Advances in liposomes in anticancer drug delivery systems

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Abstract. The tumor is a complex and severe physical illness with a mass of abnormal cells, which affects a significant number of individuals across the globe. This illness can have a profound influence on those who suffer from it, both physically and mentally, and its appearing positions and symptoms are various and mutable. Despite the challenges it presents, scientists work on treatments and medicines to improve symptoms. One of the popular treatments is drug delivery, which is the process of releasing a drug inside the human body. Nanotechnology is promising in this field because of the demand for dedicated release. As one of the nanoparticles, liposomes present an excellent performance and potential future in drug delivery. The literature review attempts to show liposome structure, features, and significant applications by considering recent research based on authoritative theories. Through the review of previous studies, it could be proposed that liposomes earn significant progress in labs but still need further exploration to make advances in clinical applications.

Keywords: Tumor, liposome, drug delivery.

1. Introduction

A tumor is an abnormal tissue mass where cells grow out of control or do not die as usual. People who contract the tumor or detect serious symptoms of their tumor are always old, as Cairns claims the increased rate of colon cancer with age [1]. This is because the tumor has a complex process of developing and spreading. Tumors have clonality, which fixes the pattern of X chromosome inactivation. After the mutation and selection, the initial abnormal tumor cells proliferate with selective advantages, which help them grow rapidly. Then, those abnormal cells cause the benign neoplasm, and the tumor cells invade different systems with the spread of benign neoplasm [2]. Patients with tumors would have several biological symptoms, such as lumps, lower urinary tract symptoms, and bleeding, depending on specific cancer types. Tumor has a worldwide impact on people. In 2020, 19.3 million people became the new cancer patients, and nearly 10.0 million people died because of cancer [3]. In this way, the healing of the tumor is significant.

The traditional healing technology is surgery, chemotherapy, and radiation. With this treatment, the medication is necessary to improve the symptoms. However, the efficacy and effectiveness of traditional medicine for cancer are discussed in recent research. For example, according to the National Cancer Institute, Everolimus, which is used for late-stage patients with cancer, may have effects such as pain and weight loss [4]. Although those medications are effective in improving cancer to some extent. Their unintentional spreading in the human body may hurt the healthy and normal cells of patients and cause extra pain and weakness for the patients in the treatment phases. As a result, targeting drug delivery is important to improve the treatment and enhance the efficacy of the medication.

Nanotechnology is a useful technology that is applied to target drug delivery. Nanotechnology has prominent advantages such as stability, biocompatibility, permeability, and precise targeting. The reasonable and appropriate application of nanotechnology can help reduce the symptoms and increase the efficacy. Major nanotechnology in targeted drug delivery is classified into Liposomes, Polymeric nanoparticles, Dendrimer nanocarriers, and Exosomes. Because advanced research about these types of nanoparticles is various, this literature review attempts to show the examples of and summarize the characteristics of the typical and cutting-edge examples in Liposomes.

2. Structure of Liposomes

Liposomes are spherical lipid vesicles consisting of single or multiple lipid bilayers. As nanoparticles, the particles of liposomes often have a 50-500 nm diameter. As shown in Figure 1, the bilayer is made of cholesterol and phospholipids. The area between the two layers is hydrophobic, while the outer surface and the inner core are both hydrophilic. Based on the basic schematic structure of liposomes, according to the different sizes and numbers of bilayers, liposomes can be further classified into small and large unilamellar vesicles, multilamellar vesicles, and multivesicular vesicles [5].

As one of the significant components of liposomes, phospholipids significantly impact the characteristics and properties of liposomes. The simple components of a phospholipid are a glycerol unit, which is bonded to a phosphate group, and two fatty acid molecules [5].

The lipids can be normally classified into natural and synthetic lipids. Although natural phospholipids are much cheaper than synthetic phospholipids, since chromatographic purification techniques are not mature enough to get a single component of natural phospholipids, researchers explored and developed synthetic lipids to apply the properties of a single part of liposomes. Semi-synthesis of phospholipids includes changes in head and tail groups, while the total synthesis of phospholipids contains the formation of ester or ether bonds linking apolar moieties to the glycerol backbone and the attachment of the polar head group [6]. The changes in the conventional structure of liposomes create new types of liposomes with improving features.

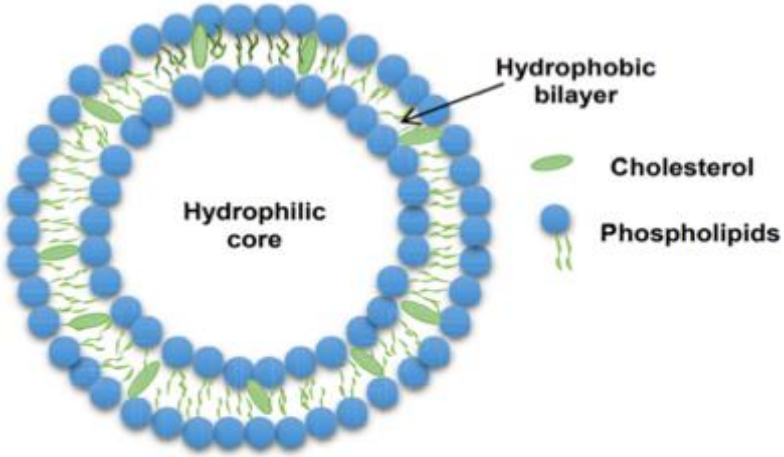

Figure 1. Schematic structure of liposomes [5]

3. Features of Liposomes

3.1. Size

Being widely used as carriers in various fields, liposomes show great advantages in medicine delivery for tumors. The tumor has a well-known effect, enhanced permeability and retention (EPR) [7]. This effect is shown in tumor tissue's newly grown blood vessels whose gaps are broader and looser than the normal tissue. The liposome uses this effect and its tiny size and function for its maximum efficacy.

3.2. Stability

From the perspective of the structure, the liposome is stable because of its enclosed structure and hydrophobic and hydrophilic surface. The water molecules repel the hydrophobic surface while presenting a self-assembly in the biolayers. The existence of hydrophilic surface coating provides steric hindrance to opsonin absorption so that the speed that liposomes is uptaken by RES cells [8]. Liposomes retain their property of stability in circulation by retaining their contents. With this property, liposomes have promising development in targeting drug delivery since the liposome can

keep the contents until it recognizes the arrival of the targeted area and then releases the drug. However, since the stability of natural and synthetic phospholipids are different, the decision between these choices depends on the specific circumstances. According to the review of Li et al., synthetic phospholipids are more stable and purer but more expensive than natural phospholipids [9].

Although liposomes are stable in the perspective of their structure, they are unstable when they are set in different environments with mutable factors such as blood circulation in the human body. So, more experiments and research are being done to improve the features and efficiency of traditional liposomes in drug delivery.

4. Applications of Liposomes

4.1. Ligand-targeted Liposome

As mentioned above, conventional liposomes still face RES uptake, opsonization, and immunogenicity setbacks. In this way, scientists developed and explored the new generation of liposomes, which have improved functions. The ligand-targeted liposome is a third-generation liposome with surface modification by applying appropriate ligands. The ligand-targeted liposome has the targeting ligands attached to its surface to selectively find the overexpressed tumor cells, as shown in Figure 2 [10].

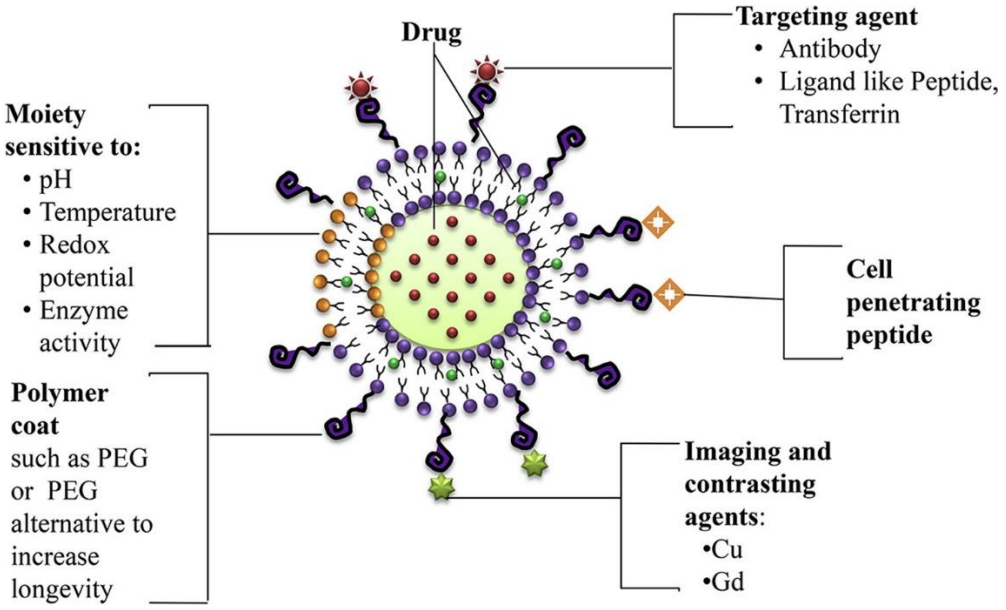

Figure 2. Structure of ligand-targeted liposome [10]

The ligand-targeted liposomes function mainly in two phases [11]. First, based on the EPR effect, ligand-targeted liposomes extravasate through the gaps between the tissue in the tumor. Then, the receptors of ligands would stop liposomes from dispersing, keep liposomes retenting in the tumor tissue, and release the drug to function. The experiments of liposomes in vitro and animal labs earned great success, but the application of liposomes in clinical medicine and treatments has not been approved because the technology is immature yet [11].

4.2. Stimuli-responsive Liposomes

Since microenvironments where targeting liposomes will arrive are complicated and particular, stimuli-responsive liposomes are designed to release the drugs in response to various biochemical environmental stimulation [10]. The response of stimuli-responsive liposomes, which are one of the big groups of targeting liposomes, mainly considers the value of PH, temperature, the amount of oxygen, redox potentials, enzyme concentrations, ultrasound, and electric or magnetic fields [5,10].

The discussion of PH-sensitive carriers was first introduced in 1980 by Yatvin et al. [12]. Then, scientists found that PH changed in different positions of tissue, and there was a difference, especially between tumor cells and normal cells. This way, PH-sensitive liposomes, which have local release triggers, can improve drug delivery efficacy and accuracy.

PH-sensitive liposomes are commonly composed of phosphatidylethanolamine (PE), which has a minimally hydrated and small head group and has five pH-sensitive types of lipid compositions, including acid-titratable. The arrangement of phosphatidylethanolamine is cone-shaped instead of normal lamellar shape. However, unsaturated PE alone does not present the capacity to compose stable liposomes, so additional compositions are needed to improve its stability. During the delivery process, the PH-sensitive liposomes stay stable until they arrive at the tumor site and react by destabilizing the lipid bilayer. Hyaluronic acid-targeted pH-responsive stealth liposomes (SL-pH- HA) improve efficacy and reduce toxicity to normal cells through the enhanced intracellular uptake processed by receptor-mediated endocytosis [13].

Despite the huge amount of vitro labs and success in animal experiments, the PH-sensitive liposomes have sluggish development during the transition from experiments to clinical applications. The quality and effectiveness of products should be further and repeatedly examined to assure their scalability, reliability, chemical stability, and safety. Moreover, recently, a voice against the base of nanotechnology in drug delivery has been aroused: the EPR effect's benefits and nanomedicine's benefits are unrelated since there is no specific nanomedicine in drug delivery for tumor patients [14].

Temperature-sensitive liposomes, which have remote induction, use the temperature as an outside trigger to release the drug. As a treatment, local hyperthermia is always used to enhance the permeability of drugs and promote the accumulation of drugs, specifically in the tumor tissue. Under normal human body temperature, temperature-sensitive liposomes remain stable, but as the temperature rises, the liposomes release the drug rapidly [15]. In the research of Zhang et al., when the temperature arrives at 42 degrees centigrade, the DOX-loaded thermosensitive liposomes release DOX more rapidly compared to its performance at 37 degrees centigrade [16]. The labs of temperature-sensitive liposomes have been processed in vitro and animals.

5. Conclusion

Liposomes have demonstrated significant advantages in cancer therapy, such as improving drug targeting, reducing side effects, and enhancing therapeutic efficacy. However, their practical application still has some limitations. First, liposomes may face chemical instability during preparation and storage, resulting in poor drug encapsulation rate, easy leakage, and loss of targeting. Second, the relatively large size of liposomes may increase the difficulty of their circulation and targeting in the body, affecting the accumulation of drugs in the tumor site. Liposomes may trigger the body's immune response to foreign substances, such as rapid recognition and removal by the RES system, shortening its circulation time. Some patients may have allergic reactions to liposome components, increasing the risk of treatment. Moreover, its effectiveness and safety in practical application still need further verification.

To address these issues, in the future, the specific receptors of tumor cells should be studied in depth, ligand-targeted liposomes with higher targeting properties should be developed, and stimulation-responsive liposomes should be used to achieve on-demand release of drugs and to reduce the accumulation of drugs at non-targeted sites, to reduce the side effects. To improve liposome stability and circulation time in vivo, attempts can be made to develop novel stabilizers. In addition, liposome technology is applied to other types of cancer treatment, such as gene therapy and immunotherapy, to broaden its application scope. Through continuous technological innovation and practical exploration, liposomes are believed to play a more important role in cancer therapy.

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