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Review Article

Tailored Liposomal Nanocarriers for Precision Breast Cancer Therapy

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Abstract

Breast cancer remains one of the most frequently diagnosed malignancies worldwide and continues to represent a major public health concern despite substantial advances in diagnostic and therapeutic strategies. Conventional chemotherapy, although effective in many cases, is often associated with non-specific drug distribution, severe systemic toxicity, limited bioavailability, and the development of multidrug resistance. These limitations significantly compromise therapeutic outcomes and patient quality of life. Liposome-based drug delivery systems have developed as a highly promising nanotechnological approach to address these challenges by improving drug solubility, stability, circulation time, and tumor selectivity. Through rational design and surface functionalization, liposomes can be engineered to achieve passive and active targeting, controlled drug release, and reduced off-target effects. This review provides an expanded and original discussion of liposomal nanocarriers developed for targeted breast cancer therapy, covering formulation strategies, classification, targeting mechanisms, stimuli-responsive systems, clinical applications, current challenges, and future perspectives.

Keywords: Liposomal nanocarriers; Breast cancer therapy; Targeted drug delivery; Nanomedicine; Stimuli-responsive systems; Precision oncology

Introduction:

Cancer continues to pose a significant global public health challenge and remains one of the foremost causes of death worldwide. Recent epidemiological data from the GLOBOCAN 2021 database indicate that breast cancer has overtaken lung cancer as the most commonly diagnosed malignancy among women. In that year alone, an estimated 2.3 million new breast cancer cases were reported globally, accompanied by approximately 680,000 disease-related deaths across 185 countries [1]. While the incidence of breast cancer varies markedly with ethnicity, socioeconomic conditions, geographical location, and healthcare accessibility, long-term epidemiological trends demonstrate a consistent rise in both incidence and mortality over the last 25 years [5].

Breast cancer arises from the malignant transformation of epithelial cells lining the ducts or lobules of the mammary gland. The disease is characterized by substantial biological and clinical heterogeneity, encompassing a wide spectrum of histopathological subtypes and molecular alterations, which complicates disease classification and therapeutic management. On the basis of histological origin, breast cancers are broadly divided into ductal and lobular carcinomas. Ductal lesions may occur in either non-invasive or invasive forms (Fig. 1). Non-invasive tumors, collectively referred to as carcinoma in situ, remain confined to the ductal or lobular structures without breaching the surrounding tissue. Among these, ductal carcinoma in situ (DCIS) accounts for nearly 90% of cases, whereas lobular carcinoma in situ (LCIS) is comparatively rare[6]. These non-invasive lesions generally exhibit favorable clinical outcomes and are biologically distinct from invasive disease.

In contrast, invasive breast cancer is defined by the capacity of malignant cells to penetrate the basement membrane and invade adjacent stromal and adipose tissues. Invasive ductal carcinoma represents approximately 80% of all invasive breast cancer cases and comprises multiple histological variants, including medullary, mucinous, tubular, and papillary carcinomas. Additional invasive subtypes include invasive lobular carcinoma, inflammatory breast cancer, and Paget's disease of the nipple and breast [7]. Less common malignancies, such as phyllodes tumors derived from stromal components and breast carcinomas exhibiting neuroendocrine differentiation, are also recognized within the invasive breast cancer spectrum [8].

Progress in molecular biology and genomics has substantially refined breast cancer classification. Investigations into tumor etiology, gene expression patterns, and clinical behavior have revealed distinct molecular subtypes within both ductal and lobular carcinomas [9]. These molecular categories are primarily defined by the expression status of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2), which serve as key biomarkers for prognostic assessment and therapeutic decision-making [4,10]. Clinically relevant subtypes include Luminal A (ER+ and/or PR+, HER2−), Luminal B (ER+ and/or PR+, HER2+), and basal-like tumors lacking ER, PR, and HER2 expression [11]. Large-scale transcriptomic analyses have further classified breast cancer into five intrinsic subtypes: Luminal A, Luminal B, HER2-enriched, basal-like and claudin-low [12, 13].

Genetic predisposition is a critical contributor to breast cancer susceptibility. Inherited mutations in tumor suppressor genes, particularly BRCA1 and BRCA2, confer a markedly increased lifetime risk of developing breast cancer, estimated at approximately 70% and 60%, respectively[6,14] . Among the molecular subtypes, basal-like breast cancer—commonly referred to as triple-negative breast cancer (TNBC)—accounts for approximately 15–20% of all cases. TNBC is associated with aggressive clinical behavior, high histological grade, absence of established molecular targets, and poor patient prognosis [10,15,16] .

Advances in the understanding of breast cancer biology have facilitated the development of sophisticated therapeutic strategies and targeted drug delivery approaches. Contemporary treatment regimens are highly individualized and are determined by tumor size, histopathological grade, molecular subtype, disease stage, proliferative activity, and lymph node involvement. Comprehensive guidelines for the diagnosis and management of breast cancer have been extensively reviewed by Moo et al. [17]. Standard care typically employs a multimodal strategy, integrating surgery, chemotherapy, endocrine therapy, radiotherapy, and immunotherapy. Notably, higher rates of disease recurrence are observed in basal-like and Luminal B tumors compared with Luminal A breast cancers [18].

Cytotoxic chemotherapy remains a cornerstone of breast cancer treatment and may be administered in either the neoadjuvant or adjuvant setting. Frequently used chemotherapeutic agents include anthracyclines such as doxorubicin and epirubicin, taxanes including paclitaxel and docetaxel, platinum-based drugs such as cisplatin and carboplatin, and antimetabolites like gemcitabine and fluorouracil [19]. In hormone receptor–positive breast cancer, chemotherapy is often combined with endocrine therapies, including tamoxifen, fulvestrant, and aromatase inhibitors such as letrozole, to enhance therapeutic efficacy [20–22]. Immunotherapeutic interventions—encompassing monoclonal antibodies, cytokine therapies, cancer vaccines, and adoptive cell transfer—are predominantly utilized in HER2-positive breast cancer [23].

Despite its widespread use, chemotherapy is associated with several inherent limitations. Poor tumor selectivity frequently leads to systemic toxicity and a broad spectrum of adverse effects [24,25]. Moreover, chemotherapy is occasionally prescribed in clinical contexts where less intensive treatment options may suffice, resulting in avoidable physical, psychological, and financial burdens for patients [26,27]. A further major obstacle is the emergence of multidrug resistance (MDR), which significantly contributes to therapeutic failure and disease relapse. MDR is commonly driven by the overexpression of ATP-binding cassette transporters, including P-glycoprotein, which actively expel anticancer agents from tumor cells and reduce intracellular drug concentrations [28–31].

Metastatic spread to distant organs remains the leading cause of breast cancer–associated mortality. Metastatic breast cancer is generally regarded as incurable and is characterized by poor survival outcomes and limited treatment options [37,38]. In response to these challenges, nanotechnology-based drug delivery platforms—such as liposomes, polymeric micelles, dendrimers, and lipid nanocapsules—have gained considerable attention as innovative tools for cancer therapy [40]. These nanoscale systems allow for controlled and targeted drug delivery through surface modification with ligands including peptides, antibodies, and proteins, thereby improving pharmacokinetics, therapeutic efficacy, and safety profiles [41–45].

First-generation nanomedicines, such as PEGylated liposomal doxorubicin (Doxil®/Caelyx®) and albumin-bound paclitaxel (Abraxane®), primarily rely on the enhanced permeability and retention (EPR) effect and represent significant milestones in the clinical application of nanotechnology for cancer treatment [46,47]. Among the various nanocarrier systems, liposomal drug delivery platforms have demonstrated particular promise due to their biocompatibility, structural versatility, and proven success in clinical settings.

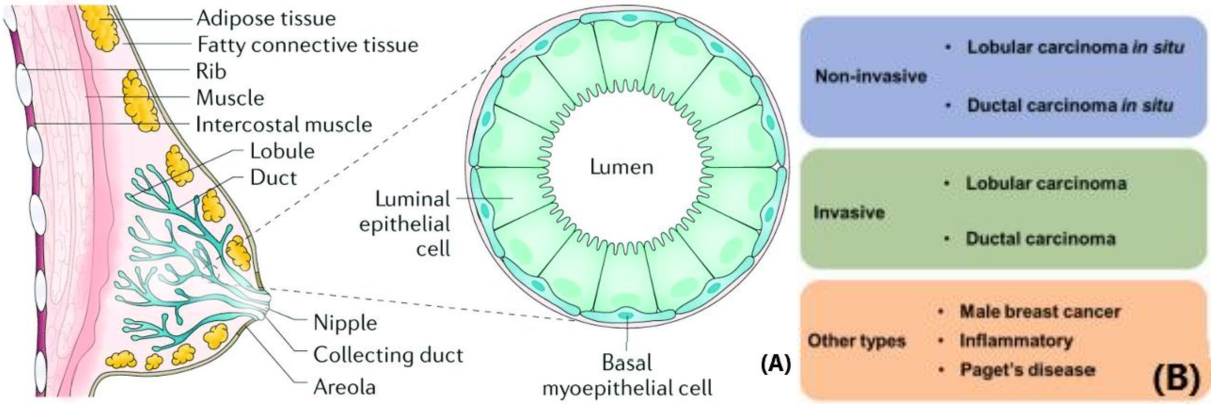

Figure 1: (A) Diagram showing ductal & lobular epithelium of breast, Ref [6]

(B) Breast cancer types

Liposomes are vesicular nanostructures that were first described in 1965 and are characterized by their spherical architecture composed of one or more concentric lipid bilayers enclosing an aqueous interior [48–50]. These vesicles are formed through the spontaneous self-assembly of amphiphilic lipids, most commonly phospholipids, when dispersed in an aqueous environment. Owing to their amphiphilic nature, phospholipids arrange themselves into bilayer structures that closely resemble biological cell membranes [51,52]. This biomimetic characteristic endows liposomes with admirable biocompatibility and biodegradability, making them highly attractive candidates for pharmaceutical and biomedical applications.

One of the most notable advantages of liposomes is their remarkable versatility in drug encapsulation. Hydrophilic compounds can be entrapped within the aqueous core, while lipophilic molecules are included into the hydrophobic region of the lipid bilayer. Amphiphilic agents may localize at the lipid–water interface, allowing liposomes to accommodate a broad spectrum of therapeutic molecules [53,54]. Furthermore, the physicochemical properties of liposomes can be finely tuned by modifying their lipid composition. Parameters such as bilayer fluidity, surface charge, hydration behaviour, and preparation method can be precisely controlled, enabling the design of liposomal systems tailored to specific drug delivery requirements [29,55].

Phospholipids of both natural and synthetic origin are the primary building blocks used in liposome formulation [56]. However, liposomes composed exclusively of phospholipids often suffer from limited physical stability, short shelf-life, and increased membrane permeability, which may result in premature drug leakage. To overcome these limitations, sterols—most notably cholesterol—are frequently incorporated into the lipid bilayer. Cholesterol plays a critical role in modulating membrane rigidity, reducing bilayer permeability, and enhancing overall liposomal stability during storage and circulation [58,59].

In addition to improving drug solubility and delivery efficiency, liposomes act as protective carriers that shield encapsulated drugs from degradation caused by enzymatic activity, chemical reactions, and environmental stressors such as variations in pH, temperature, and ionic strength[62]. The incorporation of auxiliary components can further enhance liposomal performance. Antioxidants such as vitamin E or its derivatives, counting d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), as well as polymers like chitosan and polyethylene glycol (PEG), are commonly integrated into liposomal membranes to improve stability, prolong circulation time, and optimize biodistribution profiles [63].

Overall, liposomes offer numerous advantages as drug delivery vehicles, including spontaneous self-assembly, high drug-loading capacity, and enhanced solubility of poorly water-soluble drugs, improved drug stability, excellent biocompatibility, minimal toxicity, biodegradability, and low immunogenicity [64–68]. Advances in liposomal engineering have further expanded their functionality, enabling the development of stimuli-responsive systems that discharge their payload in response to specific internal or external triggers such as pH changes, temperature variations, redox conditions, enzymatic activity, light, ultrasound, or magnetic fields. Additionally, surface functionalization strategies, including the development of immunoliposomes, have facilitated active, site-specific targeting, leading to controlled drug release, and co-delivery of multiple therapeutics, improved bio distribution, and reduced non-specific uptake by healthy tissues [69–73].

At present, four liposome-based formulations have received clinical approval for use in breast cancer therapy: Doxil®/Caelyx®, Myocet®, Lipodox®, and Lipusu®. Among these, Doxil®/Caelyx® is a PEGylatednanoliposomal formulation containing doxorubicin hydrochloride (DOX HCl) and is widely used in the treatment of several malignancies, including metastatic breast cancer [85]. Myocet® is a non-PEGylated liposomal formulation of doxorubicin that has be approved in the European Union since 2000 for use in combination regimens for metastatic breast cancer [64]. Lipodox®, another PEGylated liposomal formulation of

DOX HCl, was initially introduced in the United States as an alternative during shortages of Doxil® and has since been regarded as its generic equivalent [87]. Lipusu® is a non-PEGylated liposomal formulation encapsulating paclitaxel (PTX) and has been approved in China for the treatment of HER2-positive metastatic breast cancer [81,82]. However, comprehensive details regarding the lipid composition of Lipusu® have not been publicly disclosed. In addition to these approved products, DaunoXome®, a thermosensitive liposomal formulation of daunorubicin, has been evaluated for metastatic breast cancer but has not yet obtained clinical approval [90–92].

Notably, none of the currently approved liposomal formulations for breast cancer therapy employ active targeting strategies. Instead, their tumor accumulation relies predominantly on passive targeting mechanisms mediated by the enhanced permeability and retention (EPR) effect [93,94]. Passive targeting refers to the preferential accumulation of macromolecules and nanoscale carriers within tumor interstitial spaces as a result of the abnormal vascular architecture of tumor tissue [95]. Rapid tumor growth often exceeds oxygen accessibility, leading to hypoxic conditions that stimulate the release of pro-angiogenic factors such as vascular endothelial enlargement factor (VEGF). This process results in irregular angiogenesis, leaky vasculature, and deficient lymphatic drainage. As a consequence, nanoparticles—particularly those with diameters below approximately 400 nm—can accumulate within tumor and inflamed tissues. Nevertheless, the EPR effect is highly variable and is generally less pronounced in early-stage tumors and poorly vascularized tissues. Its effectiveness is mainly observed in solid tumors exceeding approximately 4.6 mm in diameter, with vascular pore size strongly influenced by tumor type, location, and pathological status [93,94].

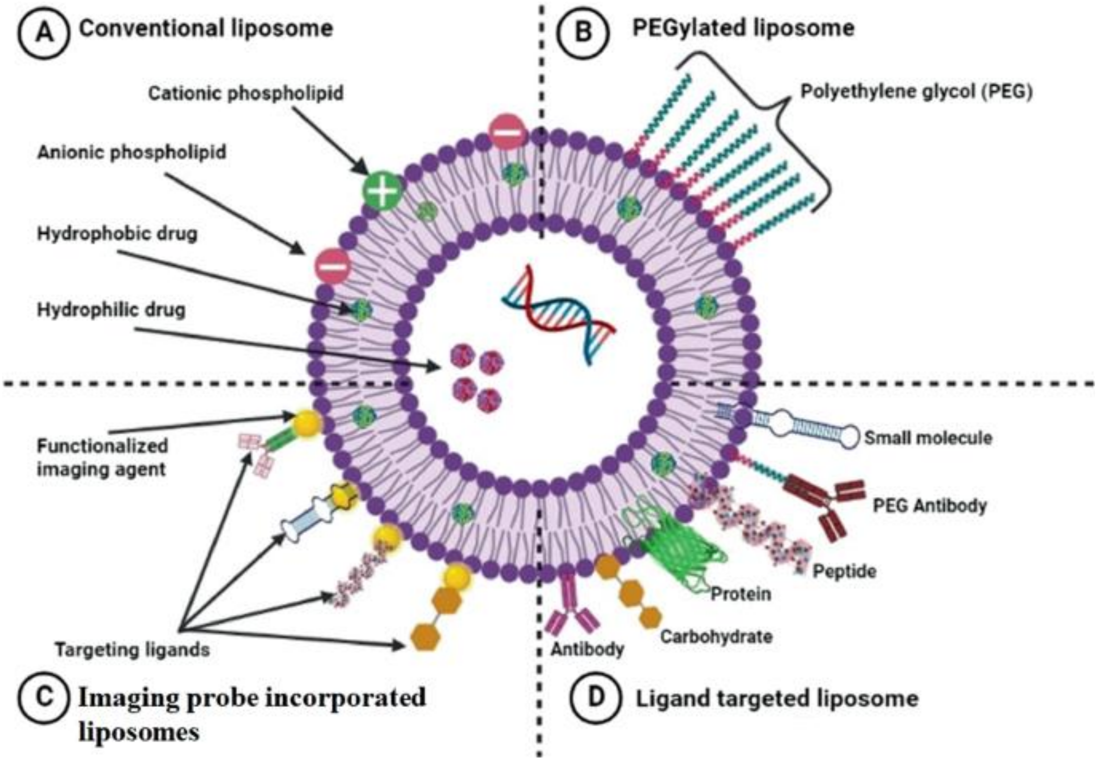

Figure 2: Liposome-based drug delivery strategies [96,97].

Following intravenous administration, non-PEGylated liposomal formulations such as Myocet® or Lipusu® circulate within the vascular compartment and are ultimately removed from systemic circulation by renal excretion or uptake by the mononuclear phagocyte system (MPS), also referred to as the reticuloendothelial system (RES) [96,97]. Nanoscale carriers with diameters of approximately 8 nm or smaller undergo limited metabolic processing and are primarily eliminated through the kidneys, whereas larger liposomes are preferentially cleared by the MPS via opsonization-mediated pathways. During opsonization, plasma proteins, known as opsonins, adsorb onto the surface of liposomal nanoparticles, marking them for recognition and subsequent phagocytosis by immune cells [98].

Surface modification of nanocarriers with inert polymers such as polyethylene glycol (PEG) can significantly attenuate opsonization. PEGylation creates a steric barrier around the nanoparticle surface, resulting in repulsive interactions with circulating blood components and conferring so-called “stealth” properties [99,100]. This stealth effect reduces MPS-mediated clearance, thereby prolonging systemic circulation and improving pharmacokinetic performance. As an illustrative example, the PEGylated liposomal formulation Doxil®/Caelyx® demonstrates a clearance half-life approximately 100-fold longer than that of free doxorubicin [101].

2. Targeted Nanoliposome-Based Approaches in Breast Cancer Therapy

Actively targeted liposomal drug delivery systems have gained considerable attention as an effective strategy to improve precision and treatment outcomes in cancer therapy. By incorporating specific targeting ligands on their surface, these systems enable preferential interaction with cancer cells, thereby enhancing therapeutic selectivity. This approach offers several important advantages, including: (i) enhanced cellular uptake of anticancer agents by tumor cells while minimizing drug exposure to healthy tissues, which in turn reduces systemic toxicity and lowers the likelihood of developing multidrug resistance (MDR); (ii) the potential to traverse physiological barriers such as the blood–brain barrier (BBB); and (iii) the ability to selectively recognize, image, and treat metastatic, recurrent, and breast cancer–linked cell populations [102].

Substantial interest in actively targeted nanomedicine has been demonstrated through both preclinical investigations and clinical evaluations, particularly for the treatment of solid tumors. Regardless of its strong theoretical appeal, however, the practical implementation of active targeting remains challenging. Successful targeting requires not only the identification of appropriate and biologically relevant receptors but also the careful modification of liposomes with targeting ligands that exhibit high binding affinity without compromising the stealth properties necessary for prolonged circulation.

To achieve effective ligand attachment, liposomal surfaces are commonly functionalized through chemical modification using reactive groups that enable the conjugation of diverse targeting moieties. Several well-established conjugation strategies are employed for this purpose, including imine and amide bond formation, disulfide linkages, thiol–maleimide click chemistry reactions, and hydrazone-based crosslinking methods [103,104]. These functionalization approaches allow precise control over ligand density and orientation, which are critical parameters for optimizing targeting efficiency and therapeutic performance.

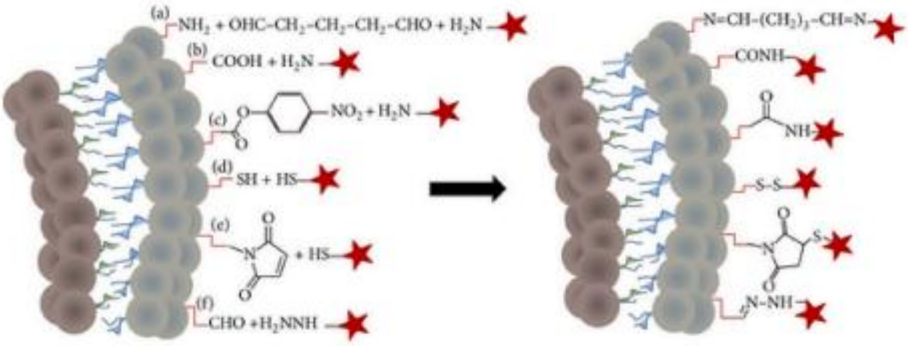

Figure 3: Overview of six principal chemical approaches (a–f) used for liposomal surface functionalization. Star symbols denote attached targeting ligands. Adapted from Ref. [105].

Among these strategies, the thiol-maleimide click chemistry reaction is particularly popular, extensively utilized for conjugation between nanoparticles and various targeting agents [106]. Substitute methods for liposomal surface functionalization include adsorption or intercalation via electrostatic or hydrophobic interactions [105,107]. A variety of targeting ligands have been explored for actively targeted liposomal systems, including small molecules, monoclonal antibodies (mAbs), peptides, and aptamers. These ligands are designed to selectively bind to molecular targets expressed on breast cancer cells or within the tumor microenvironment (TME), thereby enhancing site-specific drug delivery. Initial drug-targeting strategies predominantly relied on full-length monoclonal antibodies because of their high binding affinity and specificity. However, limitations such as restricted tissue penetration, potential immunogenicity, complex manufacturing processes, and high production costs have shifted attention toward smaller antibody-derived constructs. Antibody fragments, including antigen-binding fragments (Fab) and single-chain variable fragments (scFv), have emerged as more favorable alternatives due to their reduced size, improved permeability, and lower immunogenic potential [94,108].

Peptides represent another widely used class of targeting ligands, owing to their ease of synthesis, relatively low cost, and ability to achieve selective binding while minimizing nonspecific interactions and opsonization. Despite these advantages, peptide-based ligands are inherently vulnerable to enzymatic degradation, which can limit their stability and in vivo performance [109,110]. Small-molecule ligands, such as sorafenib, offer benefits including high membrane permeability and cost-effectiveness; however, their limited targeting specificity may reduce selectivity toward cancer cells. In contrast, aptamers—short single-stranded DNA, RNA, or peptide sequences—exhibit exceptional binding affinity and specificity toward a wide range of targets, including small molecules, proteins, viruses, and whole cells. Compared with antibodies, aptamers provide advantages such as smaller size, enhanced chemical stability, ease of large-scale synthesis, and straightforward chemical modification. Nevertheless, their clinical application is challenged by rapid systemic clearance and susceptibility to degradation in biological environments [111–113].

2.1. Cell Surface Receptor–Mediated Targeting Strategies

2.1.1. CXCR4-Directed Liposomal Systems for Cancer Treatment

C-X-C chemokine receptor type 4 (CXCR4) is a transmembrane G protein–coupled receptor that is widely expressed across numerous physiological systems. It plays a critical role in regulating cell migration, embryonic development, hematopoietic cell trafficking, and neuronal processes such as neurite and axonal outgrowth [172]. CXCR4 is present on the surface of diverse cell types, including hematopoietic and endothelial cells, neurons, stem cells, and a wide range of malignant cells. Deregulated or elevated CXCR4 expression has been strongly coupled with haematological malignancies and is recognized as an adverse prognostic marker in several solid tumors, including breast cancer [173,174].

Accumulating evidence has identified the CXCR4/CXCL12 signaling axis as a key driver of breast cancer progression and metastatic dissemination. CXCL12, also known as stromal cell–derived factor-1 (SDF-1), functions as a potent chemokine that directs CXCR4-expressing tumor cells toward organs with high CXCL12 expression, such as the lungs, bones, and lymph nodes. This chemotactic gradient facilitates tumor cell homing and colonization at distant metastatic sites [175,176]. Within the tumor microenvironment (TME), CXCR4 signaling further contributes to immune cell recruitment, stromal reorganization, and enhanced tumor cell motility, thereby supporting tumor growth and invasion.

Exploiting this biology, Lu et al. developed a CXCR4-targeted liposomal delivery system to improve the therapeutic efficacy of the CXCR4 antagonist AMD2000 [116]. AMD2000, which has been clinically approved since 2008 for the treatment of non-Hodgkin’s lymphoma and multiple myeloma, was incorporated into the liposomal formulation in a dual manner: encapsulated within the aqueous core and simultaneously conjugated to the liposomal surface. This design enabled the nanocarrier to serve both as a targeting moiety and as a therapeutic agent. Consequently, CXCR4 signalling was inhibited at the cell surface through ligand–receptor interaction and intracellular following liposomal internalization. This dual-action strategy effectively modulated immune and stromal components of the TME, resulting in its functional reprogramming and structural remodeling.

In a complementary approach, Zhang et al. reported a peptide-directed liposomal platform that combined chemotherapy with photothermal therapy to enhance breast cancer treatment outcomes [117]. This system employed a novel targeting peptide, p12 (QGSRRRNTVDDWISRRRALC), conjugated to PEGylated liposomes co-encapsulating doxorubicin (DOX) and indocyanine green (ICG), a clinically approved photothermal agent. The p12 peptide promoted selective tumor accumulation of the liposomes, thereby limiting off-target distribution and reducing DOX-associated toxicities, including cardiotoxicity and metastatic spread. In addition, ICG enabled localized photothermal activation, triggering controlled DOX release at tumor sites upon exposure to temperatures exceeding 41 °C.

Despite the therapeutic promise of targeting the CXCL12/CXCR4 axis—highlighted by the clinical use of AMD2000—important challenges remain. The regulatory complexity of this signaling pathway and the long-term consequences of sustained CXCR4 inhibition are not yet fully understood. Prolonged CXCR4 blockade has been associated with adverse hematological effects, including leucocytosis, thrombocytopenia, and splenomegaly. These toxicities are attributed to the broad physiological expression of CXCR4 in multiple organs, such as the heart, liver, spleen, and kidneys [177].

Recent advances have further expanded CXCR4-targeted nanotherapeutic strategies to include gene-silencing approaches. Guo et al. developed pH-responsive liposomes functionalized with CXCR4-targeting ligands and loaded with small interfering RNA (siRNA) against lipocalin-2 (Lcn2), a protein frequently overexpressed in epithelial cancers and closely linked to epithelial–mesenchymal transition (EMT) [114]. This combined strategy of receptor targeting and Lcn2 gene suppression significantly reduced metastatic breast cancer cell migration, particularly in triple-negative breast cancer (TNBC) models. Supporting these findings, Liu et al. demonstrated that liposomes decorated with varying surface densities of the CXCR4-binding peptide DV1 exhibited differential cellular uptake and effectively inhibited TNBC cell migration. This effect was mediated through down regulation of motility-related proteins triggered by CXCR4-dependent signalling pathways at the cell surface [115].

2.1.2. Targeting Cell Surface–Associated Nucleosomes

During programmed cell death and necrotic processes, intracellular nuclear components may be released into the extracellular environment, triggering immune responses that lead to the generation of antinuclear antibodies (ANAs) directed against these nuclear antigens. ANAs are widely used as diagnostic and prognostic markers in systemic immune-mediated diseases, with specific antibody subsets closely associated with distinct clinical conditions. For instance, antibodies against double-stranded DNA are a hallmark of systemic lupus erythematosus [178].A related group of nuclear targets, collectively known as extractable nuclear antigens (ENAs), can be isolated from cell nuclei under saline conditions and include ribonucleoproteins and non-histone proteins such as Smith (Sm), ribonucleoprotein, and scleroderma-70 (Scl-70). In addition to their established role in autoimmune disease diagnostics, these nuclear antigens have also been explored as potential biomarkers in oncology. Notably, their application in breast cancer has shown promise for improving early disease detection and clinical assessment [179,180].

Building on this concept, Torchilin and colleagues developed a monoclonal antinuclear antibody, mAb 2C5, that specifically recognizes tumor-associated cell surface nucleosomes across a range of cancer types. This antibody was employed to functionalize Doxil® liposomes, resulting in targeted nanocarriers capable of selectively binding to tumor cells. In vitro studies demonstrated a 3- to 8-fold increase in cellular uptake and internalization compared with non-targeted liposomes, with enhanced cytotoxicity observed even in doxorubicin-resistant cell lines [118,119]. Subsequent in vivo evaluation using ^111In-labeled mAb 2C5-liposomes and whole-body γ-scintigraphic imaging confirmed preferential tumor accumulation and superior antitumor efficacy in subcutaneous 4T1 murine tumor models [120].

Expanding this strategy, Narayanaswamy and Torchilin developed dual-drug liposomal systems combining paclitaxel (PTX) and salinomycin to target both bulk breast cancer cells and cancer stem cells (CSCs), with the goal of mitigating tumor growth and metastasis [121]. Despite promising preclinical results, as of 2022 no clinical trials involving mAb 2C5 have been registered on clinicaltrials.gov, prompting exploration of alternative nanocarriers, including polymeric micelles and dendrimers, for potential clinical translation.

2.1.3. Eph Receptor Tyrosine Kinases as Therapeutic Targets

Eph receptors, a family of tyrosine kinase receptors, play pivotal roles in various cellular processes such as cell-cell interactions, proliferation, differentiation, signalling, migration, and tissue morphogenesis, as well as in pathological processes [181]. Among the fourteen members of the Eph receptor tyrosine kinase family, EphA2 has emerged as one of the most extensively studied receptors in oncology. Elevated expression of EphA2 has been reported across a broad range of malignancies, including cancers of the brain, bladder, breast, lung, skin, ovary, and prostate [182]. In breast cancer specifically, EphA2 plays a central role in multiple aspects of tumor biology, including uncontrolled cell proliferation, angiogenesis, therapeutic resistance, tumor progression, cellular migration, and metastatic dissemination [183]. Importantly, aggressive breast cancer phenotypes that lack estrogen receptor alpha (ERα) expression consistently display increased EphA2 levels, further highlighting its association with poor prognosis and disease aggressiveness [183]. These characteristics position EphA2 as a highly attractive molecular target for the development of targeted therapeutic strategies.

Recognizing the therapeutic potential of EphA2, several research groups have focused on designing EphA2-directed drug delivery systems. A prominent example is MM-200, an EphA2-targeted nanoliposomal formulation encapsulating the chemotherapeutic agent docetaxel. This system has been developed for the treatment of multiple tumor types, including triple-negative breast cancer (TNBC), where effective targeted therapies are limited [122]. Phase I clinical trials (NCT03076372) have been conducted to evaluate the safety and tolerability of this approach in human subjects. However, as of 2022, detailed outcomes beyond safety assessments have not yet been publicly reported [184.]

Building on this platform, the same research group further investigated a combinatorial treatment strategy that integrates chemotherapy with immunotherapy. In this approach, docetaxel delivered via the EphA2-targeted nanoliposomal system was combined with immune checkpoint inhibitors directed against programmed cell death protein 1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4). This combination was designed to overcome tumor immune evasion, therapeutic resistance, and disease recurrence—particularly in TNBC, which is often characterized by low intratumoral T-cell infiltration and poor response to immunotherapy alone [185].

In a TNBC tumor model, treatment with EphA2-targeted liposomes co-delivering docetaxel and an anti-programmed cell death receptor-1 (PD-1) antibody produced a therapeutic response in approximately 60% of cases, with sustained resistance to tumor rechallenge and a pronounced immunomodulatory effect. In a related approach, doxorubicin (DOX)-loaded stealth liposomes were surface-functionalized with the homing peptide YSAYPDSVPMMSK and evaluated under both in vitro and in vivo conditions [124]. Notably, modification with YSAYPDSVPMMSK significantly enhanced the antitumor activity of DOX by promoting apoptosis in cancer cells, suppressing tumor progression and CD31 expression, and limiting angiogenic and metastatic potential. Collectively, these findings underscore the therapeutic promise of EphA2-targeted strategies in breast cancer and support their potential translational relevance based on encouraging preclinical and emerging clinical evidence.

2.1.4. Folate Receptor–Mediated Drug Delivery in Breast Cancer

Reduced folates are essential cofactors in amino acid metabolism and nucleic acid synthesis, playing a pivotal role in normal cell survival. Folate receptors (FRs) are glycoprotein receptors for vitamin B9, with four identified isoforms (α, β, γ, and δ) that exhibit tissue-specific expression patterns [186]. Among these, folate receptor-α (FRα) is frequently overexpressed in tumors due to the elevated requirement for folate during DNA repair and replication associated with carcinogenesis. Consequently, FRα has emerged as a biomarker and therapeutic target across multiple malignancies, including breast, ovarian, brain, lung, and colorectal cancers [187,188].

Folate-decorated, long-circulating, and pH-responsive liposomal platforms have been widely explored as therapeutic systems for metastatic, multidrug-resistant (MDR), and triple-negative breast cancer (TNBC). As an illustrative example, Gazzano et al. engineered liposomes encapsulating doxorubicin (DOX) chemically linked to nitric oxide (NO)–donating groups to overcome P-glycoprotein–mediated drug efflux in MDR breast cancer models [132]. Functionalization of the liposomal surface with folate enabled receptor-mediated internalization, promoting intracellular trafficking toward both nuclear and mitochondrial compartments. Within these organelles, DOX triggered DNA damage, cell cycle arrest, and activation of mitochondria-dependent apoptotic pathways.

In animal models, the folate-targeted liposomal formulation markedly suppressed tumor growth in breast cancers expressing P-gp and folate receptor α (FRα), whereas treatment with free DOX or the clinically approved formulation Caelyx® failed to produce comparable antitumor effects. Importantly, both primary tumor cells and cells isolated from treated tumors retained sensitivity to successive treatment cycles, suggesting sustained therapeutic efficacy and reduced propensity for resistance development.

In another approach, Deng et al. designed folate-targeted liposomes co-encapsulating DOX and functionalized with PEG chains cleavable by matrix metalloproteinase-2 (MMP-2) [133]. This strategy leveraged chemotherapy-induced immunogenic cell death to convert tumors into an in situ "vaccine" while simultaneously targeting 4T1 breast cancer cells and immunosuppressive M2 tumor-associated macrophages (M2-TAMs) via the folate receptor. Coupled with cytosine-phosphate-guanine (CpG) therapy to enhance T cell activation, this combinatorial approach not only reduced primary tumor growth but also suppressed lung metastases and metastatic nodal expansion.

Despite these advances, challenges remain for folate receptor-targeted nanocarriers. Circulating folate from diet or supplements can compete with receptor-mediated uptake, limiting therapeutic efficiency. Furthermore, the high expression of FRα in normal kidney tissues can lead to off-target accumulation, necessitating careful consideration in clinical translation.

2.2. Transmembrane Receptors as Targets in Breast Cancer Therapy

2.2.1. Biotin receptor

Biotin is a water-soluble essential vitamin that plays a critical role in numerous metabolic pathways. Cellular uptake of biotin occurs through two primary mechanisms: passive diffusion at supraphysiological concentrations and active, carrier-mediated transport at lower concentrations. The latter process is facilitated by biotin-specific receptors and sodium-dependent multivitamin transporters (SMVTs), which are widely expressed in absorptive tissues and are responsible for the transport of several vitamins and essential cofactors across cell membranes [189,190]. Increasing evidence suggests that altered expression of biotin receptors and SMVTs is associated with various malignancies, including breast cancer, thereby highlighting these transport systems as attractive targets for diagnostic imaging and targeted therapeutic delivery [191,192].

To investigate how ligand architecture influences the performance of targeted liposomal nanocarriers in breast cancer, Lu et al. engineered liposomes functionalized with double-branched biotin ligands at different surface densities [157]. Their findings revealed that liposomes modified with double-branched biotin exhibited markedly enhanced interaction with SMVT-expressing breast cancer cells, as demonstrated by increased cellular uptake in vitro and improved tumor accumulation in vivo. In addition, paclitaxel (PTX)-loaded liposomes incorporating double-branched biotin showed superior antitumor efficacy compared with non-targeted or single-ligand systems, indicating that increased ligand density on the liposomal surface can significantly enhance targeting efficiency. Building on these results, the same group further examined the effects of higher-order ligand branching by incorporating tri-branched and tetra-branched biotin moieties onto the liposomal surface, thereby providing deeper insight into the relationship between ligand multiplicity and targeting performance [158].

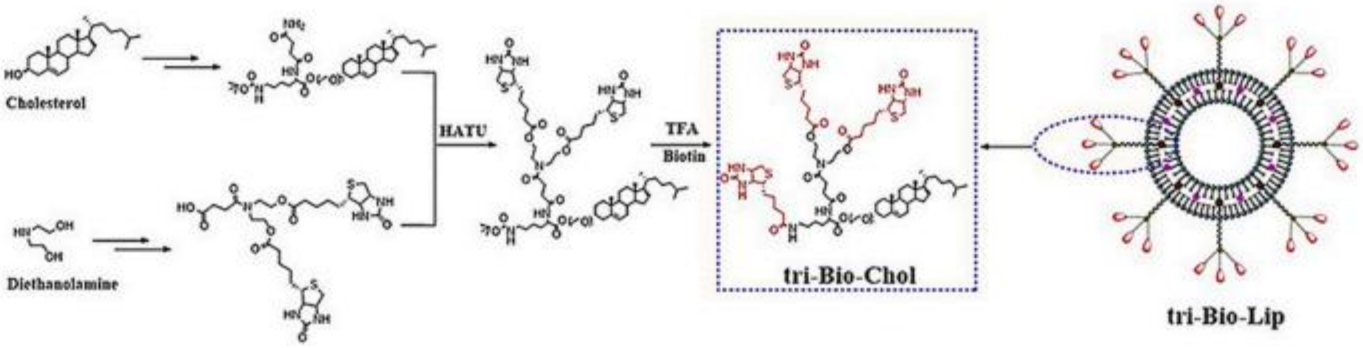

Figure 4: Example of biotin receptor-targeted liposomes:Tri-branched biotin-functionalized liposomes loaded with paclitaxel (PTX) were used to demonstrate that both ligand density and spatial orientation significantly influence cellular uptake in breast cancer cells. Adopted from Ref. [158].

Cellular uptake and cytotoxicity studies demonstrated that paclitaxel (PTX)-loaded tri-branched biotin-functionalized liposomes achieved the highest levels of internalization and anti-proliferative activity in breast cancer cells. In vivo imaging using 4T1 tumor-bearing mice confirmed these observations, highlighting that both the density and spatial configuration of biotin residues modulate the binding affinity between targeted liposomes and sodium-dependent multivitamin transporters (SMVT) on tumor cells.

Building on this concept, Huang et al. [159] developed a dual-targeting liposomal system functionalized with both biotin and glucose on a double-branched surface. This strategy significantly enhanced cellular uptake and tumor accumulation in vitro and in vivo compared with liposomes modified with a single targeting ligand. These results emphasize the importance of ligand density and multivalent presentation in optimizing receptor-mediated uptake and underscore the potential of biotin-based targeting approaches to improve the therapeutic performance of liposomal drug delivery systems in breast cancer.

2.2.2. Cluster of differentiation 44

CD44 is a widely expressed transmembrane glycoprotein involved in cell adhesion, proliferation, and migration, with aberrant expression strongly associated with tumor progression, angiogenesis, and metastasis in breast cancer, particularly triple-negative breast cancer (TNBC) [193,194]. CD44 primarily binds hyaluronic acid (HA), a major extracellular matrix component, and this interaction activates signaling pathways that promote tumorigenesis, making the CD44–HA axis an attractive therapeutic target [195,196].

Exploiting this interaction, HA-functionalized liposomal drug delivery systems have been extensively developed for targeted breast cancer therapy. Lv et al. engineered thermosensitive liposomes encapsulating the MMP inhibitor marimastat and an HA-conjugated paclitaxel (PTX) prodrug, enabling heat-triggered drug release that enhanced tumor penetration and significantly inhibited tumor growth and angiogenesis in vivo [160]. Similarly, Han et al. designed HA-conjugated gemcitabine-loaded liposomes to simultaneously target breast cancer cells and cancer stem cells, improving intracellular drug uptake while reducing systemic toxicity and therapeutic resistance [161]. In another innovative approach, Jiang et al. developed a liposomal “nanodepot” system for the co-delivery of TRAIL and doxorubicin, achieving enhanced anticancer efficacy through the simultaneous activation of complementary therapeutic mechanisms [162].

Overall, HA-decorated liposomes represent a versatile and effective strategy for CD44-mediated targeting in breast cancer, offering improved tumor selectivity, enhanced drug accumulation, and superior therapeutic outcomes.

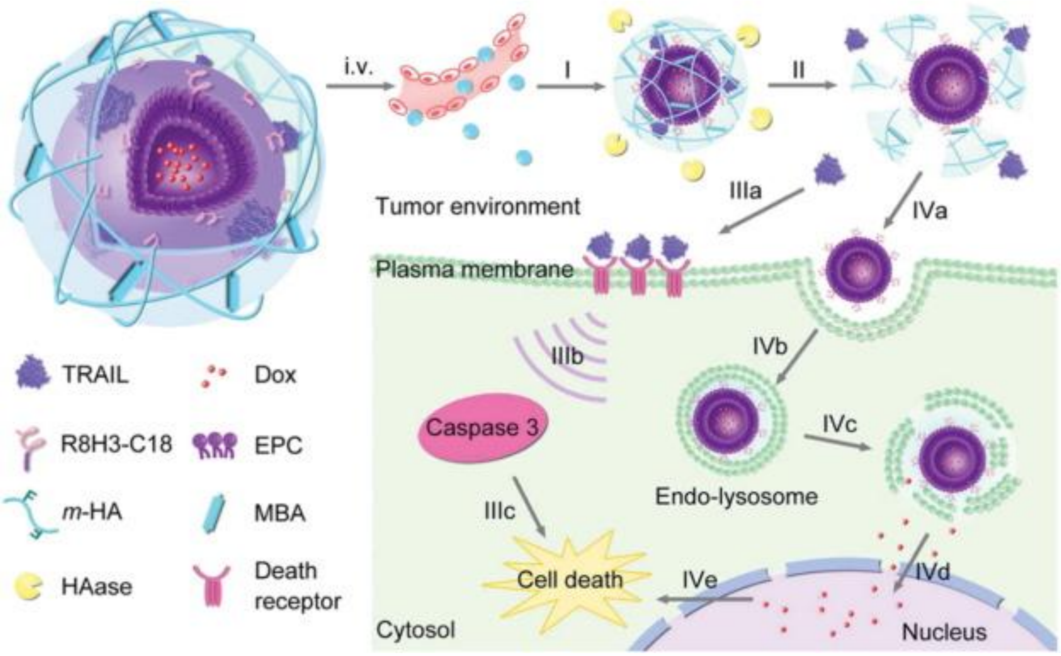

Figure 5: Illustration of the TRAIL/DOX-Gelipo design, showing the HA cross-linked outer shell encapsulating DOX and TRAIL, and the proposed multistage delivery of TRAIL to the cell surface and DOX to the nucleus as an example of CD44 liposomal targeting of breast cancer Ref [162].

The strategy employed by Jiang et al. involved loading doxorubicin (DOX) into the aqueous core of the liposomes, while tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) was confined to the outer shell of the crosslinked hyaluronic acid (HA) shell [162]. This arrangement aimed to target cancer cells overexpressing CD44, as the HA shell would degrade in the tumor microenvironment (TME) due to hyaluronidases, releasing TRAIL and facilitating liposome internalization.

Yang et al. reported that chitosan can effectively target CD44, a receptor highly expressed on breast cancer stem cells (CSCs) and within tumor tissues [164]. In their study, chitosan-functionalized liposomes loaded with gambogic acid and radiolabeled with ^89Zr were engineered to selectively bind CD44 on TNBC CSCs. These nanocarriers demonstrated efficient tumor accumulation and exhibited pronounced antitumor activity in in vivo models.

In a related investigation, Ding et al. designed chitosan oligosaccharide–based liposomes encapsulating the photosensitizer HPPH together with the hypoxia-activated prodrug TH302 for CD44-directed therapy in TNBC [163]. This multifunctional nanoplatform enabled simultaneous CD44 targeting, diagnostic imaging, photodynamic therapy, and hypoxia-responsive chemotherapy. By leveraging the hypoxic conditions generated following photodynamic treatment, TH302 was selectively activated, resulting in synergistic anticancer effects in both in vitro and in vivo models.

Furthermore, Guo et al. developed a liposomal formulation conjugated with anti–interleukin-6 receptor (IL6R) antibodies to modulate the tumor microenvironment (TME) of CD44-positive breast cancer cells in TNBC and luminal breast cancer mouse models [165]. Inhibition of IL6R signaling attenuated stemness and angiogenesis in tumor-bearing mice and significantly reduced the metastatic potential of breast cancer stem cells to the lungs.Collectively, these studies highlight the therapeutic promise of CD44-targeted liposomal drug delivery systems for breast cancer, demonstrating their potential to effectively target cancer stem cells and remodel the tumor microenvironment, thereby improving overall treatment efficacy.

2.2.3. HER1 and HER2 Receptors in Targeted Breast Cancer Nanotherapy

The human epidermal growth factor receptor (HER) family, comprising HER1 (EGFR) to HER4, is a group of receptor tyrosine kinases that regulate critical cellular processes including proliferation, differentiation, survival, and tissue repair. HER1 and HER2 are frequently overexpressed in breast cancer, contributing to uncontrolled cell growth, resistance to apoptosis, enhanced metastasis, and increased angiogenesis [197,198]. HER1 binds specific extracellular ligands from the epidermal growth factor family, whereas HER2 lacks a known endogenous ligand but forms heterodimers with other HER family members to activate downstream signaling pathways.

Overexpression of HER1 is observed in multiple breast cancer subtypes, particularly triple-negative breast cancer (TNBC), and correlates with poor prognosis. Therapeutic strategies targeting HER1, collectively referred to as anti-EGFR therapy, primarily involve monoclonal antibodies (mAbs) that block ligand binding and inhibit receptor signaling. Notable HER1-targeting mAbs include panitumumab, cetuximab (CET), and zalutumumab, which interfere with EGFR-mediated pathways, thereby reducing tumor proliferation, angiogenesis, and metastatic potential [199].

HER1-targeted liposomal drug delivery systems have been developed to improve specificity and therapeutic efficacy. For example, CET-functionalized thermo-sensitive liposomes co-encapsulating doxorubicin (DOX) and citric acid-coated iron oxide nanoparticles enabled pH-triggered chemotherapy release combined with near-infrared (NIR) photothermal therapy. In vitro studies demonstrated enhanced uptake of CET-coated liposomes in HER1-positive breast cancer cells, leading to reduced viability, while in vivo studies in tumor-bearing mice showed increased local tumor heating and improved antitumor outcomes.

To reduce limitations associated with full-length antibodies, smaller fragments such as Fab and single-chain variable fragments (scFv) have been employed. Su et al. developed a pre-targeting system using anti-PEG Fab' and anti-HER1 scFv fragments, termed a PEG-engager, which enhanced the internalization and retention of PEGylated DOX liposomes in TNBC xenograft models while minimizing off-target effects.

Aptamer-based targeting strategies have also shown promise. Kim et al. engineered theranostic liposomes containing CdSe/ZnS quantum dots for imaging and siRNA for TNBC therapy, functionalized with an anti-HER1 aptamer. This system facilitated efficient cytoplasmic delivery of siRNA and demonstrated higher tumor accumulation compared with non-targeted liposomes in vivo, highlighting the potential of aptamer-functionalized nanocarriers for receptor-specific delivery.

HER2, often overexpressed in approximately 20–30% of breast cancers, has similarly been exploited for targeted nanotherapy. Liposomes functionalized with HER2-specific antibodies, affibodies, or peptides have been shown to enhance selective tumor uptake, improve drug delivery efficiency, and reduce systemic toxicity. Dual-targeting approaches, simultaneously addressing HER2 and other tumor-associated receptors, have been investigated to overcome receptor heterogeneity and multidrug resistance, further underscoring the versatility of HER1 and HER2 as cell surface targets in breast cancer nanoliposome therapy.

2.2.4. Luteinizing hormone-releasing hormone receptor

The luteinizing hormone-releasing hormone (LHRH/GnRHR) receptor regulates reproductive hormone secretion and is minimally expressed in normal visceral tissues but highly overexpressed in several hormone-related cancers, including breast cancer, making it an attractive target for drug delivery [200,201]. He et al. developed gonadotropin-functionalized liposomes to improve the delivery of mitoxantrone, achieving enhanced uptake in LHRH receptor–overexpressing MCF-7 cells compared with receptor-negative cells. The system was further adapted for theranostic use by incorporating magnetic iron oxide nanoparticles for MRI [165,166]. In vivo, the targeted liposomes produced significant tumor growth inhibition with reduced systemic toxicity, primarily through receptor-mediated uptake and passive accumulation via the enhanced permeability and retention (EPR) effect, although imaging contrast diminished at later time points.

2.3. Intracellular Receptors as Therapeutic Targets in Breast Cancer Nanoliposomes

2.3.1. Estrogen Receptors as Intracellular Targets in Breast Cancer Nanotherapy

A substantial proportion of breast cancers overexpress estrogen receptors (ERs) and depend on estrogensignaling for tumor growth. ERs belong to the nuclear hormone receptor superfamily and exist as nuclear, extra-nuclear, and G protein-coupled receptors, with estrone (E1), estradiol (E2), and estriol (E3) serving as endogenous ligands. Among the two main subtypes, ERα is predominantly expressed in mammary tissue and drives the proliferation of ER-positive breast cancer, whereas ERβ is more abundant in the prostate, making ERα the primary therapeutic target in breast cancer [202–204]. Although endocrine therapies are effective in ER-positive disease, relapse and resistance remain significant clinical challenges [205,206].

To enhance therapeutic efficacy, several liposomal systems targeting estrogen receptors have been developed using E1 or E2 as targeting ligands. E2-modified cationic liposomes have been employed to deliver antisense oligonucleotides against ERα/β mRNA, thereby sensitizing cancer cells to chemotherapy. In parallel, E1-targeted liposomes have been engineered for intracellular drug delivery using stimuli-responsive platforms, including pH- and ultrasound-triggered systems [207]. For example, pH-responsive doxorubicin-loaded liposomes enabled enhanced nuclear delivery and increased cytotoxicity in ER-positive breast cancer cells. Similarly, Han et al. reported E1-conjugated, PEGylated paclitaxel-loaded liposomes that exhibited significantly lower IC50 values in ER-positive MCF-7 cells and superior tumor growth inhibition in vivo compared with non-targeted formulations, with rapid tumor accumulation observed within hours after administration [168–170].

2.4. Enzymes

2.4.1. Matrix Metalloproteinases as Therapeutic Targets in Breast Cancer Nanoliposomes

Matrix metalloproteinases (MMPs) constitute a family of enzymes crucial for ECM remodeling, wound healing, and angiogenesis, operating with zinc as a cofactor. Deregulated MMP activity has been implicated in various diseases, including cardiovascular disorders, inflammation, and cancer [208]. Different MMP types exhibit specificity in cleaving ECM components, categorizing them into groups like collagenases, membrane-types, and gelatinases. Among these, gelatinases, such as MMP-2 and MMP-9, have been particularly implicated in tumor progression, influencing growth, migration, invasion, and metastasis [209,210]. Elevated MMP levels in tumors correlate with adverse outcomes, including recurrence, invasion, and metastasis. However, MMPs also serve as valuable biomarkers and therapeutic targets, especially in controlled drug delivery systems. MMP-targeted liposomes have been developed to release drugs specifically in tumor tissues. For instance, liposomes functionalized with chlorotoxin, a peptide from scorpion venom known to bind MMP-2, exhibited enhanced uptake in metastatic breast cancer cells and demonstrated improved cytotoxicity and antimetastatic effects in mouse models [211,212].

In another approach, high MMP concentrations within tumors were exploited as an internal targeting mechanism. A novel liposomal co-delivery system developed by Ramadass et al. combined epigallocatechingallate (EGCG), an MMP inhibitor, with the chemotherapeutic agent paclitaxel (PTX). This synergistic system outperformed individual drug-loaded liposomes in inhibiting MMP-2 and MMP-9, suppressing invasion, enhancing cytotoxicity, and promoting apoptosis. These findings underscore the potential of MMP-targeted liposomal delivery systems in cancer therapy.

2.4.2. Tumor-Targeted Liposomal Therapy via Secretory Phospholipase A_2 Activation

Phospholipases represent a broad family of enzymes comprising more than 30 isoforms that catalyze the hydrolysis of phospholipids and are classified according to their catalytic mechanisms, structural characteristics, evolutionary relationships, and cellular localization [213]. Among these, secretory phospholipase A2 (sPLA2) has gained considerable attention due to its involvement in inflammatory disorders, atherosclerosis, and tumor progression in several malignancies, including prostate, pancreatic, and breast cancers [214–216]. A distinguishing feature of sPLA2 is its strong preference for hydrolyzing phospholipids within lipid bilayers, particularly those containing phosphatidylserine, rather than free lipids. This enzymatic specificity makes sPLA2 an attractive endogenous trigger for the development of enzyme-responsive liposomal drug delivery systems capable of localized and controlled drug release within tumor tissues.

Oxaliplatin is a platinum-based chemotherapeutic agent that inhibits DNA synthesis and is widely used in colorectal cancer treatment. Notably, phase II clinical studies have demonstrated its activity in metastatic and triple-negative breast cancer patients who had previously received anthracycline- and/or taxane-based therapies [217–221]. However, the clinical utility of oxaliplatin is limited by dose-related toxicities, including myelosuppression, peripheral neuropathy, and gastrointestinal adverse effects. To improve its therapeutic index, PEGylatedoxaliplatin-loaded liposomes have been extensively explore. One of the most advanced examples is LiPlaCis, and sPLA2-triggered liposomal cisplatin formulation. A phase I clinical trial evaluated LiPlaCis in patients with advanced or refractory solid tumors, including metastatic breast cancer (NCT01861496), but safety concerns resulted in temporary suspension and subsequent reformulation in 2009 [222]. Continued preclinical investigations and phase I/II clinical studies have since examined LiPlaCis across a range of advanced solid tumors, such as head and neck, colorectal, gastric, skin, and breast cancers [171,223–225].

In a related study, Ostrem et al. developed a sPLA2-responsive liposomal platform by carefully adjusting membrane fluidity and cholesterol content to enable enzyme-specific release of encapsulated oxaliplatin [171]. While in vitro experiments confirmed selective drug release in the presence of sPLA2, intravenous administration in sPLA2-secreting MT-3 tumor-bearing mice led to severe systemic toxicity, necessitating early termination of the study. The authors attributed this outcome to premature liposome activation in circulation, a consequence of elevated serum sPLA2 levels observed in certain outbred mouse strains—a phenomenon that may also occur in cancer patients. These findings underscore a critical translational challenge associated with enzyme-triggered liposomal systems. More recently, an mRNA-based predictive biomarker for LiPlaCis responsiveness has shown promising results in heavily pretreated metastatic breast cancer patients, supporting its progression toward randomized phase II clinical evaluation [226].

3. Challenges and Prospects of Targeted Nanoliposomal Drug Delivery

The targeted Nanoliposomal drug delivery landscape presents numerous challenges and avenues for future exploration. Phospholipases, a diverse group of enzymes with over 30 isoforms, play a pivotal role in cleaving phospholipids, offering potential targets for intervention. Among these, secretory phospholipase A2 (sPLA2) stands out due to its association with inflammatory conditions, atherosclerosis, and various cancers, including prostate, pancreatic, and breast cancers. Its preference for cleave negatively charged phospholipid head groups suggests it as an ideal candidate for targeted drug delivery, mainly in liposomal formulations.

Efforts have been made to capitalize on sPLA2's activity for controlled and localized drug release through sPLA2-responsive liposomes. For instance, the development of PEGylatedoxaliplatin-loaded liposomes aims to mitigate the toxicity commonly associated with this chemotherapy agent, especially in colorectal cancer treatment. However, challenges persist, as demonstrated by the discontinuation of clinical trials for LiPlaCis, a cisplatin-encapsulating liposomal formulation, due to safety concerns.

Recent studies have highlighted the need for precise control over drug release triggered by sPLA2. Optimization of liposomal delivery systems, such as adjusting fluidity and cholesterol levels, shows promise in vitro but faces hurdles when translated to in vivo models. Systemic toxicity observed in animal models underscores the complexity of enzyme-triggered drug release in clinical settings. Notably, variations in sPLA2 expression levels among individuals, both in animal models and cancer patients, present significant hurdles for achieving targeted drug release without adverse effects. Looking ahead, future research should address these challenges by refining nanoliposomal formulations to achieve greater specificity and efficacy. Additionally, advances in predictive models, such as mRNA-based drug response predictors, hold potential for tailoring treatment strategies to individual patients, offering a personalized approach to targeted nanoliposomal drug delivery. However, rigorous preclinical testing and clinical validation are imperative to ensure the safety and efficacy of these innovative approaches before widespread clinical adoption.

4. Summary

The consumption of functionalized liposome represents a promising approach to enhance breast cancer treatment through targeted drug delivery. By incorporating specific ligands or responsive triggers, such as those targeting over expressed receptors or enzymes in breast cancer cells, these modified liposomal nanocarriers offer precision in drug delivery while minimizing systemic toxicity. This approach enables the encapsulation of a variety of therapeutics, from traditional chemotherapeutic agents to innovative biologics and gene therapies, providing a versatile toolset for fighting breast cancer. Continued research in this area is expected to give in advanced liposomal formulations, eventually leading to improved treatment outcomes and enhanced quality of life for breast cancer patients.

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