Nanoliposomal System for Breast Cancer Therapy

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Abstract

In the midst of a plethora of nanomaterial-based drug delivery platforms, liposomes have been predominantly successful with several products conceded into clinical applications. Liposomes are well-established and effective drug delivery systems, extensively used in cancer therapy including breast cancer. In this chapter nanoliposomes designed with the breast cancer targeting feature and drug release triggering functions are emphasized. The chapter also highlights the recent advances in the nanoliposomes-based therapeutic system for breast cancer, including gene and theranostic delivery perspectives. The challenges associated with the development of liposome-based products for future clinical settings are also discussed.

Keywords

Liposome · Nanoliposomes · Breast cancer · Theranostic · Challenges · Clinical translation

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10.1 Introduction

Subsequent to skin cancer, breast cancer (BC) is the most common cancer diagnosed in women in the United States. Breast cancer can occur in both men and women, but it's far more common in women. BC is also one of the leading causes of cancer-related deaths. Every year, one million women are diagnosed with breast cancer, with approximately one new case diagnosed every 18 seconds (Bray et al. 2018). It has been estimated that the breast carcinomas cases could rise to 2.50 million by 2025, with 768,646 people dying as a result of this disease. An in-depth study of BC pathophysiology at the molecular level confirms the heterogeneous nature of this carcinoma. If detected in its early stage, then BC can be cured. The metastatic progression is the most challenging aspect in the alleviation of BC. In the current scenario, the therapeutic intervention has been drastically improved as reflected in increased patient survival rates. However, an advanced form of breast cancer that has spread to other organs could not be cured with current chemotherapeutics. BC is usually characterized by uninhibited and excessive cell growth that affects other nearby healthy tissues and organs (Nosrati et al. 2018). Nonetheless, breast cancer alleviation is very difficult to deal with despite the tremendous efforts and development in this field. Until now, chemotherapy, in addition to surgery, has been the foremost strategy to treat BC. There are serious concerns with most of the chemotherapeutic drugs such as they exert a toxic effect on normal cells and tissues (Zhu et al. 2016). In addition, multidrug resistance caused by chemotherapeutics drugs could lead to failure of treatment upon the recurrence of carcinomas (Lu et al. 2016). At the present, therapeutic intervention of BC lays stress upon biologically directed therapies, personalized treatment, and de-escalation of chemotherapy. Although the 5-year survival rate of advanced or metastasized BC is low (28%), the primary goal of targeted therapy is to prolong survival, control symptoms, and reduce cytotoxic drug toxicity, thereby improving the quality of life of BC patients (Harbeck et al. 2019).

Studies at the molecular level revealed that mutated genes' expression substantially contributes to the development and progression of BC (Yang et al. 2018). Therefore, gene therapy is a promising approach that can revolutionize the BC treatment paradigm (Cardoso et al. 2012). Nevertheless, gene therapy is also very challenging owing to the issue of the safety and efficient delivery of therapeutic genes or gene-regulating products into the nucleus of mammalian cells.

Various drug and gene delivery systems, including viral and nonviral vectors, are being explored currently (Huo et al. 2017; Li et al. 2019; Maggio et al. 2020). Liposomes (ZununiVahed et al. 2017), polymeric (Zuris et al. 2015; Chen et al. 2017), and inorganic nanomaterials (Ma et al. 2015) are examples of nonviral vectors. The clinical application of viral vectors is hampered due to safety concerns and cargo size limitations. On the other hand, liposomes are well-established potential nanocarriers for drug/gene delivery with high loading capacity, ease of preparation, and excellent physiological compatibility (Zylberberg et al. 2017, Zuris et al. 2015; Chen et al. 2017).

Liposomes are established and absolute nanomaterials for drug/gene delivery (Pattni et al. 2015; Zylberberg et al. 2017). The predominant merits of liposomes are high loading capacity, convenient preparation, and excellent biocompatibility (Zuris et al. 2015; Wang et al. 2017a, b, c). Liposomes are chiefly composed of phospholipid molecules having hydrophobic tails and hydrophilic heads, forming the amphiphilic vesicle structures in aqueous solutions. Structurally, liposomes are alienated into small unilamellar vesicles (~ 100 nm) and large unilamellar vesicles (200–800 nm) with a single bilayer, and multilamellar vesicles (500–5000 nm) containing multiple bilayers. Owing to their amphipathic nature, liposomes can successfully encapsulate both hydrophilic and hydrophobic compounds (Olusanya et al. 2018a, b; Yang et al. 2021).

The mitigation of adverse effects of anticancer drugs for the patients can be accomplished via targeted liposomes (Federman and Denny 2010). The liposomes' surface can be adapted by apt ligands to target the specific receptors of BC or its microenvironment to attain selective delivery. Triggering is one more approach that allows to control the local dose of the drug and, for example, initiate the drug release at a certain time point after accumulation of a required dose, depending upon the sensitivity of the tumor (Moussa et al. 2015). Nonetheless, liposomes represent a promising nanoparticle-based delivery system in cancer therapy including breast cancer.

In this chapter, we first discuss characteristics of breast cancer followed by recent achievements in liposome-based drug delivery for therapeutic intervention in breast cancer. The key challenges that need to be addressed to improve the utility of liposomes in clinical settings are also discussed.

10.2 Breast Cancer Characteristics and Novel Targets

The molecular mechanisms involved in BC pathophysiology, invasion, and metastasis are explicitly studied (Allred et al. 2001). The profound understanding of molecular events in BC resulted in novel targeted therapies. The different targets and receptors expressed on breast cancer cells along with their endogenous ligands and drugs that bind to them are summarized in Table 10.1.

Nonhormonal targets regulate the process of cell progression and mobility, cellular communications between cancer cells, and the microenvironment of the tumor. Hormonal targets primarily regulate cell differentiation. Steroid receptors and nonsteroid receptors are among the possible hormone targets. Signal transduction mediators, cell-cycle mediators, and angiogenesis mediators are the three categories of nonhormonal targets. There are five different types of steroid hormone receptors that have been implicated in the pathophysiology of breast cancer. Estrogen receptors (ERs), progesterone receptors (PRs), androgen receptors (ARs), glucocorticoid receptors (GRs), and mineralocorticoid receptors (MCRs) are some of them. The importance of estrogen receptors and progesterone receptors in breast cancer upregulation is well established. Vitamin D's biological actions are mediated by the Vitamin D receptor (VDR) (Haussler et al. 1998), which plays a key role in the

Table 10.1 Different class of targets and receptors

Target class	Receptor	Natural ligand	Synthetic ligand
Steroids	Estrogen receptor	Estrogen	Tamoxifen
	Progesterone receptor	Progesterone	Medroxyprogesterone acetate
	Androgen receptor	Dihydrotestosterone	Hydroxyflutamide
	Glucocorticoid receptor	Cortisol	CP-409069
Nonsteroids	Thyroid receptor	Tri-iodothyronine	–
	Vitamin D receptor	1a,25-(OH)2 D3	1a-(OH)2 D5, EB1089
	Retinoic acid receptor	Retinoic acid	All-trans retinoic acid
	Retinoic-X receptor	Retinoic acid	All-trans retinoic acid, 9-cis retinoic acid
	Peroxisome proliferators activated receptor	15-deoxy-D12,14-Prostaglandin	Troglitazone
	Farnesoid X-activated Receptor	Bile acid	SR-45023A
	Constitutive active receptor	Phenobarbital	None
Signal transduction Modulators Cell-cycle and apoptosis Modulation	Endothelial growth factor Receptor (EGFR)	Endothelial growth factors	Gefitinib, Erlotinib
	HER2/neu	–	Trastuzumab
	c-kit Ras family	Kit ligand, steel factor	Imatinib mesylate p53 - CP-31398
Angiogenesis modulation	VEGF receptor	Growth factors	Bevacizumab, Imatinib
	PDGF receptor	PDGF	Tanomastat
	Integrins	–	RGD peptide
	Matrix metalloproteinases	MMP substrate peptide	Anti-MT1-MMP

regulation of cell growth and differentiation. The VDRs are ligand-dependent nuclear receptors that regulate gene expression. In about 80–90% of breast cancer cases, VDR expression has been identified (Colston et al. 1989). Cellular retinol-binding proteins control the actions of every member of this family (Mangelsdorf et al. 1995). During breast carcinogenesis, RAR loss has been observed (Ariga et al. 2000). Thyroid hormones (tri-iodothyronine (T3) and the prohormone thyroxin) have also been studied in the context of breast cancer. T3 receptors are abundant in normal mammary epithelial cells, but how T3 acts on mammary epithelial cells at the cellular or molecular level is still unknown. The nuclear receptor superfamily includes three members (Tontonoz et al. 1994). PPARγ are transcription factors that belong to the nuclear receptor superfamily (Selliti et al. 1983). PPARγ is found primarily in adipose tissue and is expressed in both primary and metastatic breast cancers. Changes in gene expression occur when PPARγ is activated in breast cancer cells (Mueller et al. 1998). Natural prostaglandin (PGJ2) and synthetic antidiabetic

thiazolidinediones are PPARγ ligands (Schwartz 1997). Hence, PPARγ serves as an interesting target for the prevention and treatment of breast cancer.

Signal transduction moderators perform as a messenger to control the cell cycle and communication between the cell's intracellular and extracellular compartments (Aaronson 1991). The constituents of signal transduction could be categorized into cell surface receptors, growth factors, and intracellular signaling pathways.

Breast cancer has also been linked to members of the human EGFR family, particularly HER1 and HER2 (Bacus et al. 1994). HER2 is established as a promising therapeutic target for metastatic breast cancer as its activation results in neo-angiogenesis (Cobleigh et al. 1999; Viloria Petit et al. 1997).

The C-kit receptor tyrosine kinase expresses structural similarities with the macrophage colony-stimulating factor and the PDGF receptor (PDGFR) (Qiu et al. 1988). The appearance of c-Kit is critical for the maintenance of normal hematopoiesis as well as several other functions. Several studies have shown that c-Kit is expressed in both malignant and benign breast epithelia (Matsuda et al. 1993; DiPaola et al. 1997). Cancers of mesenchymal origin like human breast carcinoma have been linked to the PDGFR (Lokker et al. 2002; Bhardwaj et al. 1996). Ras is a membrane-bound GTP/GDP-binding (G) protein that converts signals from the cell surface to the nucleus (Valencia et al. 1991). Breast cancer has also been shown to regulate the expression of Rho C and RAC1. Rho C expression may also be a determinant of recurrence in axillary negative node breast cancer in patients, even in lesions just under 1 cm in length (Kleer et al. 2002).

The ability to regulate cell proliferation and apoptosis is crucial for the growth and development of cancer cells. Cyclins and CDKs have been linked to cell-cycle control (Sherr and Roberts 1999). TNF and the TNF-receptor family are two components of apoptotic cell death. Cell-cycle control and apoptosis are impossible without p53 working properly. The activation of p53 is essential for cells to respond effectively to stress stimuli like DNA damage and hypoxia (Giaccia and Kastan 1998). Growth arrest, senescence, or apoptosis are examples of the response (Asker et al. 1999). There is a link between p53 abnormalities and more aggressive tumors, early metastasis, and lower overall survival (Pharoah et al. 1999).

Angiogenesis is the formation of blood vessel networks to transport nutrients and oxygen to the tumor cells, as well as waste products. Many proangiogenic and antiangiogenic factors are involved in angiogenesis that can be used as molecular targets in the treatment of breast cancer. (Carmeliet 2000). Vascular endothelium cells are activated by angiogenesis factors such as b-FGF and VEGF, which secrete and activate MMPs and plasminogen activators. There are several factors involved in the expression of VEGF, a vascular endothelium cell-specific mitogen, which tends to increase tumor growth and angiogenesis. When VEGF binds to its receptor proteins, recognized as VEGF receptors 1 (Flt-1) and 2 (KDR/fek-1), signaling pathways that control cellular functions involved in new blood vessel formation are initiated (Ullrich and Schlessinger 1990). Small molecules with tyrosine kinase inhibitory activity or neutralizing antibodies (rhuMab-VEGF) are explored in the testing of BC for therapeutic VEGF targeting. Several proteinases, including MMPs, serine, and cysteine proteinases, are critical in the progression of cancer (Fox et al.

2001). High levels of uPA in the primary tumor have been found to have prognostic significance, including axillary node-negative breast cancer (Malmstrom et al. 2001). It has been discovered that uPA system antagonists impede tumorigenesis (Rabbani and Gladu 2002). In the integrin family, there are transmembrane subunit pairs and that is chosen from at least 16a and 8a subunits to form more than 20 heterodimeric receptors on the cell surface. Integrins a3 1 and a6 4 have been linked to the invasion and spread of mammary carcinoma (Mercurio et al. 2001). When it comes to cancer metastasis and invasion, specific modulators may be used to target members of the interleukin (IL) family, particularly a6 4 (and possibly a3 1). Another intriguing component of the angiogenesis process involves prostaglandins, which appear to be involved in cell proliferation, migration, and the ability to form new vessels (Rozic et al. 2001).

10.3 Different Types of Nanoliposomes-Based Drug Delivery in Breast Cancer

Liposomes represent an ideal approach with desirable characteristics prerequisite for targeted delivery of anticancer agents in BC therapeutic intervention. Examples of commercially available liposomes include Doxil® (PEGylated liposomal doxorubicin; Centocor Ortho Biotech Inc., USA), DaunoXome® (non-PEGylated liposomal daunorubicin; Diatos, France), and Myocet® (non-PEGylated liposomal doxorubicin; Sopherion Therapeutics, USA) (Misra et al. 2010). Liposomes can efficiently incorporate both lipophilic and hydrophilic compounds within the lipid bilayer and aqueous core phase, respectively. Liposomes possess good biocompatibility and a high drug loading capacity. Liposomes can be easily customized to achieve desirable attributes such as prolong blood circulation time and receptor-mediated site-specific dissemination (Wang et al. 2017a, b, c).

Recently, a plethora of research studies are being carried out to explore different aspects of liposomal-based therapeutic delivery to cancer cells. Functionalized liposomes are being explicitly explored at present to reap the benefits of biochemical and physiological differences between normal and cancerous tissue. The most promising strategy in tumor therapy is active targeting combined with a conjunction of other strategies, such as the stimuli-responsive targeting approach. Liposomes are transplanted with a variety of targeting ligands including peptides, dendrimers, and monoclonal antibodies employing apt surface engineering technology. Surface functionalization has played a remarkable role in the development of a liposomal delivery system for efficient targeting, endocytosis, and producing an optimal therapeutic response. Additionally, other advantages of liposomes include avoiding lysosomal degradation, high accumulation at the tumor site, and stimuli-responsive drug release at the desired location. Moreover, simultaneous diagnostic and therapeutic functions can be incorporated in liposomes (Durymanov et al. 2015). A typical structure of liposomes with their advantages is shown in Fig. 10.1.

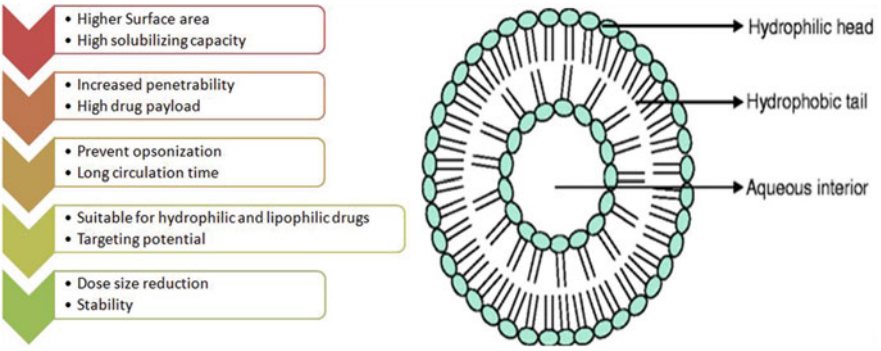

Fig. 10.1 Typical structure of conventional liposomes with advantages of nanoliposomes

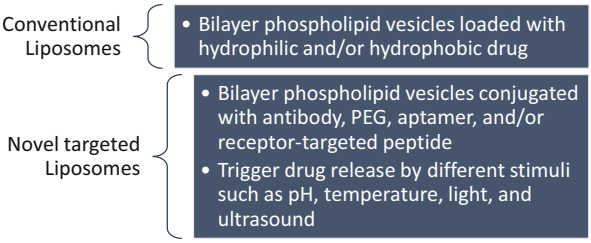

Fig. 10.2 Characteristic attributes of conventional and novel surface-engineered or stimuli-responsive liposomes

Conventional Liposomes It is constituted of phospholipid bilayers (Fig. 10.1) and, when injected intravenously, are prone to be engulfed by the reticuloendothelial system (RES), resulting in short circulation times.

They are destroyed by phagocytes because opsonin recognizes them as foreign substances.

To enhance circulation time, the outer layer of the liposomes was coated with a hydrophilic polymer, namely polyethylene glycol (PEG), and termed as PEGylated or stealth liposomes (Hatakeyama et al. 2013). It improved the electrostatic repulsive between the liposomes and serum components. Stealth liposomes prevent opsonization and hence, extended circulation half-life. Caelyx® (liposomal doxorubicin; Merck & Co., Whitehouse Station, New Jersey, USA) is an indicator of the effective use of stealth liposomes in the chemotherapeutic agent. Figure 10.2 highlights the basic characteristic attributes of conventional and novel surface-engineered targeted liposomes.

Surface-engineered Liposomes A diverse range of therapeutics, together with bioactives, have demonstrated potential anticancer efficacy via multiple mechanisms, including angiogenesis, tumor growth, invasion, and metastasis suppression. Despite their potential antitumor activity, they showed limited applications in cancer therapy (Liu et al. 2020; Feng et al. 2017). Perhaps the key reason is that their low hydrophobicity results in poor cellular uptake and devastated

physicochemical stability. Furthermore, in animals, several bioactive constituents undergo a series of reactions that transform them into water-soluble metabolites, which are then excreted in urine and bile, and some drugs are also excreted in their original form. Because of their hydrophilic nature, they generally show low serum protein binding and are rapidly cleared up by the reticuloendothelial system (RES) (Zhan et al. 2014). Novel liposomal formulations are being developed that are surface-modified with a low molecular weight lipid conjugate and can be used in place of PEG. The formulations had very good stability characteristics in ion- and protein-rich mediums. Adsorption of proteins to the liposomal surface did not affect the cellular interaction. The limitation of PEGylation includes its potential to cause impaired cellular interactions, allergic reactions to be triggered, and an increase in IgM production after repeated dosing.

Multifunctional Liposomes The multifunctional liposomes transport therapeutic molecules with excellent targeting and imaging properties. Liposomes with a single functionality face numerous challenges, and multifunctional liposomes have the potential to solve these problems. The formulation of nanoscale liposomes with a wide range of functions was made possible by combining surface-functionalization and modification techniques. Liposomes with two ligands, such as two peptides (Yuan et al. 2015), two ligands, and two anticancer drugs (Zhang et al. 2017), targeting ligand and an imaging agent (Erdogan and Torchilin 2017; Portnoy et al. 2011; Al-Jamal et al. 2008), have been reported by various studies (Fig. 10.3).

Liposomes containing iron-oxide or metal have therapeutic and imaging properties in one package. The imaging in core and ligand on the liposome surface of a multifunctional carrier are decorated. HER-2 overexpressing breast cancer was imaged using an immunoliposome-encapsulated nitroxide sensor developed by Burks and coworkers (Burks et al. 2010). These multifunctional liposomes have been shown to preferentially generate an intracellular EPR signal in the cells overexpressed with HER-2. High nitroxide concentrations resulted in greatly reduced EPR spectral transmissions and endocytosis of liposomes produced by a cell-activated contrast-generating technique.

Stimuli-responsive Liposomes The slow release of drugs from liposomes could be attributed to passive diffusion as the main mechanism of release from them. Stimuli-responsive liposomes can modulate the release rate of encapsulated drugs. Liposomes do not release their contents unless structural changes are induced by an endogenous or exogenous stimulus. These liposomes provide rapid release of drugs at the desired target sites and reduce the risk of the emergence of MDR tumors. Endogenous stimuli include pathological changes in the target cancer tissues, such as reduced pH (Karanth and Murthy 2007), overexpression of specific enzymes, and abundance of reducing agents (Deshpande et al. 2013).

Temperature-sensitive liposomes Encapsulated bioactives are released near the liposome's phase transition temperature, where the lipid membrane transitions

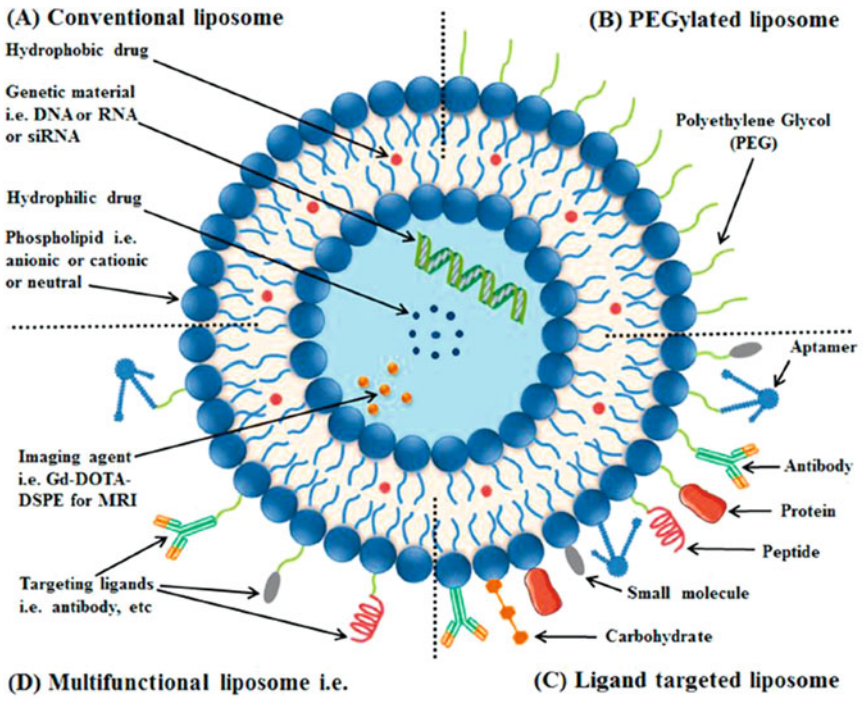

Fig. 10.3 Liposomes and characteristics of its different types: Conventional liposomes are made of phospholipids (**a**); PEGylated/stealth liposomes contain a layer of polyethylene glycol (PEG) at the surface of liposomes (**b**); targeted liposomes contain a specific targeting ligand to target a cancer site (**c**); and multifunctional such as theranostic liposomes, which can be used for diagnosis and treatment of breast tumors (**d**). (Reproduced from Riaz et al. 2018)

from its gel to liquid crystal phase (Yatvin et al. 1978). Lipid bilayer transient pores are created by the incorporation of lysolipids into the liposomal membrane. These transient pores allow the rapid release of the encapsulants. Hyperthermia is the medical term for heating a tumor to a temperature that is slightly higher than normal (40–43 °C). Hyperthermia increases liposome uptake by two to three times (Leopold et al. 1992). Celsion Corporation has developed a thermoresponsive liposomal formulation of DOX, i.e., ThermoDox® for the treatment of various cancers, including breast cancer. ThermoDox®, when given intravenously and combined with hyperthermia, exhibited a potentially inhibiting effect on tumor growth.

Enzyme-Responsive Liposomes Several enzyme concentrations are elevated in several pathological conditions, including cancer. Enzyme-responsive liposomes were developed using this approach (de la Rica et al. 2012; Yan and Boyd 2007). Secreted phospholipase A2 (sPLA2) levels increase substantially of various inflammatory conditions, atherosclerosis, and cancer. Prostate, breast, and pancreatic cancer exhibited elevated levels of sPLA2 (Dennis et al. 2011; Dong et al. 2006;

Graff et al. 2001). Hence, sPLA2 responsive liposomes loading Doxorubicin were formulated with 1,2-distearyl-sn-glycero-3-phosphocholine (DSPC), 1,2-distearyl-sn-glycero-3-phosphoethanolamine (DSPE), cholesterol, and DSPE-PEG. The developed enzyme responsive liposomes exhibited a higher (2.5 times) decrease in tumor growth than conventional liposomes in a mouse model of prostate cancer. MMPs play a significant role in tumor growth, invasion, and metastasis (Curran and Murray 2000; Chambers and Matrisian 1997). Zhu et al. (2012) described enzyme MMP responsive liposomes comprising two kinds of components: TATp-PEG −1,2-dioctadecanoyl-sn-glycero-3-phosphoethanolamine and mAb 2C5-PEG-MMP2 cleavable peptide-1,2-dioleoyl-sn-glycero-3-phosphoethanolamine to target hepatocellular tumor; PEG was attached to the phospholipid DOPE via an MMP-2 cleavable peptide linker. These MMP-sensitive peptides act as a linkage between the lipids and the polymer. The conjugated liposomes with polymer prevent liposome uptake. The peptide is cleaved when it comes into contact with MMPs at the target site, resulting in the dissociation of the polymer and finally uptake of liposomes. Liposomes' galactose ligand is protected from cellular uptake by the PEG group, which forms a barrier on their surface. MMP-2 overexpression in HCC, on the other hand, cleaves the linker and releases PEG. The exposed galactose ligand then binds to HCC cells' asialoglycoprotein receptors. Gal-PEG-DOPE (0.5 percent) liposome uptake was significantly enhanced in the presence of over 5 mcg/mL hMMP-2 in HepG2 cells, according to Terada et al. (Terada et al. 2006). An elevated level of a serine protease known as urokinase plasminogen activator (uPA) is reported in several human cancers, including breast, colon, bladder, and ovarian (Liu et al. 2001). Tumor angiogenesis, progression, and metastasis are aided by uPA (Duffy 2002). In peptides containing the consensus sequence Ser-Gly-Arg-Ser-Ala, the enzyme cleaves the Arg-Ser bond. Liposomes encapsulating uPA-cleavable peptides could thus discharge their encapsulated payload while they come into contact with uPA at tumor sites. It was discovered by Basel et al. that uPA-responsive liposomes in a hyperosmotic medium can be stabilized with a copolymer cage on their surface (Basel et al. 2011).

pH-sensitive Liposomes Because of lactic acid production and ATP hydrolysis, the pH around the tumor cells is lower than healthy tissue (Gerweck and Seetharaman 1996). The endosomal or lysosomal partitions of tumor cells have low pH, which can be utilized to construct pH-responsive liposomal delivery models. The pH-sensitive liposomes systems are fabricated for extracellular or endosomal/lysosomal triggered release. The pH-responsive liposomes have been optimized so that they can transform at various stages between pH 7.4 and 5.0 to efficiently deliver anticancer agents at target sites. If pH is low because of pathological conditions like inflammation, infection, or malignancy, the pH-sensitive liposomes become soft and leaky (Torchilin et al. 1993). The pH-sensitive liposomes are intricately fabricated to circumvent the obstacles such as recognition and endocytosis by the RES, so that they could efficiently release their anticancer agents in the endosome and partially into the cytosol (Budker et al. 1996). Antitumor drugs, antigens, antisense oligonucleotides, and plasmid DNA have been delivered in vitro cytoplasmically

using these methods (Legendre et al. 1992). Liposomal systems encoded with specific ligands can bind to and be taken up by cells, allowing for pH-mediated intracellular drug delivery (Harel and Kato 2007). Accumulation in low pH compartments, such as endosomes and lysosomes, can be utilized to trigger drug release after internalization in tumor cells. Karve and associates reported pH-sensitive immunoliposomes encapsulating DOX for site-specific delivery (Karve et al. 2009). The study demonstrated that pH-sensitive liposomes prevent the growth of cancer cells in a much better way than simple immunoliposomes, and hence, could potentially enhance the therapeutic prospect via liposomal chemotherapy.

10.4 Advances in Nanoliposomes-Based Drug Delivery for Therapeutic Intervention in Breast Cancer

Cationic liposomes are being investigated as a possible efficient method for gene delivery. The complex formed between encapsulated plasmids DNA (Kaneda et al. 1989) and cationic lipids of liposomes is termed as lipoplex (Alino et al. 1996; Crystal 1995). The lipoplex can be fused with the plasma or endosome membrane to transport into cells (Sharma and Sharma 1997). The lipid composition, lipid/DNA ratio, and particle size of the liposome–DNA complex greatly impact their transfection efficiency (Zou et al. 2000). The limitation of cationic liposomes is their poor specificity. This limitation can be addressed by modifying cationic liposomes with cell-specific targeting moieties. For direct cytosolic delivery of liposomes, several cell-penetrating peptides have been implicated. For breast cancer gene therapy, antiangiogenesis strategies involve nonviral vectors (Feldman and Libutti 2000). Angiostatin and endostatin gene therapy is one way to deliver angiogenic polypeptide inhibitors. Previously, liposomes complexed with plasmids encoding angiostatin (PCI-Angio) or endostatin (PCIEndo) exhibited successful inhibition of angiogenesis in BC cells (Chen et al. 1999). Such liposomal delivery of antiangiogenic genes could represent promising therapeutic prospects. The wild-type p53 gene was also included in a liposome–plasmid complex used to treat naked mice injected with breast carcinoma cells (Lesoon-Wood et al. 1995). Xu et al. investigated a cationic immunoliposome tagged with single-chain antibody Fv fragment (scFv) for systemic p53 tumor suppressor gene therapy for treating BC (Xu et al. 2001). The scFv-tagged immunolipoplexes significantly improved transfection efficiency and extended the animals' survival time. However, the scFv-targeted immunoplex's expression was found to be low. A new expression strategy for anti-TfRscFv was reported by Xu and colleagues (Xu et al. 2002). In this, the scFv was covalently coupled to the liposome via a cysteine at the 3′ end of the protein and a maleimide group on the liposome. According to the findings, the immunological activity and targeting ability of the scFv were not affected by this conjugation. The scFv-cys-targeted tumor cells with a cationic liposome–DNA complex (lipoplex) markedly improved transfection efficiencies in BC models. BC cells overexpress the human HER-2/neu oncogene, and research has shown that the

E1A gene acts as a tumor inhibitor gene by reducing HER-2/neu transcription. tgDCC-E1A, a stable E1A lipid complex, was developed by Yoo and coworkers using cationic liposomes and plasmid DNA encoding E1A (Yoo et al. 2001). In accordance with the results of preliminary tests carried out on animals as well as on humans, researchers moved forward with clinical trials to see if delivering the E1A gene via liposomes would be safe and would have an effect on tumor response when administered to cancer patients with an advanced form of BCs. Recent advancements in the use of liposomes as a diagnostic tool underscore the use of imaging techniques and the recognition of diverse molecular targets. There are numerous medical imaging techniques that make use of liposomes as nanomedicines. Some of these methodologies encompass ultrasound, nuclear imaging, fluorescence, and magnetic resonance.

Fluorescence imaging is the most commonly used diagnostic tool. Imagining the position of the biomolecule, enzyme activity as well as gene expression is also possible in living cells or tissues. Functionalized quantum dot–liposome (f-QD-L) was developed by encompassing quantum dots by PEG (QD) for cancer diagnosis (Chen et al. 2000). There has been a lot of interest in NIR fluorescence imaging because of the low photon absorption and scattering (Min et al. 2014). Rare-earth-doped nanoparticles are one material under consideration for use in NIR fluorescence (Eliseeva and Bunzli 2010; Bunzli 2010). Using a liposome-nanoparticle hybrid, Soga and coworkers found that it has a strong NIR fluorescence component.

Radiofrequency pulses are commonly used in MRI for whole-body imaging (Sun et al. 2008). Liposomes can encapsulate a wide range of contrast agents like fluorophores, enabling efficient implementation and controlled release of probes for better image analysis (Kamaly et al. 2009; Soenen et al. 2011). Studies have been reported in which liposomes were concomitantly loaded with the MRI contrast agent Gd-DTPA and doxorubicin (DOX) (Tagami et al. 2011). The simultaneous delivery of Gd-DTPA and DOX allows controlled drug release in a tumor's microenvironment where localized heating could potentially trigger the release of a drug. Another paramagnetic MRI contrast agent is ferrimagnetic iron oxide (FMIO) nanoparticles, which have been used in the preparation of liposomal MRI probes (Mikhaylov et al. 2011). An external magnetic field was used to target the liposomal FMIO nanoparticle cluster at tumors and the tumor microenvironment.

Medical ultrasound, which is defined as sound waves with frequencies greater than 20,000 Hz, is another commonly used noninvasive diagnostic imaging technique. (Cheng et al. 2010) Ultrasound imaging is performed by directing ultrasound pulses into tissue and measuring the echoes caused by the tissue at various reflection angles. Contrast agents for ultrasound imaging, like MRI, have the ability to label specific tissue types or tumors. Acoustic liposomes (ALs), which contain perfluoropropane gas, can be used as ultrasound imaging probes (Deckers and Moonen 2010). For passive tumor tissue localization, high-permeability/high-retention acoustic liposomes can be used because of their small diameter (100 nm) and high retention effect (90% retention). With the help of high-frequency ultrasound (HF-US), acoustic liposomes can be used to test both drug delivery efficiency and antitumor efficacy (Ferrara et al. 2009). Using HF-US imaging, a cisplatin-loaded

AL was evaluated for its antitumor effects (Kodama et al. 2011). Nuclear imaging is another noninvasive imaging technique that uses small molecule radioactive tracers (Srivatsan and Chen 2014). PET (positron emission tomography) works by detecting gamma rays emitted from the destruction of positrons of radioactive materials. SPECT (single-photon emission computed tomography) is able to detect gamma rays directly emitted from isotopes such as 99mTc (Rahmim and Zaidi 2008). Various research studies have been reported indicating that liposomes can encapsulate radionuclide tracers inside their aqueous compartment or within a chemically engineered lipid bilayer (Henriksen et al. 2015; Ogawa et al. 2014; Seo et al. 2008; Petersen et al. 2011). Ferrara and colleagues designed temperature-sensitive liposomes using a combination of PET and fluorescence imaging (Paoli et al. 2010). They used 18F- or 64Cu-labeled lipids in liposome preparations, which embody the fluorophore Alexa Fluor 750 as a hydrophilic model drug. The tumor fluorescence images correlate well with PET and ex vivo fluorescence images when using a stable liposome formulation. Hence, a combination of PET and optical imaging techniques could be very beneficial for alleviating tumors.

188Re-labeled DSPC-based liposomal doxorubicin was fabricated and evaluated their targeting efficiency and antitumor effects in a C26murine tumor model by SPECT imaging (Chang et al. 2010). In in vivo micro, SPECT/CT imaging was used to assess the liposomes tumor targeting by measuring their biodistribution and pharmacokinetics. The bimodal radiochemotherapeutic 188Re-liposome-DOX showed greater tumor inhibition and a longer median survival time than either single-functionalized 188Re-liposomes or liposome-DOX.

10.5 Challenges in Translation of Nanoliposomes-Based Drug Delivery in Clinical Settings

The advancements in the development of liposome delivery systems are progressing at a fast pace, in light of the demand for the new stratagems for breast cancer therapy. However, a well-built understanding or road map on the design of the new liposome formulation for BC is lacking somewhere. Selection of the targeting and triggering modalities depends on the molecular subtypes of the tumor and the ongoing conventional treatments. Although the conventional liposome-encapsulated chemotherapeutic drug-based formulation is being frequently used in the clinical practice in BC treatment, still there are countless obstacles in the clinical implementation of these novel and advance versions of liposome formulations (Yang et al. 2021). With triggerable liposomes, the triggering mechanisms need to be further explored while designing such liposome formulations. For example, the selection of the phospholipid component for light-triggered liposomes needs to be in accordance with desired photo-induced mechanisms. In a photochemical pathway, for instance, photooxidative reaction, unsaturated phospholipids should be used in the formulation (Yang et al. 2021). Furthermore, active ingredients employed in the triggerable liposome formulation should be optimized to weigh up their benefits and risks to healthy tissues (Yang et al. 2021). From the perspective of the clinical applications,

the far-reaching development of liposome technology will ultimately benefit BC patients. Recent studies confirmed that various liposome constructs loaded with drugs can reduce the intensities of cardiotoxicity, address drug resistance, and improve the overall drug release profile. Modification of the liposome surface with targeting ligands offers surplus opportunities for designing site-specific therapy and curtailing the nonspecific effect of conventional chemotherapeutic drugs. The new genera liposomes with triggering features also allow efficient control of payload release and thus substantially augmenting the therapeutic outcomes for BC patients. Advance forms of liposome formulations could magnify the assortment of drug delivery options for the treatments of BC by efficaciously addressing the critical problems of drug toxicity and limited therapeutic effects.

10.6 Conclusion

The liposomes represent a promising approach as efficient and targeted delivery of anticancer agents to various tumor sites in BC alleviation. The advantages of encapsulating the drug in the nanoliposomal carrier are improved solubilization of the drug, increased half-life, prolonged circulation, selective accessibility of the drug to the target site, and substantially overcoming of multidrug resistance. The advanced and modified versions of liposomes as discussed in this chapter curtail the highly desirable characteristic features of tumor cell recognition and internalizing that could contribute substantially to the therapeutic intervention of BC. Precise molecular targeting can be accomplished with these smart generations of nanoliposomes, besides enhanced pharmacokinetic and biodistribution of anticancer agents. The integrated approaches such as theranostic liposomes or antibody-targeted ones can be efficiently employed for targeting small molecule drugs as well as biological agents with anticancer activity and can provide a new landscape in the liposomes-based BC therapeutic front. Earlier, PEGylated liposomes have addressed critical pharmacological concerns accompanied with the conventional drug delivery system, such as disruption by blood lipoproteins, uptake by RES, and rapid clearance from blood circulation. Now PEGylated liposomes are approved by regulatory authorities and have successfully reached the market. However, the clinical success of PEGylated liposomes is hampered by some grave limitations, such as a lack of tumor cell specificity. Therefore, to increase the target specificity and the amount of released therapeutic agent at the tumor site, stimuli-sensitive liposomes and multifunctional carriers such as theranostic liposomes have been designed. The increasing complexity of advanced versions of liposomal formulation needs rigorous in vitro and in vivo preclinical studies for their translation to the clinics. Certainly, recent research studies demonstrate that new generation liposomes could be a viable anticancer therapeutic tool in the treatment of BC.

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