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Review

Liposome-based drug co-delivery systems in cancer cells

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ABSTRACT

Combination therapy and nanotechnology offer a promising therapeutic method in cancer treatment. By improving drug's pharmacokinetics, nanoparticulate systems increase the drug's therapeutic effects while decreasing its adverse side effects related to high dosage. Liposomes are extensively used as drug delivery systems and several liposomal nanomedicines have been approved for clinical applications. In this regard, liposome-based combination chemotherapy (LCC) opens a novel avenue in drug delivery research and has increasingly become a significant approach in clinical cancer treatment. This review paper focuses on LCC strategies including co-delivery of: two chemotherapeutic drugs, chemotherapeutic agent with anti-cancer metals, and chemotherapeutic agent with gene agents and ligand-targeted liposome for co-delivery of chemotherapeutic agents. Definitely, the multidisciplinary method may help improve the efficacy of cancer therapy. An extensive literature review was performed mainly using PubMed.

Contents

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1. Introduction

Cancer, a leading cause of worldwide death, is considered as a biocomplex phenomenon since different factors affect the outbreak of the disease. Various strategies including surgery, chemotherapy, radiotherapy, targeted therapy, immunotherapy, hyperthermia, hormone therapy, stem cell therapy, and mixtures of these methods have been developed for cancer treatment [1–7].

Chemotherapy is the ultimate treatment choice for several types of cancers; however, it presents critical limitations such as a lack of specificity, toxic side effects and development of drug resistance [8–13]. Most of the anticancer agents currently administered by confirmed therapeutic protocols are systemically circulated without special localization to cancer tissue. This widespread biodistribution of drugs results in both anticancer activities and off-target adverse activities. Combination therapy, using several different anti-cancer agents, is also developed as an optimistic method for the treatment of cancer. Combinatorial drug treatments have proven to be feasible because they activate the inhibition of several mechanisms or multiple connection points of a single mechanism. The advantages of combination therapy are supported by clinical studies showing synergistic effects that are greater to the sum of the therapeutic outcomes of each drug [14–18]. Although co-delivery (simultaneous delivery) of chemotherapeutic systems facilitate improvement in cancer therapy, their achievement is mainly hindered as a result of the inadequate accessibility of anticancer agents to tumor tissue, requiring high doses, rapid abolition, poor solubility and inappropriate bioavailability. Therefore, to mitigate the difficulties associated with traditional and combinational chemotherapies, there is a call for developing an ideal drug delivery system that could improve the therapeutic effect of drugs while decreasing their toxic side effects [19].

Nanomedicine presents a novel direction and a potent form of drug therapy that can enhance drug performance and overcome aforementioned limitations. Given that most of nanomedicines approved by the US Food and Drug Administration (FDA) were not specifically considered to have selectivity toward biological targets, they are first-generation of nanomedicines [20–26]. Application of nanotechnology in cancer treatment is widely expected to produce novel therapeutics for successful cancer treatment while reducing side effects to normal tissues. Nanotechnology has a critical role in cancer therapy regarding the application of different nanovectors such as liposomes, micelles, dendrimers, metal nanoparticles (NPs), carbon nanotubes (CNTs), natural and synthetic polymer NPs, and polymer–drug conjugates [27–36].

Among the various investigated delivery systems, liposomes hold great promise in the realm of drug delivery. Liposomes are spherical structures that are formed by one or several concentric lipid bilayers surrounding discrete aqueous spaces. Liposomes present several distinctive characteristics compared with other drug delivery systems including biocompatibility, no immunogenicity, ability for self-assembly, ability to load both hydrophilic and hydrophobic agents and improve their solubility, ability to carry large drug payloads and protect the encapsulated agents from the external media [37–40], ability to reduce the toxicity of the encapsulated agent and the exposure of sensitive tissues to toxic drugs coupled with the ability of site-specific targeting and improving penetration into tissues. Certainly, for drug formulation, liposomes are the most versatile and sophisticated nanoparticle type since they have the capacity to deliver several biologically active compounds and macromolecules (*e.g.* DNA, peptides, proteins and imaging agents) (Fig. 1.A), both in their lipid bilayer (*i.e.*, hydrophobic molecules) and in their lumen (*i.e.*, hydrophilic molecules) [41,42]. Therefore, they not only present a variety of benefits, but can enlarge their scope of drugs to get their optimized pharmacological effects [43,44]. However, unmodified liposomes are rapidly cleared by phagocytic cells of the reticuloendothelial system (RES) in blood circulation. To overcome this challenge, surface of liposomes are coated with a biocompatible and inert polymer such as polyethylene glycol (PEG). The polymer layer surrounding the outer of liposome prevents them from rapid clearance by the RES [45,46]. The goal of liposome-based cancer treatment is to improve drug efficacy, reduce toxicity, specify their targeting and minimize other limitations. In pursuit of this goal, different platforms have been extensively developed including modifications in liposomes (changes in lipid composition, charge, surface coatings and ligands) and drug formulations, one of which is LCC.

Liposome-based combinatorial drug delivery can be highly beneficial for cancer therapy and overcome most of the current challenges each technique faces with [47–51]. By understanding the current developments in liposomal-based drug co-delivery systems and their challenges, future research will improve the existing systems and address the limitations. In this Review, we provide an overview of the developed combination drug delivery systems based on liposomes in cancer treatment and include most of *in vitro*, *in vivo* and clinical studies.

2. Classification of liposomal drug delivery systems

Liposomes may have one or bilayer membranes. Vesicle size is a critical parameter in defining the half-life circulation of liposomes, and both number and size of bilayers affect the amount of drug loading in the liposomes. Size of liposome can differ from very small (25 nm) to large (2.5 μm) vesicles (Fig. 1.B). Additionally, On the basis of their size and number of bilayers, liposomes are grouped into two types: (1) unilamellar vesicles and (2) multilamellar vesicles (MLV). Unilamellar vesicles can also be classified into two subgroups: (1) small unilamellar vesicles (SUV) and (2) large unilamellar vesicles (LUV). In unilamellar liposomes, the vesicle has a single phospholipid bilayer sphere surrounding the aqueous solution. In multilamellar liposomes, vesicles have an onion-like structure. Classically, several unilamellar vesicles will be formed inside of the other vesicle, forming a multilamellar structure of concentric phospholipid spheres separated by water molecules, (Fig. 1.B) [52].

2.1. Liposome composition

Different composition of liposome can affect the drug delivery system including liposomes, binding ability, distribution and the way their contents are released (Tables 1, 2). Liposomes need a positive charge using cationic lipids in their composition, in order to bind to the nucleic acids [53]. For example, for the treatment of multidrug resistance (MDR)/cancer immunotherapy, mixtures of small interfering RNA (siRNA)/plasmid DNA (pDNA) and hydrophobic drug can be used [54]. Additionally, by controlling the composition of liposome membrane, the physicochemical characteristics of the liposome surface, including fluidity, charge and permeability may be changed. It is reported that by optimizing the formulation of liposomes, decrease of Pgp-mediated MDR may be achieved [55]. Since liposome-based drug delivery systems are administered systematically, their interaction with cells should be also taken into account. It is supposed that the inside surface of blood vessels, endothelial cells as well as cancer cells and tumor endothelial cells contain negatively charged components like glycosaminoglycans that may affect the liposomes distribution and their uptake by these