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Multifaceted polymersome platforms: Spanning from self-assembly to drug delivery and protocells

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ABSTRACT

Biologically inspired self-assembly processes of amphiphilic copolymers have received an increasing attention for creating innovative and highly advanced functional materials for various biomedical applications. Polymersomes are versatile nanosystems with tremendous potential due to their increased colloidal stability, tunable membrane properties, chemical versatility, and the ability to accommodate a broad range of drugs and biomolecules. In this review, we present the principles of copolymers self-assembly and associated parameters that control the resulting self-assembled morphologies, and various methodologies developed for fabrication of polymersomes. We attempt to discuss how polymersome platforms can be applied for versatile biomedical research, from simple passive nanocarriers for drug delivery to functionalized polymersomes for active targeting approaches and advanced nanoreactors, and protocells to mimic structure and functions of biological systems.

Abbreviations: ABTS, azinobis(3-ethylbenzothiazoline-6-sulfonic acid); AD, Alzheimer's disease; AON, antisense oligonucleotides; AP, artificial peroxisome; AqpZ, aquaporin; BBB, blood–brain barrier; BSA, bovine serum albumin; CalB, candida antarctica lipase B; Cath B, cathepsin B; CC, cytochrome C; CMT, critical micellization temperature; CPK, creatine phosphokinase; CPO, chloroperoxidase; CWC, critical water content; DEX, dextran; DMF, dimethylformamide; Dox, doxorubicin; Dtx, docetaxel; EAB, ethyl-p-aminobenzoate; EAT, Ehrlich ascites tumour; EGFR, epidermal growth factor receptor; FITC, fluorescein isothiocyanate; GM, glutamate; GOx, glucose oxidase; H_2O_2, hydrogen peroxide; HA, hemagglutinin; Hb, haemoglobin; HCl, hydrochloric acid; HER2, human epidermal growth factor receptor 2; HRP, Horse radish peroxidase; HYA, hyaluronan; IgG, immunoglobulin G; LamB, maltoporin; LCST, lower critical solution temperature; LDH, lactate dehydrogenase; Lf, lactoferrin; LF2K, lipofectamine 2000; LPO, lacto peroxidase; Lz, lysozyme; Mb, myoglobin; mPEG, methoxy poly(ethylene glycol); MreB, membrane related cytoskeletal actin-like protein; MW, molecular weight; OmpF, outer membrane protein F; OVA, ovalbumin; P(Asp), poly(α,β-aspartic acid); P(Asp-AE), poly((2-aminoethyl)-α,β-aspartamide); P(Asp-AP), poly((5-aminopen-tyl)-α,β-aspartamide); P2MMA, poly(glycerol monomethacrylate); P2VP, poly(2-vinylpyridine); P4VPQI, poly(*N*-methyl-4-vinyl pyridinum); PAA, poly(acrylic acid); PAMA, poly(2-aminoethylmethacrylate); PAzoMA, poly(6-[4-(4-methoxyphenylazo) phenoxy] hexylmethacrylate); PBD, poly(butadiene); PBLG, poly(γ-benzyl glutamate); PCL, poly(3-caprolactone); PCR, polymerase chain reaction; PDEA, poly(2-(diethylamino)ethylmethacrylate); PDEAMA, poly(2-diethylaminoethylmethacrylate); PDLLA, poly(D,L-lactide); PDMS, poly(dimethylsiloxane); PDPA, poly(2-(diisopropylamino)ethyl methacrylate); PDS, poly(distearin); PEE, poly(ethyl ethylene); PEG, poly(ethylene glycol); PEO, poly(ethylene oxide); PGA, poly(L-glutamic acid); PI, polyisoprene; PIAT, poly(3-(isocyano-L-alanyl-aminoethyl)thiophene); PLA, poly(lactic acid); PLE, poly(leucine); PLys, poly(lysine); PMHDO, poly(6-methyl-1,2-heptadiene-4-ol); PMOXA, poly(2-methyloxazoline); PMPC, poly(2-(methacryloyloxy)ethyl phosphorylcholine); PMPA, polyelectrolyte mediated protein adsorption; PMPS, poly(methylphenylsilane); PNIPAm, poly(*N*-isopropylacrylamide); pPEGMA, poly(polyethylene glycol methacrylate); PPO, poly(propylene oxide); PPP, polyphospazene; PPS, poly(propylene sulfide); PQ, paraquat; PS, polystyrene; PTMBPEC, poly(2,4,6-trimethoxybenzylidenepentaerythritol); PTMC, poly(trimethylenecarbonate); Ptx, paclitaxel; RAFT, reversible addition fragmentation-transfer; RFP, red fluorescence protein; SBS, styrene-block-butadiene-block-styrene; SiO_2, silica; sLe^x, Sialyl Lewis X; SOD, superoxide dismutase; Tf, transferrin; THF, tetrahydrofuran; XPS, X-ray photoelectron spectroscopy.

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Contents

1. Introduction

Molecular self-assembly is one of the nature's fundamental processes, in which existing parts or components generate the well-organized structures or systems, ranging from micro to nanoscale. Mimicking the nature's technologies, particularly the self-assembly, has received an increasing attention for the creation of new functional materials for various biomedical applications, especially for drug delivery purposes [1–3]. The design of components that self-orient among themselves to desired structures and functions is the key to self-assembly based applications. The membranes of living cells and cellular vesicles consist of lipid bilayers made of self-assembling phospholipids. As a biologically inspired approach, amphiphilic copolymers have been exploited for the formation of self-assembling structures towards potential biomedical applications [4,5]. The amphiphilic copolymers contain both hydrophilic and hydrophobic blocks linked covalently, which self-assemble in dilute aqueous solutions and form various molecularly ordered superstructures [3,4]. The copolymers self-organize in a selective solvent for one of the two blocks, in which the solvent selective block is compatible with the solvent, whereas the other block is incompatible, inducing the self-assembly process. The self-assembly process in aqueous solutions results from the strong repulsion between the two incompatible blocks, also known as long range repulsion forces, that induce the blocks of the copolymers to segregate. At the same time, there are short range attractive forces between the incompatible blocks due to the covalent linkage, keeping them together. These two opposing forces cause microphase separation of the incompatible blocks, leading to the formation of different self-assembled superstructures. The self-assembly is typically driven by non-covalent interactions, such as hydrophobic interactions, hydrogen bonds, electrostatic forces and Van der Waals interactions [3,6].

Typically, polymersomes are hollow spheres consisting of an aqueous interior surrounded by a polymer bilayer membrane. The hydrophobic blocks of the amphiphilic copolymers are protected from the aqueous environment within the bilayer by the hydrophilic blocks, which are exposed inside and outside to the aqueous environment [7]. Among other self-assembled nanostructures, the morphology of the polymersomes has attracted considerable attention due to their unique tunable physicochemical properties in terms of composition, size, surface, membrane properties like thickness, permeability, responsiveness, and chemical functionalities; all these can be modulated for specific applications. Polymersomes can dramatically improve pharmacological properties of therapeutic agents like pharmacokinetics, drug exposure kinetics, and cell/tissue-specific targeting, resulting in enhanced therapeutic efficiency and efficacy. Furthermore, copolymers can offer desirable biological properties, such as biodegradability, biocompatibility and negligible toxicity, which are essential requirements for therapeutic applications. In addition, multiple functionalities can be introduced into a single polymersome to improve the performance of the nanocarriers (see elsewhere for details [8,9]). Rapid progress in synthetic polymer chemistry offers wide possibilities to synthesize a broad spectrum of polymers with high diversity in terms of nature, properties and composition, leading to a spectacular variety of building blocks, in order to design polymersomes. Among others, amphiphilic di- or triblock copolymers are predominantly studied for vesicle formation [10–13]. Nevertheless, other types of polymers such as alternating copolymers [14] and graft copolymers [15–17] have also been explored to a lesser extent (Fig. 1). Unlike diblock copolymers, triblock