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Engineering polymersomes for intracellular biopharmaceutics delivery

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Abstract
Biopharmaceutics, such as proteins, nucleic acids, antibodies, have emerged as promising candidates for the treatment of a variety of diseases due to their high specificity and greater bioactivity. However, the intrinsic low biological stability and poor cell membrane penetration ability of biopharmaceutics has largely hindered their utility. Developing efficient cytosolic delivery platforms is, therefore of vital importance to overcome these hurdles and to advance the clinical translation of biopharmaceutic-based therapy. Polymersomes have emerged as superb nanovesicles for sophisticated biophamraceutic delivery, owing to their hydrophobic membranes to protect proteins from enzymatic degradation and vast watery cores for protein loading. This perspective summarizes the current design and applications of polymersomes for the intracellular delivery of therapeutic biopharmaceutics.
Keywords: Polymersomes, biopharmaceutics therapy, intracellular delivery, cancer therapy

Background

Biopharmaceutics, such as enzymes, chimeric proteins, antibodies, and cytokines, are now revolutionizing the cancer therapy field.[1, 2] As compared with the traditional small molecule drugs, these biotherapeutics have the advantages of high specificity and greater biological activity.[3] Nowadays, clinically approved biomacromolecules drugs are mostly designed to target extracellular biomolecules.

The clinical translation of biopharmaceutics against intracellular targets is more challenging, as they need to overcome the intracellular barriers, including cell membrane penetration, endosomal escape, and cytoplasmic release, in addition to extracellular barriers. It is therefore of great significance to develop clinically useful strategies for the safe and efficient intracellular delivery of therapeutic biomacromolecules.

Cytosolic delivery of biopharmaceutics is challenging due to their large size, intrinsically vulnerable structure, and incompetent membrane penetration.[4] Nevertheless, dramatic progress has been made in the development of intracellular delivery in the past few decades. These strategies include non-viral nanoparticles,[5] protein conjugates,[6] electroporation,[7] and virus vehicles.[8] Featuring low immunogenicity, ease of manufacture, and good safety,[9, 10] non-viral nanoparticles like liposomes,[11] polymeric micelles,[12] nanogels,[13-15] polymeric nanocapsules,[16] inorganic nanoparticles,[17] and polymersomes,[18] have been developed to accomplish intracellular delivery of biopharmaceutics. In particular, polymersomes hold tremendous potential for encapsulation and delivery due to their excellent stability, a vast watery core for loading hydrophilic biopharmaceutics, and a sufficient surface for the facile introduction of targeting ligands.[19] In this perspective, we summarize the current development of polymersomes for the intracellular delivery of biopharmaceutics and, highlight the advanced strategies to facilitate the clinical translation of nanopolymersome-based biotherapeutics.

Why Polymersomes?

Polymersomes are nanovesicles with a large watery lumen that is separated by a thick membrane, like liposomes. Unlike liposomes, formed from low molecular weight lipids, polymersomes are generally self-assembled from amphiphilic macromolecules, including diblock, triblock, graft polymers, dendrimers, and polysaccharide-polymer conjugates.[20-22] The

inherent high molecular weight of the hydrophobic block in polymersomal membrane affords thicker membranes, greater colloid stability, and largely inhibited membrane fluidity over liposomes. The large watery lumen makes polymersomes an ideal nanovehicle for the encapsulation of hydrophilic biopharmaceutics, like proteins, siRNA, and plasmid DNA. The thick membrane not only stabilizes the polymersomes but also separates the encapsulated biomolecules from the outer environment, avoiding the enzymatic degradation and deactivation of payloads. Meanwhile, the release behaviors of cargoes can be well controlled by tuning the membrane characteristics of polymersomes including bio-degradability, stimuli-responsivity, and permeability.[23] Furthermore, to specifically deliver biopharmaceutic drugs to disease sites, active targeting polymersomes can be easily prepared by decorating specific ligands (antibodies, peptides, folate, etc.) onto the surface of polymersomes.

Conventional polymersomes for biopharmaceutic delivery

Owing to the pioneering work of Eisenberg, Disher, and co-workers, tremendous attention has been paid to polymersomes for their unique characteristics as a drug delivery system.[21, 22] The conventional polymersomes were mainly formed from high molecular weight diblock (AB) or triblock (ABA) copolymers with a highly asymmetric property with a ratio of hydrophilic to total mass $f_{hydrophilic}$ < 20% (Figure 1). In one study, biocompatible and biodegradable poly(ethyl oxide)-*b*-poly(L-lactide) (PEO-*b*-PLA) and poly(ethyl oxide)-*b*-poly(ε-caprolactone) (PEO-*b*-PCL) diblock amphiphiles were used to prepare polymersomes as a potential oxygen carrier for hemoglobin (Hb) encapsulation.[24] The authors reported that the Hb encapsulation efficiency can be easily controlled by adjusting the diblock copolymer concentration, and up to 20% encapsulation efficiencies were achieved. Moreover, Hb encapsulated polymersomes demonstrated comparable oxygen binding.

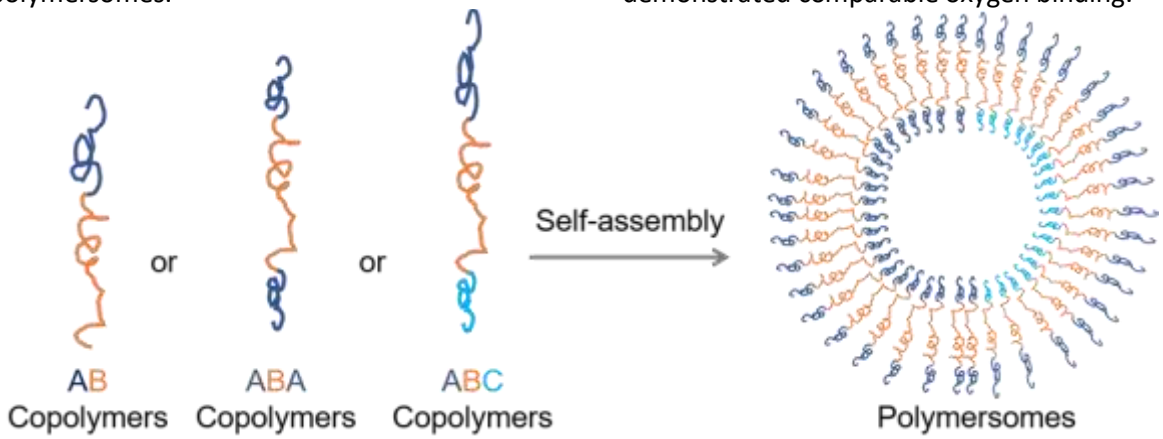

Figure 1. Schematic illustration of self-assembly of block copolymers into polymersomes. (A and C represent hydrophilic polymers; B represents hydrophobic polymers).

Polymersomes have also been shown to serve as a therapeutic nanoreactor to achieve protein delivery *in vivo* for cancer treatment.[25] Polyion complex (PIC) vesicles (PICsomes) were prepared through the self-assembly of PEG-*b*-PAsp and homo-P(Asp-AP) molecules.[26] The PICsomes encapsulated L-asparaginase (ASNase) in the inner aqueous phase of PICsomes, segregating the enzyme from the external environment. The ASNase-loaded PICsomes (ASNase@PICsomes) exhibited a prolonged half-life (16 h) and enhanced enzymatic reaction as compared with free ASNase.

Stimuli-responsive polymersomes for biopharmaceutic delivery

The drug release behaviors of biopharmaceutic-loaded polymersomes largely affect the therapeutic efficacies and the bioavailability of the cargo. Therefore, it is highly desired to design stimuli-responsive polymersomes that could self-destruct or swell in response to external or internal stimuli to control the drug release upon arrival at the target site. The first oxidation-responsive polymeric vesicles based on an ABA copolymeric amphiphiles, poly(ethyl glycol)-*b*-poly(propylene f sulfide)-*b*-poly(ethyl glycol) (PEG-PPS-PEG), was reported by Hubbel and

coworkers.[27] The polymersomes were rapidly destabilized due to the oxidative conversion of PPS from a hydrophobe to a hydrophile, poly(propylene sulphoxide), and ultimately poly(propylene sulphone) in the presence of H_2O_2. Glucose oxidase (GOx) was further loaded into the polymersomes, and the storage stability and GOx activity was dramatically extended.[28] Our group constructed pH and reduction dual-responsive polymersomes from PEG-SS-poly(2-diethyl amino)ethyl methacrylate) (PEG-SS-PDEA) for intracellular protein delivery.[29] The cationic nature of PDEA could facilitate the endo-/lysosomal escape of protein-loaded polymersomes. The proteins are likely further released in the cytoplasms due to the cleavage of disulfide bonds triggered by endogenous GSH, resulting in efficient cytosolic protein delivery. Recently, a poly-prodrug formed polymersomes co-loaded with ultra-small iron oxide nanoparticles and glucose oxidase (GOD) was developed by Ge and coworkers.[30] These polymersomes enabled the cascade reactions of glucose consumption in the presence of GOD to generate H_2O_2 to accelerate iron ion release. The released iron following the reaction with H_2O_2 via Fenton reaction produced hydroxyl radicals, resulting in the cleavage of thioketal bonds, and further triggered the release of conjugated drug at the tumor site.

Chimeric polymersomes for biopharmaceutic delivery

Although polymersomes possess a large watery core, they generally exhibit inferior loading of water-soluble agents including proteins. Chimeric polymersomes are a novel type of polymersome with asymmetric membranes prepared from triblock copolymers. Typically, the longer hydrophilic chains (such as PEG, polysaccharide, etc.) are preferentially segregated into the outer layer of polymersomes, and the shorter hydrophilic chains (usually a charged segment) are mainly located in the inner layer. As compared with the conventional polymersomes discussed above, chimeric polymersomes have polyionic blocks in the watery interior, which favor high biopharmaceutic loading through electrostatic interaction. Meanwhile, the asymmetric structure of triblock copolymers facilitates the formation of a curvature structure, often affording polymersomes with small sizes. (Table 1) For example, biodegradable chimeric polymersomes formed from PEG-PCL-PDEA asymmetric triblock copolymer displayed efficient loading of various exogenous proteins, including bovine serum albumin (BSA), cytochrome C (CC), lysozyme (Lys), ovalbumin (OVA), and immunoglobulin G (IgG).[31]

Table 1. Key features of conventional and chimeric polymersomes

Polymersomes	Polymers	Membrane structure	stability	Loading of biomacromolecules	Ref
Conventional Polymersomes	Diblock copolymers (AB), triblock copolymers (ABA)	Symmetric membrane	stable	Relatively low loading content and efficiency. The cargos are loaded into the polymersomes through hydrophilic interaction	21, 22, 24, 25, 26
Chimeric Polymersomes	Asymmetric triblock copolymers (ABC)	Asymmetric membrane. Typically, the inner membranes are charged	Higher than conventional polymers-omes	The cargos are loaded through electronic interaction between cargos and the charged inner membrane of polymersomes	31, 32, 33

Tumor-targeted polymersomes for *in vivo* biopharmaceutic delivery

For *in vivo* application, an ideal nanocarrier should have good stability, excellent targetability, and stimuli-responsivity for fast drug release in target cells. Our group reported the construction of a series of ligand-functionalized, reversible disulfide cross-linked chimeric polymersomes for highly efficient protein delivery to different cancer cells *in vivo*.[18, 32] In one study, we found that apolipoprotein E peptide-directed and reduction-sensitive chimeric polymersomes (ApoE-CP) induce potent protein therapy for orthotopic human glioblastoma (GBM) xenografts in nude mice.[33] The polymersomes were self-assembled from PEG-*b*-poly(dithiolane trimethylene carbonate-*co*-trimethylene carbonate)-*b*-polyethyleneimine (PEG-P(TMC-DTC)-PEI) and ApoE-peptide modified PEG-P(TMC-DTC) (ApoE-PEG-P(TMC-DTC)). Interestingly, ApoE-CP showed a decent blood-brain barrier (BBB) crossing, efficient accumulation, and penetration in the U-87 MG tumor. More importantly, saporin loaded ApoE-CP caused complete tumor growth inhibition in orthotopic U-87 MG tumor-bearing nude mice. These chimeric polymersomes formulations of therapeutic proteins have great potential for safe and efficient GBM therapy.

Recently, polylipopeptide-based chimeric polymersomes, defined as lipopepsomes, have been developed from asymmetric PEG-*b*-poly(α-aminopalmitic acid)-*b*-poly($_L$-aspartic acid) triblock polypeptide as a simple and multifunctional nanoplatform for targeted saporin delivery to orthotopic lung tumor *in vivo*.[34] Polypeptides are one of the most used materials for drug delivery owing to their excellent biodegradability and biocompatibility, and several polypeptide-based nanomedicines are currently under clinical trials.[35, 36] In this study, the cRGD-decorated lipopepsomes achieved nearly quantitative encapsulation of saporin with superb stability due to the existence of the lipid-lipid packing effect in the membrane and exhibited a potent lung tumor suppression. Similarly, chimeric lipopepsomes with positively charged segments were readily prepared from PEG-*b*-PAPA-*b*-PLL triblock copolymer as a virus-mimicking carrier for targeted siRNA delivery to the orthotopic A549 lung tumor.[37] The lung cancer-specific cell-penetrating peptide CPP33 modified siPLK1-loaded lipopepsomes (siPLK1-CPP33-CLP) exhibited enhanced tumor accumulation, significant tumor growth inhibition, and elevated survival rate.

Conclusion and Perspectives

The past decade witnessed the increasing exploration and development of polymersomes as biopharmaceutic delivery vehicles, both *in vitro* and *in vivo*. There is no doubt that polymersomes show outstanding potential in protein delivery. It should be noted, however that polymersomes are still in early development stage, no polymersome-based protein therapeutics have entered the clinical trial to date, and some requirements need to be considered when designing a new polymersome-based platforms for biopharmaceutic delivery. First of all, the fragile property and immunogenicity of biomacromolecules should be taken into consideration. One of the most important issues we need to address is to improve the stability of the biopharmaceutic-loaded polymersomes to prevent the undesirable premature release and increase the blood circulation time of protein drugs. Second, to increase the bioavailability of biopharmaceutic drugs, we need to develop more disease-specific approaches, such as to mount antibodies onto the surface of the polymersomes and develop bio-/virus-mimicking polymersomes (incorporating specific membrane proteins into the membrane of polymersomes), to deliver drugs. Third, the safety of the synthetic materials used to construct polymersomes should be carefully evaluated. To advance the clinical translation of polymersomal protein therapeutics, we recommend using FDA approved materials, which could have great biocompatibility and biodegradability, and are easy for large-scale production. We believe that with the continuous effort and interdisciplinary research, polymersome-based biotherapeutics will become a safe and effective treatment for various human diseases.

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