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Review

Natural liposomes and synthetic polymeric structures for biomedical applications

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ABSTRACT

In the last decades, the development and design of drug delivery systems have attracted great attention. Especially siRNA carriers have been of special interest since discovered as suitable tool for gene silencing. Self-assembled structures consisting of amphiphilic molecules are the most investigated carriers with regards to siRNA delivery. Liposomes as drug vehicles already found their way into clinical use, as they are highly biocompatible and their colloidal stability and circulation time in blood can be significantly enhanced by PEGylation. Fully synthetic polymersomes inspired by these natural structures provide enhanced stability and offer a wide range of modification-possibilities. Therefore, their design as carrier vehicles has become of great interest. This mini-review highlights the possibilities of using polymeric vesicles for potential drug delivery and gives a brief overview of their potential regarding fine-tuning towards targeted delivery or triggered drug release.

Contents

1. Introduction

Since the discovery of RNA interference (RNAi) as novel therapeutic strategy for gene silencing by Fire et al. in 1998 [1] and Elbashir et al. in 2001 [2,3], the development of suitable carrier systems for (synthetic) siRNA targeted towards specific disease relevant genes became of great interest. Despite their high efficiency for siRNA delivery, viral vectors are limited in application due to possible inflammatory and immunogenic responses [4]. Therefore, the design of novel non-viral delivery strategies is a rapidly growing field. Among them, the direct chemical modification of siRNA [5] as well as loading the cargo into carrier systems such as nanoparticles have been widely studied. Polymeric nanoparticles consisting of biodegradable or biocompatible polymers like chitosan have been successfully used for the delivery of siRNA into the lungs of mice in order to silence GAPDH or EGFP [6,7]. Another approach for the development of non-viral siRNA delivery vectors is inspired by naturally occurring structures such as eukaryotic membranes. Systems based on self-assembled structures out of amphiphilic molecules are the most prominent and well-studied siRNA carriers [8].

An important example for such amphiphilic molecules are natural occurring lipids [9]. Up to a certain concentration, these lipids are soluble on a molecular level in water, but above a critical concentration aggregates are formed [10]. In order to minimize the repelling interactions with water the hydrophobic tails cluster

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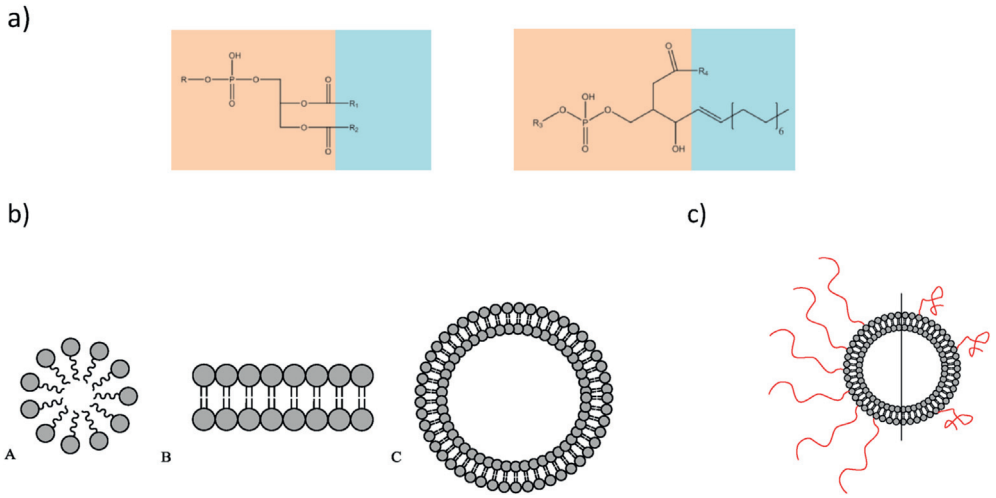

Fig. 1. a) Schematic structure of left) phosphoglycerides and right) sphingophospholipids with the polar head (orange) and the apolar tail (blue); b) schematic 3D structures of self-assembled lipids with A) micelle, B) bilayer and C) vesicle; c) PEG modification of liposomes with high density (left) and low density (right).

together while the hydrophilic heads repel each other due to sterical and electrostatical hindrance. This way, three dimensional assembled structures like micelles, bilayers, or vesicles are formed (Fig. 1b) [11].

If composed of (phospho-)lipids (Fig. 1a), the latter ones are also usually called liposomes [12–14] and can be both single-component systems and multi-component systems, which means that other molecules like for example cholesterol are also incorporated. This is also the case for the natural cell membrane, where cholesterol plays an important role for the membranes viscosity according to the fluid mosaic model from Singer and Nicholson [15].

2. Liposomes for drug delivery

Due to their structure shown in Fig. 1b, liposomes allow the encapsulation of a high variety of drugs such as hydrophilic (inside the core), hydrophobic (in the hydrophobic part of the membrane) as well as amphiphilic molecules (as part of the membrane). The loading of siRNA cargo into "man-made" liposomes is a very prominent strategy [16] due to the biocompatibility of the constituents and the simple preparation by only mixing the different components. "Lipoplexes", which are formed due to electrostatic interactions between positively charged lipids and the negatively charged siRNA [17], were identified to enhance the efficiency of siRNA delivery in contrast to using naked siRNA [18]. Numerous studies on cationic lipidic vectors have been reported [19], among them 1-oleoyl-2-[6-[(7-nitro-2-1,3-benzoxadiazol-4-yl)amino] hexanoyl]-3-trimethylammonium propane (DOTAP) [20] or N-[1-(2, 3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) [21]. A major drawback of using cationic lipids is the potential undesired interaction with negatively charged serum proteins as well as possible inflammation response [22–24]. The addition of cholesterol or other neutral lipids such as distearoyl phosphatidylcholine (DSPC) [25] to lipoplexes in order to form multi-component liposomes is a successful method to overcome the above mentioned problems [26,27]. In addition, cholesterol offers the opportunity of simple modification strategies with for example ligands. Another approach to circumvent the described drawbacks is the surface modification of liposomes with poly (ethylene glycol) (PEG) (see Fig. 1c) [28]. The conformation of PEG on a liposomes' surface is dependent on many factors such as density of the grafted polymer mirroring the available space the polymer chains can capture [29]. In case of low grafting density, each PEG chain has enough space to be in coiled-structures, but when the grafting density is increased, the chains are forced to elongate due to the steric hindrance between two chains. In the presence of this highly biocompatible polymer, reduced aggregation as well as prolonged blood circulation time of liposomes was obtained [30–32]. The so-called "stealth-liposomes" [33] already found their way into clinical use [34,35]. The most prominent and commercially available among them is Doxil™, which is a liposomal formulation with doxorubicin (DOX) as drug for anticancer treatment [36,37]. Doxorubicin belongs to the group of anthracyclines that have an antineoplastic effect but also cause several side effects like for example cardiotoxicity [38]. Encapsulation of DOX in liposomes was found to reduce the drug accumulation in heart and to increase its localization in tumor cells [39]. The latter feature was contributed mainly to the prolonged half-life in blood circulation of the PEGylated liposomal system [39,40].

In recent studies, our group introduced a promising alternative to PEG, namely hyperbranched polyglycerols, in order to synthesize stealth-liposomes [41]. These structures bear several hydroxyl groups that can be used for post-modification with ligands. In addition, it is known, that protein adsorption on corresponding modified monolayers is reduced in comparison to PEG-modified ones [42,43]. By comparing the stability of the two kinds of sterically stabilized liposomes in human blood serum by dynamic light scattering applying the method after Rausch et al. [44], we found out that the hyperbranched structures in contrast to linear PEG can prevent aggregation of investigated liposomes in human serum altogether, indicating their potential as drug delivery system [41].

According to the fact, that neutral lipids and PEG-modified ones are limited in electrostatic interactions with siRNA, the formulation of more complex systems needs a little more effort than just mixing the components. Among the several approaches, the lipid film method is the most prominent one in order to synthesize highly PEGylated liposomes [8]. In principle, a dried thin lipid film with all liposomal components is dissolved with a concentrated siRNA solution [45]. Downsizing and size-control can further be done by sonication [46–48] or by extrusion through a polycarbonate membrane with defined pore sizes [41,49].

The synthesis of lipids often requires multiple steps and several purification methods [50]. Therefore Langer and Anderson developed a new class of "lipidoids" [51] which are lipid-like materials, that can be synthesized rapidly. A combinatorial library was provided and the new components screened in animal models regarding efficiency and safety for siRNA delivery. By this, a