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Liposomes in Breast Cancer Treatment and Research Progress

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Abstract: Breast cancer is one of the significant threats to women's health worldwide, and traditional treatment methods have many limitations. Liposomes, as a novel type of nanocarrier for drugs, have attracted widespread attention due to their unique structural and functional advantages. This paper provides a detailed introduction to the structural composition and preparation methods of liposomes, as well as their diverse applications in breast cancer treatment, including conventional liposomes, long-circulating liposomes, thermosensitive liposomes, pH-sensitive liposomes, and ligand-modified liposomes. It also discusses the progress of liposomes in clinical research. This paper argues that, despite the great potential of liposomes in breast cancer treatment, many challenges remain. Future research should focus on developing stimuli-responsive liposomes, optimizing preparation processes, and enhancing their safety and efficacy in clinical applications to promote liposomes as an important means for the precise treatment of breast cancer.

Keywords: Liposomes, Breast Cancer, Drug Delivery

1. Introduction

Cancer has always been one of the leading causes of human mortality. Among them, breast cancer is the most common malignant tumor worldwide, posing a significant threat to women's health. From 1990 to 2019, the number of global breast cancer cases increased from 876,990 to 2,002,350, with an average annual growth rate of 0.33%. It is estimated that the number of global breast cancer cases will reach 2,539,750 by 2025[1]. Currently, there are various treatment options for breast cancer, mainly based on the subtypes of breast cancer, individual patient conditions (such as age, health status, genetic mutation status, etc.), and disease stages (such as locally advanced or metastatic). For example, endocrine therapy can be used for breast cancer patients with positive estrogen or progesterone receptors; for patients with overexpression of human epidermal growth factor receptor 2 (HER2), HER2-targeted therapy can be used. In addition, conventional cancer treatment methods such as chemotherapy, immunotherapy, mastectomy, breast-conserving surgery, and radiotherapy are also widely used in the treatment of breast cancer[2]. However, each treatment method has its limitations. Surgery may cause physical trauma, and the non-specific effects of radiotherapy and chemotherapy can damage normal cells, while the issue of drug resistance in endocrine therapy also needs to be addressed urgently.

Liposomes have received widespread attention because of their multiple advantages in the treatment of breast cancer. Liposomes, composed of a phospholipid bilayer similar to human cell membranes, can encapsulate drugs, protect them from the effects of the body's environment, achieve

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sustained release, and reduce the distribution of drugs in normal tissues. In addition, liposomes can be modified on the surface to achieve targeted delivery to tumor cells, increasing the concentration of drugs in tumor tissues, thereby enhancing therapeutic effects[3].

2. Basic Introduction to Liposomes

2.1. Structure and Composition

Liposomes are artificial membrane structures composed of a lipid bilayer that can encapsulate drugs within to form microvesicles. In an aqueous environment, the hydrophilic heads of phospholipid molecules will insert into the water, while the hydrophobic tails will extend into the air. After processing such as stirring, phospholipid molecules can spontaneously form a bilayer structure, constituting spherical liposomes with diameters ranging from 25 to 1000 nm. The interior of liposomes is an aqueous environment that can encapsulate water-soluble drugs or molecules. This structural basis allows liposomes to interact with biological membranes, thereby achieving drug delivery and release. In addition, the external surface of liposomes can be modified in various ways, such as adding polyethylene glycol to enhance their stability and circulation time, or combining with targeting ligands to achieve targeting of specific cells or tissues. Liposomes share many similarities with biological membranes in structure and function, and these similarities endow liposomes with unique advantages in drug delivery and biomedical research[4,5].

2.2. Preparation Methods

2.2.1. Thin-Film Method

Thin-Film Method involves forming a lipid film on the inner wall of a rotary evaporator, followed by hydration with a buffer solution or aqueous solution to prepare multilamellar vesicles (MLVs). First, accurately weigh a certain amount of lipids (such as dipalmitoyl phosphatidylcholine, DPPC, or 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine) and dissolve them in a mixed solvent of methanol and chloroform. Under a pressure of 200–300 mbar, use a rotary evaporator to evaporate the solvent in a water bath at 35–45°C, forming a uniform lipid film. Then, place the film in a high vacuum environment (5–10 mbar) to dry until the weight is constant (4 hours or overnight). Preheat the dried film with water or buffer solution above the phase transition temperature of the lipids, then add an appropriate amount of water or buffer solution to fully hydrate the lipids. Hydrate in a closed rotary evaporator, maintaining the temperature above the phase transition temperature, and intermittently shake and ultrasonically treat. Finally, further process the formed MLVs in an ultrasonic bath to ensure their uniformity. The prepared liposomes should be stored in plastic centrifuge tubes, replaced with nitrogen, frozen in liquid nitrogen, and stored at -80°C.

2.2.2. Proliposome Method

The proliposome method involves dissolving lipids in a mixed solvent of water and ethanol to form a lipid paste, followed by the preparation of MLVs by gradually adding water or buffer solution. First, weigh an appropriate amount of lipids and add 96% ethanol and buffer solution (final lipid: ethanol: buffer solution ratio of 1:1:2, w/w/w). Stir the mixture in a 60°C water bath until a uniform lipid paste is formed. After cooling to room temperature, gradually add water or buffer solution and continue stirring to form MLVs. Continue stirring at room temperature, then ultrasonically treat in an ultrasonic bath to optimize the particle size and uniformity of the liposomes[6].

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2.2.3. Reverse-Phase Evaporation Method

Reverse-Phase Evaporation Method is a method of forming liposomes through the evaporation of organic solvents. First, dissolve DPPC, hydrogenated soy phosphatidylcholine (HSPC), and N-(carboxymethyl polyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine s odium salt (DSPE-mPEG2000) in an appropriate amount of chloroform in a molar ratio of 85: 10:5, then add an appropriate amount of ether and chloroform, briefly vortex mix to form a un iform organic solution. Use a rotary evaporator to remove the organic solution at 25°C and -0. 07 MPa, ultimately forming liposomes.

The above methods each have their advantages and disadvantages, and the specific method chosen depends on the specific experimental requirements. For example, factors such as the particle size of liposomes, drug encapsulation efficiency, and experimental scale will affect the choice of method. The thin-Film Method and proliposome method are the most basic and commonly used preparation methods, suitable for small-scale liposome preparation in the laboratory. The reverse-phase evaporation method prepares liposomes with larger sizes and stable membrane structures[7].

3. Classification of Liposomes for Breast Cancer Treatment

3.1. Conventional Liposomes

Although conventional liposomes encapsulating anticancer drugs such as parthenolide (PTL) can enhance drug stability and ensure therapeutic efficacy upon reaching the tumor site, they lack polyethylene glycol (PEG) and ligand modifications on their surface, making them susceptible to phagocytosis by the reticuloendothelial system. Additionally, macrophages participate in lipid cholesterol metabolism, which can engulf and accumulate lipids, leading to premature drug release and reduced drug delivery efficiency.

To overcome these challenges, specific modifications are often required for liposomes in practical applications. These modifications aim to evade phagocytosis by the reticuloendothelial system, thereby delivering drugs to tumor cells with minimal loss and achieving efficient drug release in the tumor microenvironment while minimizing toxicity to normal cells. Through these strategies, we can improve the efficiency of drug delivery and therapeutic outcomes, leading to better treatment results for patients.

3.2. Long-circulating Liposomes

Considering the limitations of conventional liposomes being easily phagocytosed by the reticuloendothelial system, Xue-Qin Wei and Kai Ba developed a novel long-circulating liposome drug delivery system. This system coats the liposome surface with bovine serum albumin (BSA) to enhance the bioavailability and stability of curcumin (Cur) and extend its circulation time in the body.

For both curcumin liposomes (Cur-Lips) and BSA-coated curcumin (BSA-Cur-Lips) liposomes, no significant drug burst release was observed, and the presence of albumin can enhance the structural stability of liposomes and slow down the release of Cur. After being coated with albumin, the macrophage phagocytosis of Cur-Lips was significantly reduced. In summary, albumin coating is a promising method for developing a long-circulating delivery system for liposomal curcumin, characterized by low phagocytosis, slow drug release, enhanced stability, and non-toxicity, making this system widely applicable in practice[8].

Xueqi Li, Jianwei Li, and others designed and synthesized a novel nucleic acid-liposome derivative, which was achieved by introducing a hydrophobic hexyl chain between the guanine-rich nucleic acid sequence and DSPE-PEG2000, and then combining the derivative with larotaxel. PEG modification reduces the immune recognition and clearance rate of liposomes. The liposomes accumulate in tumor

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tissue for a long time and have high stability in the bloodstream. Targeting reduces the distribution of drugs in non-target tissues, further extending the effective circulation time of the drug. These characteristics together endow the liposomes with a good long-circulating effect, enabling them to deliver drugs to tumor tissues more effectively, improve therapeutic effects, and reduce drug resistance[9].

3.3. Special Functional Liposomes

3.3.1. Thermosensitive Liposomes

Thermo-sensitive liposomes undergo a phase transition under near-infrared light irradiation, changing from a colloidal crystalline state to a liquid crystalline state. This change increases the fluidity and permeability of the membrane, thereby promoting the high-concentration accumulation of drugs in tumor tissue. Xin Jin and others designed a thermo-sensitive liposome for the treatment of triple-negative breast cancer. This system combines the photosensitizer indocyanine green (ICG) with PTL to respond to near-infrared light.

Under near-infrared light irradiation, ICG can convert light energy into heat energy, working synergistically with PTL to effectively kill tumor cells by inducing the generation of intracellular reactive oxygen species and disrupting the mitochondrial membrane potential. Experimental results show that the tumor inhibition rate of nude mice treated with thermo-sensitive liposomes is 2.08 times that of the paclitaxel treatment group, and the weight loss of nude mice treated with thermo-sensitive liposomes is less, indicating good safety. This not only improves the therapeutic effect but also reduces systemic toxicity, providing a new strategy for cancer treatment[10]. Sherif Ashraf Fahmy and others designed and prepared three thermo-sensitive liposome systems, respectively, for encapsulating cisplatin drugs, supramolecular complexes of cisplatin, and hydrophobic platinum drugs picoplatin. Thermo-sensitive liposomes can effectively encapsulate the above three platinum drugs and trigger drug release at elevated temperatures, enabling liposomes to release drugs locally in tumors, enhance anti-tumor activity, and reduce toxicity to normal tissues, making it a promising strategy for breast cancer treatment[11].

3.3.2. pH-sensitive Liposomes

Tumor tissues often present an acidic environment due to anaerobic glycolysis and carbon dioxide accumulation, with a pH value between 5.5 and 7.0, in stark contrast to the normal tissue pH of about 7.4. This pH difference provides an opportunity for the development of pH-sensitive liposomes that can release drugs in the acidic tumor microenvironment while remaining stable in normal tissues. This strategy minimizes drug leakage in the bloodstream and ensures that therapeutic agents are specifically released at the tumor site.

Prashant Pandey and others designed a liposome formulation with dioleoyl-sn-glycero-3-phos phoethanolamine (DOPE) and cholesterol hemisuccinate (CHEMS) as key lipid components, en dowing the liposomes with pH sensitivity. By integrating pH sensitivity and ligand targeting, e fficient release and specific delivery of 5-fluorouracil in the tumor microenvironment were achi eved. Both in vitro and in vivo experiments have shown significant anti-tumor effects and low systemic toxicity, demonstrating its potential and safety in cancer treatment[12]. E. R. Gomes a nd others fused key lipid components with tumor cell-derived exosomes and doxorubicin (Dox) to form a new pH-sensitive liposome formulation. This fusion utilizes the cell targeting ability of exosomes and the pH sensitivity of liposomes to further improve drug targeting and therap eutic effects[13].

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3.3.3. Ligand Liposomes

Ligand-modified liposomes can achieve specific recognition and binding to cancer cell surface receptors by combining specific targeting ligands, such as antibodies, peptides, or small molecules, on their surface. For example, HER2-targeting ligands can specifically bind to breast cancer cells overexpressing HER2, thereby precisely delivering drugs to tumor cells.

Jafrin Jobayer Sonju and others designed a liposome formulation based on pH-sensitive liposomes composed of DOPE and CHEMS, modified with a ligand-mimetic peptide with high affinity for the HER2 receptor, and loaded with Dox. This liposome delivery system can significantly enhance the uptake of nanoliposomes by HER2-positive cancer cell lines, increase the accumulation of Dox in tumors, and effectively enhance anti-tumor efficacy while reducing off-target side effects[14]. In addition, Dilip Kumar Arya and others designed a dual-ligand functionalized liposome by combining an HER2 receptor antibody and a tumor-penetrating peptide, co-loaded with two anti-cancer drugs to achieve targeted therapy for breast cancer cells. The liposome has good drug loading capacity, sustained release characteristics, cell uptake ability, and anti-tumor activity, while showing good biocompatibility[15].

4. Clinical Research Progress of Liposome Therapy in Breast Cancer Treatment

In clinical studies, various liposomal formulations have demonstrated diversified application prospects. For example, the combination of paclitaxel liposomes and anti-HER2 targeted therapy has shown significant efficacy and a lower incidence of adverse effects in HER2-positive breast cancer. The paclitaxel liposome, leveraging liposomal encapsulation technology, has significantly reduced the toxicity of the drug to normal tissues, thereby effectively decreasing the occurrence of adverse effects. The main adverse events observed in the study included myelosuppression (34.8%), gastrointestinal reactions (18.4%), and fluid retention (4.6%), most of which were controllable.

Irinotecan liposomes have exhibited good antitumor activity and safety in metastatic triple-negative breast cancer. Additionally, a functionalized liposomal nanoparticle platform that integrates chemotherapy, phototherapy, and immunotherapy has achieved efficient antitumor effects and significantly enhanced tumor targeting ability through folic acid modification. This platform uses near-infrared irradiation to trigger photodynamic therapy and activate the prodrug tirapazamine, achieving efficient chemotherapy while avoiding the problem of exacerbated hypoxia associated with traditional photodynamic therapy. The clinical application of these innovative liposomal formulations provides new ideas and approaches for breast cancer treatment. With the conduct of more clinical trials, liposomal formulations are expected to offer more precise and effective therapeutic options for breast cancer patients[16].

In the clinical research of liposome therapy for breast cancer, key issues are mainly focused on drug delivery efficiency, safety, individual differences, and optimization of combination treatment regimens. By optimizing the design of liposomes, adjusting dosages and administration schedules, integrating genetic testing, and conducting multicenter clinical trials, these challenges can be effectively addressed. These efforts will provide safer and more effective treatment options for breast cancer patients and further promote the clinical application of liposomes in breast cancer therapy.

5. Summary and Outlook

Liposomes, as an emerging type of nanocarrier for drugs, have demonstrated broad application prospects in the treatment of breast cancer. They are capable of efficiently encapsulating various therapeutic components, including chemotherapeutic drugs, photosensitizers, and immunomodulators, thereby enabling targeted drug delivery and controlled release. In addition,

liposomes can enhance the solubility and stability of drugs, significantly improving therapeutic efficacy while reducing drug side effects.

Despite significant progress in the treatment of breast cancer with liposomes, numerous challenges remain. The limitations of the enhanced permeability and retention (EPR) effect restrict the distribution and penetration of liposomes within tumor tissues. Moreover, the complex in vivo environment, such as the presence of blood components and enzymatic activity, may also affect the stability of liposomes.

Future research directions should focus on developing stimuli-responsive liposomes that integrate the tumor microenvironment and external stimuli. These liposomes can achieve precise drug release under specific conditions, such as acidic environments, enzymatic activity, or light exposure, thereby further enhancing therapeutic efficacy and reducing side effects. In addition, to promote the application of liposomes in breast cancer treatment, it is necessary to optimize the preparation processes of liposomes, enhancing their safety and efficacy in clinical applications. This includes developing more efficient encapsulation technologies, extending the circulation time of liposomes, and reducing their immunogenicity. Meanwhile, actively conducting clinical trials will also provide important evidence for the widespread application of liposomes. Through these efforts, liposomes are expected to become an important tool in breast cancer treatment, offering patients more precise and effective therapeutic options and further advancing the field of breast cancer therapy.

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