	[304]
Light responsive	Doxorubicin	Ovarian, breast and lung cancers	Drug release upon NIR laser irradiation Modification with HER antibody increases targeted delivery	[305]
pH responsive	Doxorubicin	Glioma	High tumor targeting ability Specific tumor recognition High internalization capacity Endo-lysosomal escape Suppressing invasion Inducing apoptosis	[262]
pH sensitive	Doxorubicin	Breast cancer	PEGylation decreases ability of pH-sensitive liposomes in DOX delivery and cancer suppression	[280]
pH sensitive	Doxorubicin	Lung cancer	Effective pH-sensitive delivery of peptidomimetic-DOX conjugate Drug release at pH level of 6.5 Increased cellular uptake	[281]
Redox responsive	Doxorubicin	Liver cancer	Apoptosis induction Selective targeting of liver cancer stem cells due to modification with CD133- and EpCAM-targeted peptides Exposure to GSH induces degradation of disulfide bond	[285]
Redox responsive	Doxorubicin Lonidamine	Glioma	Lysosomal escape and entering into mitochondria Apoptosis induction Proliferation inhibition	[286]
Redox sensitive	Doxorubicin	Osteosarcoma	Zeta potential of −26 demonstrating high stability of nanostructures Increased cellular uptake of drug Tumor growth suppression Improving survival time	[291]
Redox responsive	Doxorubicin	Osteosarcoma	Functionalization of liposomes with hyaluronic acid in targeted delivery Release of DOX in response to redox for suppressing cancer progression in vivo	[306]

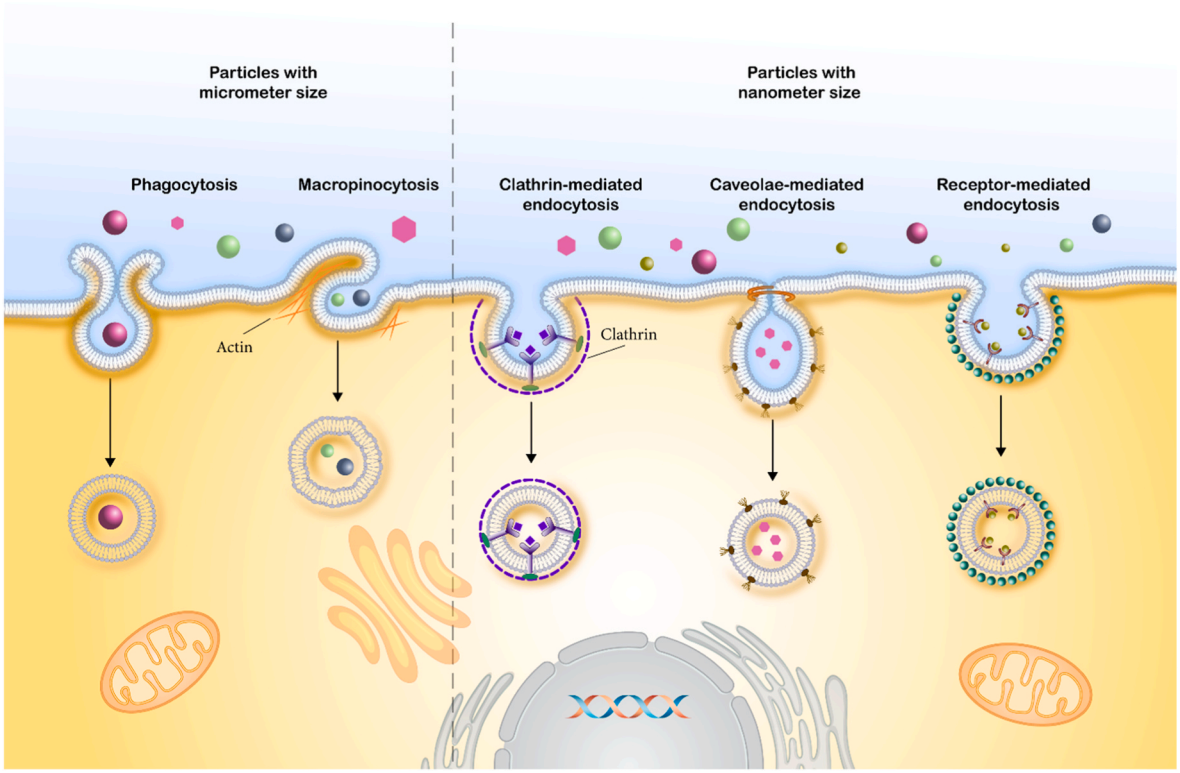

Fig. 7. The different pathways used by particles in entering into cells.

pharmacological activity in DOX-loaded liposomes [322]. Selenium is an important micronutrient that is a cofactor for antioxidant enzymes and is vital for cell growth and life maintenance. Selenium has been used for purpose of chemoprevention and cancer treatment [323–325]. Selenium nanoparticles are used in cancer therapy and they can internalize in cancer cells via endocytosis [326–328]. Therefore, it can be used for liposome modification instead of PEG. It has been reported that selenium-functionalized liposomes can deliver DOX to cancer cells via macropinocytosis and clathrin-mediated endocytosis [329]. Another study demonstrates that DOX-loaded liposomes are taken up in cancer cells (HepG2 and A375 cells) via lipid rafts-mediated endocytosis. It was shown that internalization of liposomes was dependent on cationic lipid DOTAP and fusogenic lipid DOPE [330]. One of the limitations related to studies is that they have only shown that DOX-loaded liposomes can internalize in cancer cells via endocytosis [331–333]. However, particle size, zeta potential, rigidity and even composition of nanoparticles can greatly affect internalization [80,334]. Therefore, it is highly suggested to investigate such parameters in future studies related to cellular uptake and endocytosis of DOX-loaded liposomes in cancer cells. In section 4, it was shown that ligands can increase internalization of liposomes to tumor cells via binding to receptors. Modification of liposomes with RGD can lead to integrin-mediated endocytosis of DOX-loaded nanostructures in cancer cells, confirming why such surface modification is of importance in increasing cellular uptake [335]. Another experiment also demonstrates that sterically stabilized DOX-loaded RGD-modified liposomes enter cancer cells via integerin-mediated endocytosis [336]. These studies demonstrate that endocytosis is the most common pathway for DOX-loaded liposomes in entering cancer cells [337–339]. Table 5 shows mechanisms used by DOX-loaded liposomes in entering into cancer cells. Table 6 summarizes the clinical studies.

Table 5
The internalization mechanism of DOX-loaded liposomes in tumor cells.

Nanoparticle	Cancer type	Internalization mechanism	Ref
Selenium-functionalized liposomes	Lung cancer	Clathrin-mediated endocytosis Macropinocytosis	[329]
DOX-loaded liposomes	Hepatocellular carcinoma Melanoma	Lipid rafts-mediated endocytosis	[330]
DOX/gold nanoparticles coated with liposomes	Cervical cancer	Endocytosis	[340]
RGD-modified liposomes	Melanoma	Integrin-mediated endocytosis	[335]
Sterically stabilized DOX-loaded liposomes	Melanoma	Integrin-mediated endocytosis	[336]
Lactoferrin-modified DOX-loaded liposomes	Glioma	Receptor- and ansorption-mediated transcytosis	[341]
Disachharide-modified liposomes	Hepatocellular carcinoma Melanoma Breast cancer Cervical cancer	lectin-mediated endocytosis	[342]
GE11-modified liposomes	Non-small cell lung cancer	EGFR- and clathrin-mediated endocytosis	[343]
Folate-functionalized liposomes	Lung cancer	Receptor-mediated endocytosis	[344]

8. Conclusion and remarks

Chemotherapy failure has been a common word in recent years and a factor responsible for death of many people around the world. Therefore, what is solution for this problematic issue? Nanocarriers can mediate targeted delivery of chemotherapeutic agents that not only improve cytotoxicity of anti-cancer agents, but also prevent drug resistance development. Therefore, it is suggested to use nanostructures for delivery of chemotherapy agents. DOX was chosen for this review, as it is one of the most common drugs used in cancer therapy. Activation of oncogenic pathways, apoptosis inhibition, induction of pro-survival

Table 6
A summary of clinical trials using DOX-loaded liposomes in cancer patients.

Nanovehicle	Phase	Remark	Clinical number
Doxorubicin hydrochloride liposome	Phase I	20 mg/10 ml injection of nanoparticles in treatment of ovarian cancer	NCT03681548
Doxorubicin HCl liposome	Phase II	Treatment of metastatic breast cancer patients and its comparison with docetaxel	NCT00193037
Doxorubicin hydrochloride liposome	Phase I	Treatment of ovarian cancer patients with 30 participants	NCT02237690
Liposomal doxorubicin	Phase I	Intraductal and intravenous administration in treatment of invasive breast cancer	NCT00290732
PEGylated liposomal doxorubicin	Not applicable	Co-administration of nanoparticles and docetaxel in treatment of patients	NCT03221881
Doxorubicin hydrochloride liposome	Phase II	A combination of nanoparticles and bevacizumab in treatment of recurrent or metastatic breast cancer	NCT00445406
ThermoDox	Phase I/II	Thermodox with approved hyperthermia in treatment of recurrent breast cancer	NCT00826085

autophagy, overexpression of drug efflux transporters and down-regulation of onco-suppressor factors are responsible for development of DOX resistance in cancer. There are several reasons showing that nanoparticles are of importance for DOX delivery. Among different kinds of nanostructures, liposomes were selected for this purpose, since they show high biocompatibility and they have been used in clinical course for treatment of patients. Therefore, translating findings of current review can be beneficial in treatment of cancer patients in near future. It has been demonstrated that liposomes can mediate co-delivery of DOX with phytochemicals to induce apoptosis and DNA damage in sensitizing cancer cells to chemotherapy. Besides, small molecules developed in laboratories can also sensitize tumor cells to DOX chemotherapy. The role of liposomal nanocarriers is to increase internalization of these drugs in cancer cells. In addition to co-drug delivery, co-gene and -drug delivery by liposomes has been also beneficial in chemosensitivity. It has been reported that miRNAs, siRNA and shRNA can be used with DOX in cancer suppression and liposomes can mediate their delivery. The limitation is that there is no experiment regarding co-delivery of DOX and CRISPR by liposomes in cancer therapy. In addition to biocompatibility and high entrapment efficiency of liposomes, their surface modification is easy and based on studies, ligands and peptides have been conjugated to surface of liposomes for increasing their specificity in purpose of DOX delivery. The DOX-loaded liposomes internalize in tumor cells via endocytosis and ligand-modified liposomes choose receptor-mediated endocytosis. The use of phototherapy can increase efficiency of liposomes in reversing DOX resistance. Besides, stimuli-responsive liposomes such as pH-, redox- and light-responsive liposomes can mediate precise release of DOX at tumor site. These discussions reveal that liposomes are promising carriers in field of DOX delivery and cancer suppression.

According to Table 6, a number of DOX liposomes are being currently used in treatment of cancer patients. Therefore, milestone progress has been made in treatment of patients, but there are still some challenges that should be considered for clinical applications. The major benefit of liposomal nanostructures is that they carry low concentration of DOX that prevents chemoresistance and reduces side effects. Moreover, liposomes provide sustained release of DOX. Although clinical studies have shown good efficacy of DOX-loaded liposomes in treatment of cancer patients, the optimal dosage still should be determined and how many times (frequency) these nanoparticles should be administered, since they can prolong circulation of DOX in bloodstream and therefore, the administration repeats decrease compared to DOX alone. Another challenge is that some of the researches cannot be translated into clinic, since the production of such liposomes (especially tumor targeted and stimuli-responsive liposomes) is time-consuming and expensive, and therefore, future studies should focus on clinically scalable liposomes for DOX in cancer therapy.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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