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Review

The Role of Liposomal Delivery Systems in the Treatment of Triple Negative Breast Cancer

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Abstract: This study aims to highlight the potential of liposomal nanocarrier systems in addressing the challenges associated with the treatment of triple-negative breast cancer (TNBC) and to provide a literature-based foundation for their use in targeted therapeutic approaches. This study evaluating the efficacy of liposomal drug delivery systems in TNBC treatment, along with current developments reported in the literature. Particular emphasis is placed on surface modifications involving PEGylation, antibodies, aptamers, and small molecules, and their impact on therapeutic success. TNBC accounts for approximately 20% of all breast cancer cases and represents a highly aggressive subtype characterized by treatment resistance and high metastatic potential. Conventional treatment methods often fall short, with recurrence observed in about 40% of cases and mortality reaching 80–90% due to therapy-resistant tumors. Liposomes have garnered attention due to their ability to enhance drug bioavailability, reduce systemic toxicity, and provide tumor site-specific targeting. Numerous formulations have been developed, ranging from PEGylated liposomes to antibody- and aptamer-conjugated systems, demonstrating therapeutic efficacy in various TNBC cell lines and animal models. Given the aggressive nature of TNBC and the limited treatment options, liposomal nanocarrier systems offer a promising alternative. The integration of these systems with specific targeting modifications may lay the groundwork for future personalized and more effective TNBC therapies. To facilitate clinical translation, it is essential to establish standardized production protocols, streamline regulatory processes, and strengthen interdisciplinary collaborations.

Keywords: Triple-Negative Breast Cancer, Liposome, Targeted Therapy, Drug Delivery Systems, Nanotechnology

1. Introduction

Breast cancer is the most common type of cancer in women today. The World Health Organization's Agency for Research on Cancer (IARC) reported that 1 in 20 women will be diagnosed with breast cancer in their lifetime, and if current rates continue, there will be 3.2 million new cases of breast cancer and 1.1 million breast cancer-related deaths annually by 2050 (1). TNBC (Triple-Negative Breast Cancer) is one of the most aggressive and difficult to treat types of breast cancer. This type of breast cancer is characterized by reduced/absent expression of estrogen (ER), progesterone (PR) and human epidermal growth factor receptor 2 (HER2). Current treatment options for TNBC vary depending on the specific subtype and stage of the tumor and include surgical interventions as well as conventional treatments such as adjuvant (postoperative) or neoadjuvant (preoperative) chemotherapy, radiotherapy and immunotherapy (2,3). However, approximately 40% of TNBC tumors relapse and the development of drug resistance and metastatic features results in death in 80-90% of patients (4,5). The lack of universally applicable specific molecular targets in TNBC treatment further increases the risk of death (6,7). Considering the current treatment challenge in TNBC, the development of nanocarrier-based drug delivery systems as an alternative to conventional cancer therapies is of great importance. One of the most widely used of these systems is liposomes (8,9).

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In this review, the mechanisms and interactions of signaling pathways that constitute the molecular basis of TNBC and the conventional treatment of TNBC and the structural properties, production techniques, drug encapsulation methods and therapeutic treatment potentials of liposomes, which are the next generation drug delivery systems, will be discussed comprehensively.

1.1. Triple Negative Breast Cancer (TNBC)

Triple negative breast cancer (TNBC) is one of the most difficult subtypes of breast cancer to treat, characterized by the absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expression. The lack of response to hormonal or HER2-targeted therapies poses serious limitations to the systemic treatment of this tumor type. TNBC accounts for approximately 15-20% of all breast cancers and is associated with high recurrence rates, a tendency for early metastasis and poor prognosis (10). Therefore, chemotherapy is often used as the main treatment approach in TNBC patients. However, targeted therapies such as immune checkpoint inhibitors and poly (ADP-ribose) polymerase (PARP) inhibitors have shown promise, especially in patients carrying BRCA1/2 mutations (4).

The fact that TNBC has a highly heterogeneous structure at the molecular level necessitated the identification of different subtypes and accordingly, six basic molecular subtypes were defined according to gene expression profile: Basal-like 1 (BL1), Basal-like 2 (BL2), Immunomodulatory (IM), Mesenchymal (M), Mesenchymal Stem Cell-like (MSL) and Luminal Androgen Receptor (LAR) (11). The BL1 subtype is characterized by high expression of genes sensitive to DNA repair mechanisms (e.g. BRCA1, TP53) and responds well to platinum-based chemotherapy or PARP inhibitors (12-14). In the BL2 subtype, growth factor signaling pathways and metabolic processes predominate; EGFR inhibitors and metabolic-targeted agents are potential treatment options in this subtype (13). In the pathogenesis of triple negative breast cancer (TNBC), key pathways such as EGFR, AR, Notch, Wnt/β-catenin, Hedgehog (Hh) and TGF-β regulate processes such as cell proliferation, invasion, survival and metastasis (Figure 1). Dysregulation of these pathways promotes aggressive tumor behaviors, increases resistance to therapy and offers potential targets for targeted therapies.

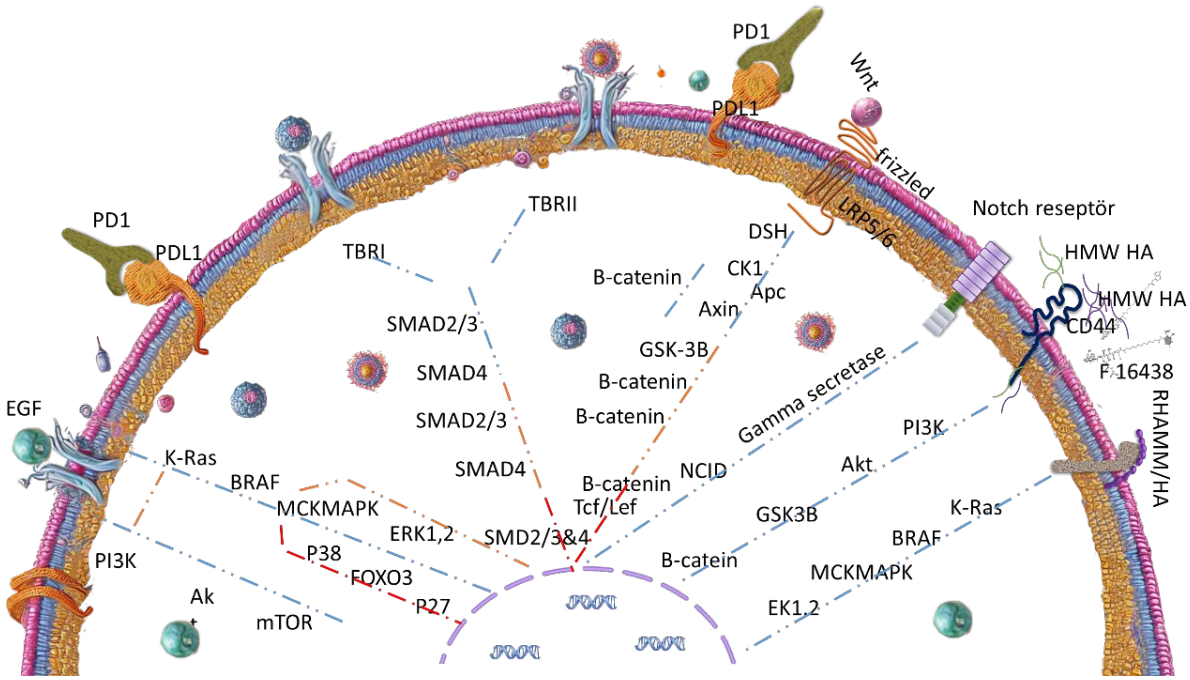

Figure 1. Overview of Signaling Pathways Involved in the Pathogenesis of TNBC

1.1.1. Strategy for targeted treatment of TNBC

Identification of cell surface receptors is of great importance for the development of target-specific ligand selection and liposomal drug delivery systems in the treatment of TNBC. The division of the disease into subtypes according to phenotypic and genotypic characteristics makes it possible to create individualized treatment strategies. In particular, the fact that the basal-like subtype is common only in TNBC cases increases the importance of this approach (10). Many cellular targets such as androgen receptor (AR), leptin receptor (LEPR), Hsp90, ICAM-1, TRAIL, CDKs, glucocorticoid receptors and Mucin 1 (MUC1) have been shown to be overexpressed in TNBC. Among these targets, AR is involved in the transcriptional regulation of breast cancer-related genes (11), while LEPR expression was reported to be increased in 92% of patients and responsible for the development of cancer stem cells (12). In metastatic TNBC, ICAM-1, a cell membrane-associated glycoprotein, as well as the PD-1 receptor found on T cells, which suppresses the immune response, have been reported to be effective in disease progression (13). Low oxygen levels in the tumor microenvironment lead to the activation of the hypoxia-inducible factor HIF-α, which causes chemotherapy resistance and facilitates the adaptation of tumor cells to processes such as epithelial-mesenchymal transition, angiogenesis, gaining immortality and metastasis (14). Therefore, strategies to suppress HIF-α appear promising in the treatment of TNBC (15). TRAIL-1 and TRAIL-2 receptors that trigger apoptosis have the potential to initiate the formation of the DISC complex that mediates cell death. Therefore, the use of TRAIL receptor agonists in combination with chemotherapeutic agents may offer a new approach in the treatment of TNBC (16).

In conclusion, overexpressed receptors and changes in the tumor microenvironment in TNBC guide targeted drug development efforts and pave the way for more effective individualized treatment approaches.

1.2. Liposomes

Liposomes were first described by D. Bangham in 1964 and derived from the Greek words “fat” (lipos) and “body” (soma). Their bilayer structure, composed of phospholipids, cholesterol, sphingolipids and hydrophilic polymers, allows them to transport both lipophilic and hydrophilic drugs. They offer significant advantages in cancer treatment with their structures suitable for surface modifications (e.g. PEGylation), long circulation time, controlled release, pharmacokinetic improvement and tumor targeting (17). Liposomes also provide benefits such as increasing drug solubility, overcoming multidrug resistance, enabling drug accumulation at the target site and reducing systemic toxicity. At the same time, they can extend their biological half-life by protecting the drugs they contain against environmental factors; their size, surface charge and other physicochemical properties can be easily adjusted (18). Parameters such as particle size, stability, surface properties and controlled release profile should be optimized for an effective liposomal therapy (19). Liposomes usually accumulate in tumor tissues through the “Enhanced Permeability and Retention (EPR) effect”; abnormal vasculature and inadequate lymphatic drainage favor this accumulation. This allows liposomal systems below 200 nm to be advantageous in tumor targeting, whereas the passage of such nanoparticles in healthy tissues is highly limited (20). Intensive research in recent years has expanded the use of liposomal drug delivery systems in cancer treatment and contributed to the development of new formulations (21).

1.2.1. Structure of liposomes

Liposomes, known as amphipathic nanocarriers, have a spherical bilayer structure containing one or more phospholipid layers that can be produced from cholesterol and natural/synthetic phospholipids (Figure 2). Lipophilic and hydrophilic substances are encapsulated in the lipid bilayer and the inner aqueous region, respectively (20). Liposomes are classified according to their size and number of lamellae (lipid bilayer). Along with multilamellar structures such as multilamellar (ML, 0.5-5 μm) and multivesicular (MV, >1 μm), unilamellar liposomes are also divided into three groups: small (20-200

nm), large (>200 nm) and giant (≥1 μm). Structural features, especially the number of lamellae and vesicle diameter, are among the parameters that directly affect drug loading capacity (22).

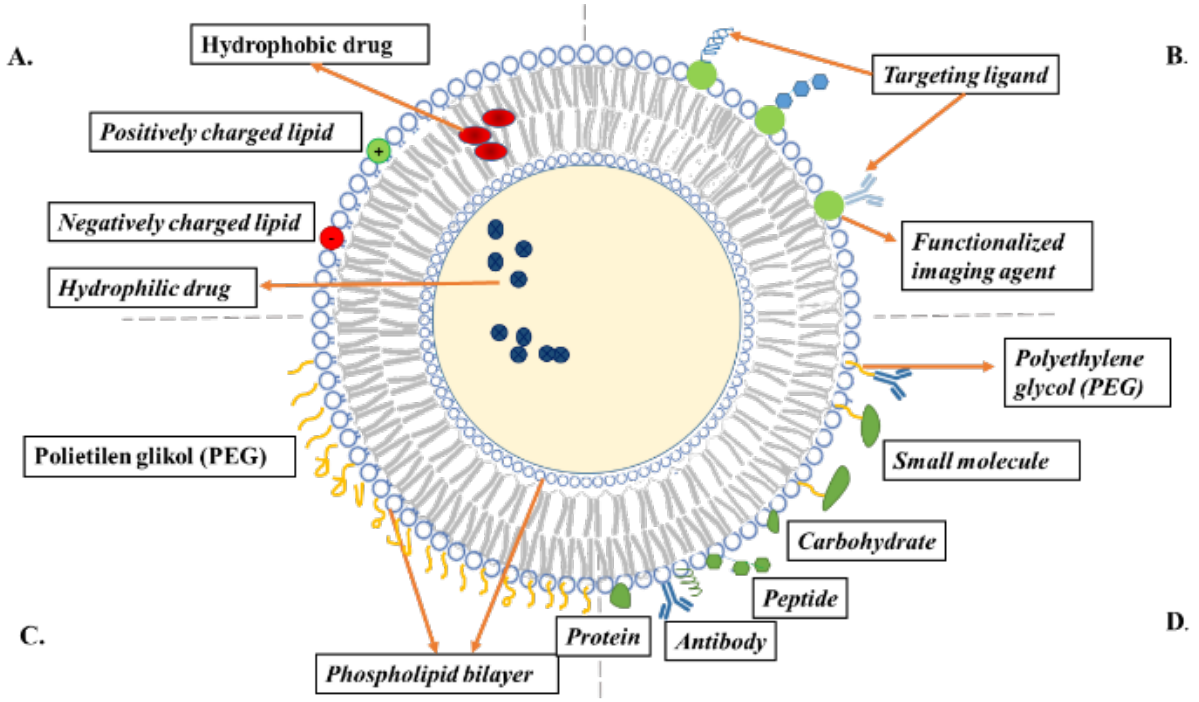

Figure 2. A. General Representation of Liposome Structure B. Functionalized Liposome Structures; (a) Conventional Liposome, (b) Theranostic Liposome, (c) Polyethylene Glycol (PEG) Coated Liposome, (d) Ligand-Targeted Liposome

1.2.2. Synthesis methods of liposomes

Liposomes can be synthesized by multiple methods. In this section, the most widely used methods such as thin film hydration, solvent injection, reverse phase evaporation, dehydration-rehydration, supercritical fluid, microfluidics, freeze-thaw, detergent dialysis and sonication are discussed. Table 1 evaluates the advantages and disadvantages of these methods and provides a brief overview of their effectiveness, scalability and application-specific suitability (20,23,24).

Table 1. Advantages and Disadvantages of Liposome Synthesis Methods

Liposome Synthesis Method	Methodology	Advantages	Disadvantages
Thin Film Hydration	• Lipids are dissolved in organic solvents. • This solution is evaporated to obtain a thin lipid film. • The film is mixed with water to form liposomes.	• Easy to apply. • It is a common and well-known method.	• Scaling is difficult. • Complete removal of organic solvent is difficult.
Solvent Injection	• Lipids are dissolved in organic solvent. • The solution is injected into water.	• It's simple, fast and scalable.	• Size distribution is heterogeneous. • Low encapsulation efficiency.
Reverse Phase Evaporation	• Lipids are dissolved in solvent, dried. • Dissolve again with organic solvent and add water. • Emulsion is formed by sonication.	• Provides high encapsulation efficiency.	• There is a risk of organic solvent residues.

Table 1 (Continued)

Detergent Dialysis	• Phospholipids are dissolved with a certain amount of detergent. • The detergent is gradually removed by dialysis or column chromatography.	• Homogeneous and controlled liposomes suitable for encapsulation of proteins and biomolecules are formed.	• Processing time may be long. • There is a risk of detergent residue.
Supercritical Fluids	• Phospholipids and other components are dissolved in supercritical CO_2. • Liposomes are formed by removing the solvent or adding the aqueous phase.	• It is an environmentally friendly method. • Low solvent residue. • Scalable. • Can work at low temperature, so biomolecules are not damaged.	• High cost. • Limited lipid solubility. • Difficult to optimize.
Dehydration-Rehydration	• Lipids are dispersed in water. • Water is removed to form a film. • The film is rehydrated with water to obtain large liposomes.	• Large liposomes are formed and provide high encapsulation efficiency.	• There is size heterogeneity
Microfluidics	• The lipid solution (organic phase) and the aqueous phase are passed through separate microchannels. • At the junction of the microchannels, controlled mixing and solvent diffusion takes place. • Liposomes are formed and collected from the system.	• Size distribution is narrow and controllable. • Repeatability is high. • Low solvent consumption. • Fast and scalable.	• The cost is high. • Optimization is difficult. • Production volume is low.

1.2.3. Liposome analysis methods

Characterization of liposomes requires extensive physicochemical analysis to ensure their performance in vitro and in vivo (Table 2). Parameters such as size, polydispersity index (PDI) and zeta potential of liposomes are of critical importance (25). Size distribution is determined by methods such as dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA), while PDI reveals the monodispersity or polydispersity state of the sample (22). Zeta potential is used to assess the colloidal stability of liposomes and interparticle electrostatic interactions; A zeta potential evaluated beyond the threshold of positive or negative 30 mV reduces the risk of particle aggregation. Furthermore, the morphological structure of liposomes is examined by methods such as electron microscopy (TEM) and cryo-TEM to determine their shape, lamellarity and phase behavior (Tc, phase transition temperature); these parameters have a direct effect on the drug encapsulation efficiency (EE) and release profile of liposomes (24). Encapsulation efficiency is defined as the ratio of the amount of free drug to the amount of encapsulated drug, and this ratio can be measured by both direct and indirect methods (such as UV-Vis, fluorescence spectroscopy, HPLC, LC-MS) (20).

Table 2. Liposome Analysis Methods

Characterization Parameter	Features	Techniques Used	Important Points
Size and Polydispersity Index (PDI)	• Average size of liposomes (usually between 50-200 nm) and indicates uniformity of size distribution within the sample. • Small size allows long circulation time; low PDI (<0.3) indicates monodispersity.	• Dynamic light scattering (DLS) • Nanoparticle Tracking Analysis (NTA)	• DLS makes measurements based on Brownian motion; • NTA provides confirmatory information by tracking individual particle motions.
Zeta Potential	• Electrical charge on the surface of liposomes; values of +30 mV or -30 mV and above indicate stability.	• Zeta potential measurement (electrokinetic methods, laser Doppler)	• It is influenced by environmental factors such as pH, temperature, ionic strength and viscosity. • Surface charge is critical in determining colloidal stability.
Shape (Morphology)	• The structural arrangement of liposomes includes morphological features such as bilayer (lamellar) structure, roundness and homogeneity.	• Transmission Electron Microscopy (TEM) • Cryo-TEM • Atomic Force Microscopy (AFM)	• Structural changes can occur during TEM sample preparation. • Cryo-TEM has the advantage of preserving the original structure. • AFM, on the other hand, offers a high-resolution 3D image.
Lameller Structure	• Determining the number of layers of liposomes affects encapsulation efficiency and drug release profile.	• 31P-NMR, SAXS, trapped volume measurements	• The interlayer phospholipid ratio is important in the lamellarity calculation.
Phase Behavior	• The fluidity and phase transition temperature (Tc) of the lipid membrane affect properties such as drug passage through the membrane, fusion, stability and protein binding.	• Differential Scanning Calorimetry (DSC) • Thermogravimetric Analysis (TGA) • FTIR • XRD	• Phase behavior varies depending on the physicochemical properties of the membrane; accurate measurement is important in predicting stability and release profile.
Encapsulation Efficiency (EE)	• The ratio of the amount of encapsulated drug to the total amount of drug used indicates the efficiency of the liposome formulation.	• UV-Vis • HPLC • LC-MS • ^{1}H-NMR	• Measurement is done by direct (liposome digestion) or indirect (free drug analysis) methods. • It should be determined by accurate separation methods.

Table 2 (Continued)

Drug Loading and In Vitro Release	• Method of drug loading into liposomes and determination of release profile; active and passive loading methods kullanılarak ilacın kontrollü salımı sağlanır.	• Dialysis method, standard drug analysis techniques (UV, HPLC etc.)	• Dialysis bag should be selected appropriately. • In vitro performance is evaluated by calculating the cumulative release percentage.

1.3. Characteristics of various liposomal nanocarriers used in TNBC treatment

The therapeutic efficacy of liposomal nanocarriers varies depending on the type, size and formulation method of liposomes used. Especially in the treatment of TNBC, carrier size directly affects the circulation time; liposomes in the range of 50-200 nm are considered ideal due to both the low risk of elimination by RES and the advantage of accumulation in tumor tissues (26). The reticuloendothelial system (RES), together with the mononuclear phagocyte system (MPS), clears nanoparticles from the circulation. Particles below about 10 nm are rapidly eliminated by the kidneys, while larger particles are retained in the RES organs via the MPS (27). Conventional liposomes can be converted into "stealth" form by coating them with polymers such as poly (ethylene glycol) (PEG). This modification prolongs circulation time by preventing opsonization and delays recognition by RES. The bilayer structure of liposomes increases drug stability against external factors, while their self-assembly properties, together with their high encapsulation capacity, low toxicity and immunogenicity, make them versatile carriers (28). Furthermore, selective accumulation in tumor cells can be achieved through “active targeting” by adding targeted ligands to their surfaces.

1.3.1. Target-specific liposomal systems in TNBC therapy

Two basic approaches are adopted for target-specific liposome design. In the first, ligands are directly incorporated into the drug carrier system, while in the second, target molecules are bound by modifying the surface of previously prepared liposomes. Surface modification is more advantageous in terms of reducing drug release problems. The targeted efficacy of liposomes depends on many factors such as the properties of the ligand used (binding efficiency, structure, conjugation type), the physicochemical parameters of the carrier (size, surface charge, biodegradability) and the structure of the therapeutic agent and its interaction with the target site. In addition, tumor type, size and receptor expression intensity are also important clinical parameters that determine treatment success. Liposomes modified with specific molecules such as antibodies, peptides, folates, aptamers have the ability to recognize and selectively bind to target cell receptors. Antibody-coated immunoliposomes, the first example of these systems, were found to be more effective than non-target specific ones (29). Peptide ligands with low molecular weight and easy penetration into the cell are also effective tools for tumor targeting. In particular, folic acid, which is non-immunogenic and can be taken into the cell by endocytosis, stands out as a safe and effective targeting tool in TNBC treatment.

1.3.2. Liposomes developed with peptide-based targeting in TNBC treatment

Recent studies have revealed that peptides can be effective carriers for the delivery of chemotherapeutic drugs due to their high selectivity, low toxicity and strong affinity to the target tissue. Peptide functionalized liposomes are designed to target receptors overexpressed in cancer cells, tumor tissues and angiogenic vasculature (14).

G-protein coupled receptors (GPCRs), growth factor receptors (EGFR, ErbB, HER) and integrin receptors have been considered ideal targets due to their widespread presence in various cancer subtypes and tumor vasculature. Liposomal formulations conjugated with peptides specific for these receptors are reported to provide tumor site-specific targeting and efficient drug release (15,30). In particular, the G-protein coupled CXCR4 receptor interacts with CXCL12 to promote cell migration in various cancers

including TNBC. However, long-term use of CXCR4 antagonists has limitations (31). Therefore, liposomal systems that optimize CXCR4 signaling based on peptide density have been developed. Liposomes modified with DV1 peptide offer an alternative option to existing antagonists by providing high resistance to CXCR4, low toxicity and possible immunosuppressive effect (19).

In addition, liposomes functionalized with EMC peptide enable controlled drug delivery by enabling tumor microenvironment-specific release of drugs such as doxorubicin and tariquidar under the influence of MMP-2 enzyme. In the treatment of TNBC, a miRNA sense strand silencing the Slug gene was loaded into liposomes modified with DSPE-PEG2000-tLyp-1 peptide; when combined with functionalized liposomes carrying vinorelbine, tumor growth was reported to be almost completely inhibited (32).

1.3.3. Liposomes developed with antibody-based targeting in TNBC treatment

Antibodies with a molecular weight of approximately 150 kDa are Y-shaped glycoproteins produced by the immune system against antigens and are widely used in the functionalization of nanocarrier systems. The Fab region of antibodies binds to the target antigen, while the Fc region is usually used for conjugation to the nanoparticle surface. Antibody binding to liposomes is achieved by adsorption, covalent binding (carbodiimide, maleimide, "click" chemistry) or avidin-biotin interaction. Covalent methods are particularly advantageous in terms of stability and binding efficiency, and carbodiimide and maleimide chemistries stand out in this context (33).

There are various liposomal systems developed with target-specific antibodies for the treatment of TNBC. For example, cetuximab, developed against EGFR, shows synergistic effect with chemotherapy and radiotherapy; its combination with taxanes is also applied in TNBC treatment (34). Atezolizumab, a monoclonal antibody targeting PD-L1, has received FDA approval for use in combination with nab-paclitaxel in metastatic TNBC and is the first immune checkpoint inhibitor approved in TNBC. Similarly, other ICI agents such as pembrolizumab are being actively investigated. Necitumumab and nimotuzumab, which bind to EGFR, are IgG1 class monoclonal antibodies being evaluated in TNBC. Panitumumab is another EGFR-specific antibody being developed for triple negative inflammatory breast cancer (35). Sacituzumab govitecan is a combination of a TROP2-targeted IgG1 antibody and the topoisomerase inhibitor SN-38 and is particularly effective in TNBC subtypes with high TROP2 expression (36). In antibody-based systems, Guo et al. recently developed dual antibody liposomes targeting ICAM1 and EGFR simultaneously. This system enabled more efficient cell binding and endocytosis compared to conventional single-targeted constructs and significantly increased therapeutic efficacy in TNBC cells when used in combination with liposomal doxorubicin (37,38).

1.3.4. Liposomes developed with polymer-based targeting in TNBC treatment

One of the most common methods to increase the stability of liposomes and prolong their circulation time is polyethylene glycol (PEG) coating. PEGylation is considered a passive targeting strategy and can increase the solubility of liposomes and prolong their circulation time up to tenfold, resulting in higher accumulation in target tissues. PEGylated liposomes can be made more selective by active targeting strategies. For this purpose, functional groups such as amino, carboxyl or maleimide can be added to the ends of PEG chains to form covalent bonds with specific ligands. Thus, targeting ligands added to the vesicle surface recognize specific cell surface receptors, allowing the drug to be delivered directly to the tumor microenvironment (39).

Apart from PEG, other biopolymers are also used for coating. For example, hyaluronic acid (HA) shows high affinity for CD44 receptors, which are overexpressed in TNBC. HA-coated liposomes thus easily enter target cells, while their negative charge reduces protein adsorption and prolongs the circulation time. Chitosan oligosaccharide (CO) coated liposomes are similarly used in CD44-targeted diagnostic and therapeutic applications. The HA-coated liposomal system containing epalrestat (EPS) and

doxorubicin (DOX) developed by Dong et al. suppressed epithelial-mesenchymal transition (EMT) and reduced cancer stem cells in TNBC. Animal studies in 4T1 tumor model showed that this system significantly inhibited tumor growth and metastasis (40). In conclusion, liposomes coated with polymers such as PEG, HA and CO stand out as effective drug delivery systems in aggressive cancer types such as TNBC due to their high biocompatibility, target-specific binding and strong antitumor effects.

1.3.5. Liposomes developed with aptamer-based targeting in TNBC treatment

Aptamers consist of artificially synthesized short DNA or RNA sequences and bind to their targets with high specificity and binding affinity. Due to their small size, low immunogenicity and structural stability, they have attracted attention as an alternative to antibodies in targeted drug delivery systems. Aptamers are usually attached to liposomes via chemical conjugation to the ends of PEG chains or lipid components. Electrostatic interactions can also be used, but this method is rarely preferred as it can disrupt the secondary structure of the aptamer (41,42). Aptamers integrated into liposomes by covalent binding techniques enable selective accumulation in target tumor cells. This increases cytotoxic efficacy and minimizes systemic side effects (43). Unlike antibodies, aptamers do not elicit an immune response because they do not carry an Fc region and can remain in tumor tissue for a longer time (44). The anti-CD44 aptamer Apt1, which shows high affinity for the CD44 receptor, was used by Alshaer et al. on liposomes carrying siRNA. This system, complexed with protamine, provided effective targeting in cancers where CD44 is overexpressed, including TNBC, and was shown to successfully suppress related gene expression (45). In conclusion, aptamer-based targeting systems offer significant potential for tumor specificity, biocompatibility and drug efficacy in the treatment of TNBC.

1.3.6. Use of liposomes targeted with other ligands in TNBC treatment

Small water-soluble molecules such as folate acid (FA) and biotin are widely used as targeting ligands for liposomal drug carriers due to their low immunogenicity, low cost and easy conjugation (46). Belfiore et al. developed liposomes loaded with N-alkylisatin (N-AI) functionalized with PAI-2 (SerpinB2) to target uPA/uPAR receptors. This system provided higher cellular uptake and cytotoxicity, particularly in MDA-MB-231 cells compared to MCF-7, which showed low uPAR expression. The findings revealed the potential of uPAR expression-dependent targeting in TNBC (47). Barbosa et al. reported that pH-sensitive, folate-modified paclitaxel (PTX)-loaded liposomes showed significant cytotoxic effect in MCF-7 and MDA-MB-231 cells and low toxicity in normal cells (48). In another study with curcumin-loaded, folate-modified PEGyl liposomes, 3.5-fold higher cytotoxicity and significant tumor shrinkage were achieved compared to non-targeted systems (49). Finally, Guo et al. developed a non-cationic liposome-hydrogel hybrid system carrying CRISPR plasmids containing Cas9 and guide RNA targeting the Lipocalin 2 (Lcn2) gene. This system suppressed Lcn2 expression up to 80% in TNBC cells and reduced tumor volume by 77% in animal models (50).

These studies show that small molecule ligands and gene editing technologies can significantly improve treatment efficacy when combined with targeted liposomal therapeutic approaches in aggressive tumors such as TNBC.

2. Conclusion and Recommendations

Liposomal nanocarriers, developed to improve drug efficacy and reduce side effects, offer a promising strategy, especially for treatment-resistant cancer types. Given the limitations in the treatment of TNBC, it is noteworthy that these systems are an effective alternative to conventional approaches. FDA-approved liposomal formulations such as Doxil®/Caelyx®, Myocet®, Lipodox® and Lipusu® have improved treatment success by enabling targeted drug release via PEGylation and EPR. The efficacy of liposomes in challenging tumor types such as TNBC, thanks to their ability to increase bioavailability, reduce systemic toxicity and provide tumor-specific drug delivery, has made them an important tool in oncological therapy. In the future, innovative approaches such as the development of liposomal

formulations personalized according to the genetic and biochemical structure of the tumor; pH, temperature or enzyme sensitive smart systems, immunotherapy combinations and multifunctional carriers are predicted to be at the forefront. In order to translate these advances into clinical practice, it is necessary to establish standardized production protocols, accelerate regulatory processes and strengthen academia-industry collaboration. Moreover, the integration of digital technologies such as artificial intelligence and machine learning into these processes will make significant contributions at many stages, from formulation development to prediction of treatment response. In conclusion, liposomal drug carriers have the potential to not only support current therapies, but also to be the cornerstone of future personalized and targeted oncological therapies.

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