Advanced Drug Delivery Reviews 115 (2017) 46–56

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Dual-functional drug liposomes in treatment of resistant cancers☆

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ARTICLE INFO

Article history:
Received 27 December 2016
Received in revised form 15 April 2017
Accepted 18 April 2017
Available online 20 April 2017

Keywords:
Dual-functional liposomes
Multidrug resistance
ABC transporters
Cancer
Cancer stem cells

ABSTRACT

Efficacy of regular chemotherapy is significantly hampered by multidrug resistance (MDR) and severe systemic toxicity. The reduced toxicity has been evidenced after administration of drug liposomes, consisting of the first generation of regular drug liposomes, the second generation of long-circulation drug liposomes, and the third generation of targeting drug liposomes. However, MDR of cancers remains as an unsolved issue. The objective of this article is to review the dual-functional drug liposomes, which demonstrate the potential in overcoming MDR. Herein, dual-functional drug liposomes are referring to the drug-containing phospholipid bilayer vesicles that possess a dual-function of providing the basic efficacy of drug and the extended effect of the drug carrier. They exhibit unique roles in treatment of resistant cancer via circumventing drug efflux caused by adenosine triphosphate binding cassette (ABC) transporters, eliminating cancer stem cells, destroying mitochondria, initiating apoptosis, regulating autophagy, destroying supply channels, utilizing microenvironment, and silencing genes of the resistant cancer. As the prospect of an estimation, dual-functional drug liposomes would exhibit more strength in their extended function, hence deserving further investigation for clinical validation.

Contents

Abbreviations: ABC transporters, ATP binding cassette transporters; ALD, adrenoleukodystrophy; APL, acute promyelocytic leukemia; APTEDB, extra-domain B-specific aptide; ATP, adenosine triphosphate; ATRA, all-trans retinoic acid; BBB, blood-brain-barrier; BCRP, breast cancer resistant proteins; BIRC5, baculoviral inhibitor of apoptosis repeat-containing 5; COX-2, cyclooxygenase-2; CQ, chloroquine phosphate; DDS, drug delivery system; DOPE, dioleoylphosphatidylethanolamine; DOTAP, 1,2-dioleoyl-3-trimethylammonium-propane; DQA, dequalinium; DSPE-PEG_{2000}-c(RGDfK), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[(polyethylene glycol)-2000]- c(RGDfK); EPR, enhanced permeability and retention; GLUT, glucose transporters; HCQ, hydroxychloroquine; HIF-1α, hypoxia-inducible factor-1α; LRP, lung resistance-related proteins; MAN, *p*-aminophenyl-α-D-mannopyranoside; MDR, multidrug resistance; MMP-9, matrix metalloproteinase-9; mPEG2000-Hz-PE, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(poly(ethyleneglycol))-750]-phospatidylethanolamine hydrazone; MRI, magnetic resonance imaging; MTS, mitochondrial targeting sequence; NFkB, nuclear factor-kappa B; ODN, oligonucleotide; OXPHOS, oxidative phosphorylation; PEG, polyethylene glycol; P-gp, P-glycoprotein; PIPDR, pH-induced physiological drug resistance; PNA, peptide nucleic acid; PTD, protein transduction domain peptide; PTX, paclitaxel; RES, reticuloendothelial system; RGD, arginylglycylaspartic acid; RNAi, RNA interference; siRNA, small interfering RNA; TF, transferrin; TNF, tumor necrosis factor; TOM, translocase of the outer membrane; TPGS1000, D-a-tocopheryl polyethylene gylcol 1000 succinate; TPP, triphenylphosphine; TRAIL, TNF-related apoptosis-inducing ligand; VCAM-1, vascular cell adhesion molecule-1; VE-Cadherin, vascular endothelial cadherin; VEGFR-1, vascular endothelial growth factor receptor-1; VM, vasculogenic mimicry.

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Nanoformulations for combination or cascade anticancer".

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http://dx.doi.org/10.1016/j.addr.2017.04.006
0169-409X/

1. Introduction

1.1. Overview of drug liposomes

Liposomes are phospholipid vesicles composed of single or multiple concentric lipid bilayers enclosing aqueous spaces (shown in Fig. 1) [1]. Liposomes were first described by Bangham et al. in 1965, and were first used to encapsulate amyloglucosidase and ^{131}I-albumin by Gregoriadis et al. in 1971 [2,3]. Since then, liposomes have been used as a drug delivery system, and extensively investigated for five decades [4]. As a result, liposomes have become one of the most successful drug carriers in detection and treatment of a variety of diseases.

Albeit the coverage is slightly different from that described by Cattel et al. [5], the 'generations' of liposomes could be categorized into the following three generations.

The first generation of liposomes is a kind of regular liposomes without any modification, and mainly consist of phospholipids and cholesterol. The sizes of these liposomes are in the range of 50 to 450 nm [6]. As nanoscale drug carriers, the liposomes are biocompatible, and biodegradable with low toxicity. In addition, the liposomes are also controllable in view of the production and the quality specification [7]. For instance, the liposomes are able to load both hydrophilic and lipophilic compounds using the passive loading method, by which a wide range of therapeutic drugs can be incorporated into the liposomes [8]. As successful examples, amphotericin B liposomes had been approved for treatment of fungal infection (e.g., Ambisome, Amphotec, and Abelcet) [9]. However, these liposomes demonstrated obvious drawbacks, including low loading efficiency of hydrophilic drug, easy leakage of drug from liposomes, and rapid clearance of liposomes by the reticuloendothelial system (RES) in blood circulation. Accordingly, the first generation of regular liposomes were almost abandoned until the active drug loading and sterically stable liposomes were invented [10].

The second generation of long-circulation liposomes is a kind of modified liposomes by coating their surface with inert polymeric molecules, such as oligosaccharides, glycoproteins, polysaccharides, and synthetic polymers [11]. Among these hydrophilic molecules, polyethylene glycol (PEG) polymer is a successful material which has been used to stabilize the liposomes. During the process, a number of active drug loading methods had been invented as well in reaching a high drug encapsulation efficiency of drug. The active drug loading method is a remote encapsulation approach, which drives drug into the liposomes by the difference of chemical gradient between inside and outside membrane of the liposomes. The chemical gradients include pH gradient, ammonium sulfate gradient, and calcium acetate gradient, etc. As a result, the liposomes have been assigned favorable properties, including the altered bio-distribution, the reduced drug leakage, and the prolonged circulation in the blood. The improved properties are associated with the steric hindrance effect offered by hydrophilic polymer, which could prevent the modified liposomes from being rapidly eliminated by the RES [12]. Accordingly, a number of liposomes were approved successfully in clinical treatment or under clinical trial evaluations. As successful examples, several formulations of pegylated doxorubicin liposomes have been approved for treatment of cancers, such as Caelyx, Myocet, and Doxil [13]. Although great achievements have been made, the long-circulation liposomes exhibit some drawbacks as well, such as low cellular uptake, and poor selectivity in cancer cells.

The third generation of liposomes is a kind of targeting liposomes by incorporating specific molecules or functional materials on the liposomes. The liposomes may possess passive, active, and physicochemical targeting properties. Both of the first and the second generation of liposomes belong to the passive targeting carriers, which display the lymphatic affinity due to the lipophilic membrane of liposomes, and exhibit the increased accumulation in tumor site due to the enhanced permeability and retention (EPR) effect [14]. Besides of possessing the passive targeting properties, the third generation of liposomes are assigned specific targeting effects, including active, and physicochemical targeting effects. Active targeting liposomes could target cancer

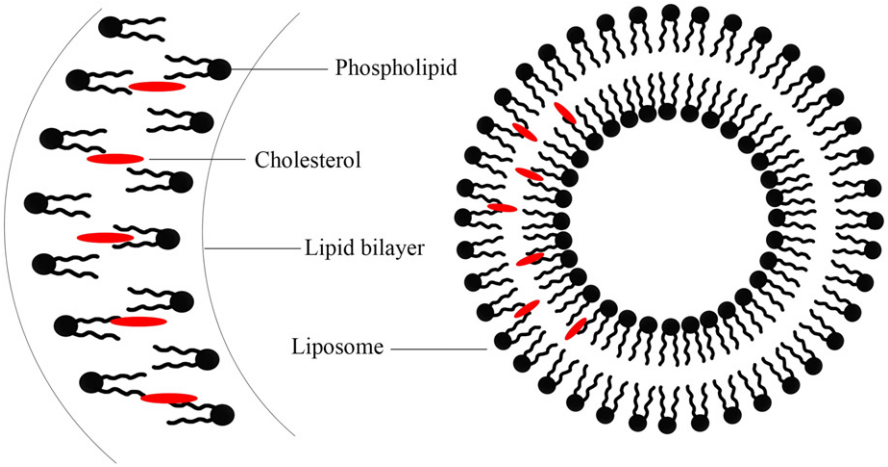

Fig. 1. Basic structure for bilayer vesicles of liposomes.