Critical update on 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer science

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ABSTRACT: 2-Methacryloyloxyethyl phosphorylcholine (MPC) is a custom methacrylate with a zwitterionic phosphorylcholine moiety on the side chain. In the past 25 years, MPC has been used as a building block for a wide range of polymeric biomaterials because of its excellent resistance to nonspecific protein adsorption, cell adhesion, and blood coagulation. Recently, MPC polymers with specific features have been used in bioengineering and nanomedicine. This review focuses on three topics that highlight the latest findings on MPC polymers, that is, specific recognition of C-reactive protein (CRP), cell-membrane-penetration abilities, and lubrication properties. These developments will extend the applications of this biomimetic material from bioinert polymers to biosensing, CRP inhibitors, prodrug carriers, subcellular bioimaging, cell manipulation, and joint replacement. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 41766.

INTRODUCTION

Since the early period of biomaterial science, one of the top priorities has been to develop artificial materials that can resist nonspecific protein adsorption and blood coagulation because nonspecific adsorption of proteins and biomolecules leads to undesired biological reactions such as blood clotting, inflammation, immunoreactions, bacterial adhesion, biofilm formation, cell adhesion, and cell differentiation. The cell membrane in living organisms provides the cell with an intrinsically inert barrier for biomolecules and signals. Based on the molecular structure of phosphatidycholine in the outer leaflet of eukaryotic plasma membranes, a synthetic molecule, 2-methacryloyloxyethyl phosphorylcholine (MPC), was developed to endow material surfaces with biologically inert functions such as those possessed by endothelial cells in blood vessels.[1] A zwitterionic phosphorylcholine (PC) group in the side chain of MPC is responsible for its bioinert properties, as a result of impaired electrostatic interactions and the formation of a thick hydration shell with a rich content of highly mobile free water around the PC group.[2–13] Furthermore, MPC, a methacrylate monomer, can build various molecular architectures with tunable properties via a series of polymerization techniques including living radical polymerization.[14–17] Because of the reactivity of methacrylate, MPC-based materials have a wide range of applications in biomedical fields. This is in sharp contrast to natural phospholipid, which is composed of saturated or unsaturated fatty acids with a headgroup incorporated via ester linkages and has low reactivity. As a result of the commercial success of the mass production of MPC, many researchers have synthesized numerous MPC polymers, some of which have been used as biomaterials. MPC polymers can be used alone or in combination with other materials, including plastics, metals, and ceramics.[18–20] Now, MPC polymers have successful applications in nanobiosciences, bioconjugation on colloidal surfaces, and biosensing.[21–25]

In recent years, MPC polymers have attracted further attention because of the discovery that they have other properties in addition to their bioinert nature. The first topic is that MPC polymers can be used as synthetic receptors for C-reactive protein (CRP). This is a paradigm shift because the MPC unit was believed to repel any proteins. The second is direct penetration of amphipathic MPC polymers across the plasma membrane without overt cytotoxicity. The ability to diffuse into cytoplasm is surprising because almost all macromolecules from synthetic sources are unable to cross the plasma membrane barrier without breaking up the lipid bilayer or without alerting well-organized biological security systems. The third is hydrated

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biomimetic lubrication of surfaces modified with poly(MPC) grafts. These three aspects of MPC polymer science all arise from the physicochemical nature of the zwitterionic PC group. Importantly, the original antifouling properties of MPC polymers and these new properties are synergistic in biological environments. In the following sections, we focus on the details of these important advances in MPC polymer science.

ARTIFICIAL LIGAND FOR CRP

The PC headgroups in C-polysaccharides and lysophosphatidyl-choline present in oxidized low-density lipoprotein (LDL) or in damaged plasma membranes are known to bind specifically with CRP in the presence of calcium ions.[26,27] Human CRP is a nonspecific acute-phase plasma protein produced by hepatocytes in the liver on stimulation by endogenous proinflammatory cytokines. Its systemic level in circulation sharply increases by up to 1000-fold compared with normal conditions (0.8 mg L^{-1}) within 24–48 h of injury.[28] The binding of CRP to the PC receptor activates classical complement pathways in damaged tissue, leading to an innate immune cascade. It has been reported that CRP is connected to atherosclerosis and increases the risk of cardiovascular diseases.[29,30] The CRP–PC interaction triggers many systematic biological responses in living organisms, so it is important to understand the activation dynamics of CRP against PC at the molecular level at the foci of inflammation and infection. The physiologically intact form of human CRP is a pentraxin of molecular weight of 115 kDa. Each protomer (23 kDa) is arranged in a symmetric pentagon by noncovalent bonding and has a recognition domain for the PC

group in a calcium-binding pocket.[31] Interaction of CRP with two calcium ions has an intricate profile, in which the PC-binding pocket coordinates with two calcium ions in series with different dissociation constants [$K_{D,1} = 0.03$ mmol L^{-1} (mM); $K_{D,2} = 5.45$ mM].[32]

To elucidate the role of the surrounding ionic microenvironment in the activation dynamics of CRP against PC, a plasma membrane mimetic surface was developed on a sensor surface using a custom MPC polymer, which consists of a random copolymer of MPC, n-butyl methacrylate (BMA), and p-nitrophenyloxycarbonyl-poly(ethylene glycol)-methacrylate (MEONP) [poly(MPC-co-BMA-co-MEONP), PMBN] (Figure 1).[33] PMBN spontaneously forms a CRP-responsive PC monolayer on an amine-functionalized self-assembled monolayer (SAM) via covalent bonding between the active ester in MEONP and the amine group. The hydrophobic BMA units act as molecular spacer for the bulky PC groups, but also help to orient hydrophilic PC toward the liquid phase. The engineered PC surface is biomimetic as it has a lateral PC density equivalent to that of phospholipid vesicles. Moreover, the homogeneous PC monolayer enables the sole focus to be on the mechanism of the CRP–PC interaction by excluding other possible molecular receptors for CRP that are otherwise present on a damaged plasma membrane such as other lipids, glycans, and proteins. Furthermore, the covalent anchoring to the substrate makes the biomimetic surface much more robust than natural cell membranes or supported lipid layers. Therefore, the surface can be regenerated by strong detergents for repeated use in many assays and biosensing applications. Binding experiments
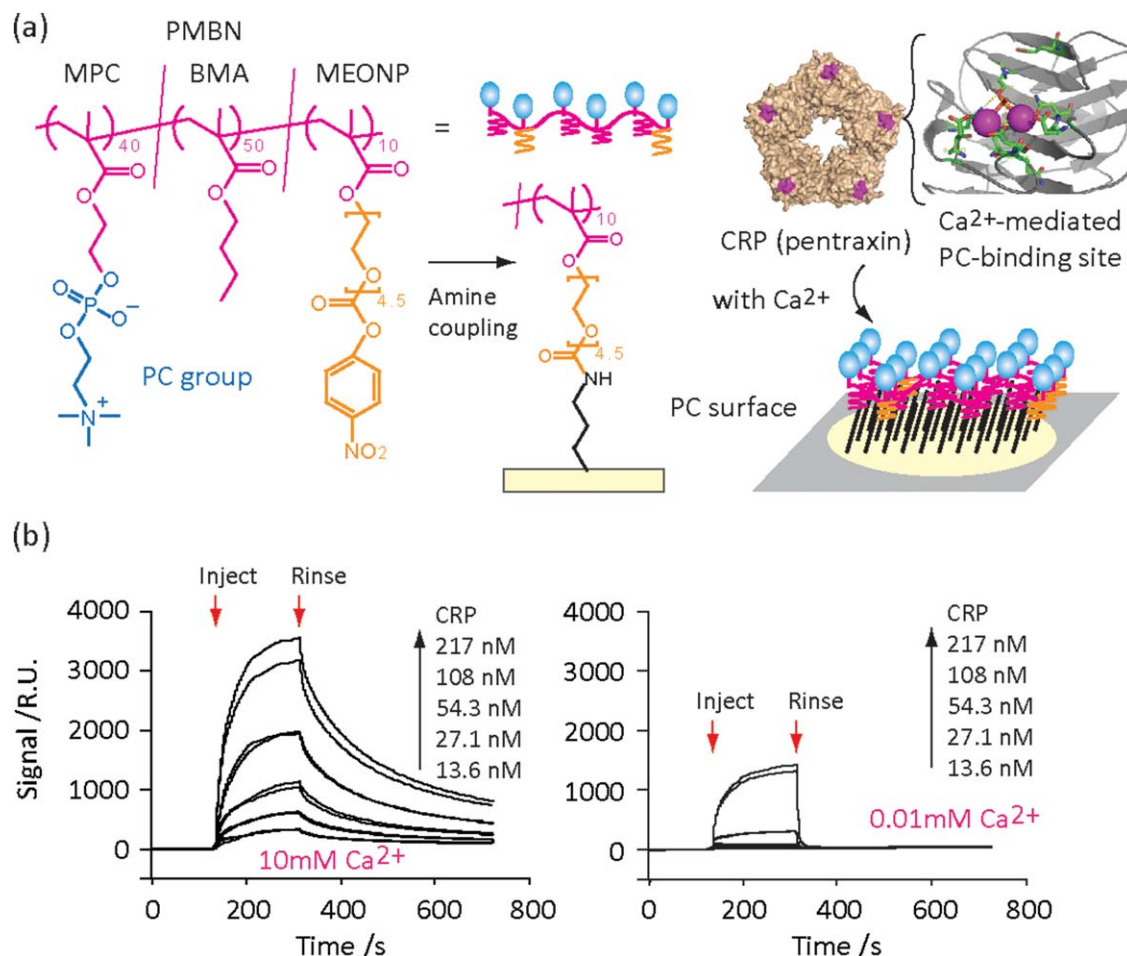
Figure 1. (a) Schematic diagram of covalent deposition of biomimetic MPC polymer (PMBN) monolayer on amine SAM-formed substrate for investigating binding kinetics of CRP on PC surface mediated by Ca^{2+}. (b) SPR sensorgrams showing a sharp contrast of association and dissociation processes of CRP adsorption onto the PC surface in HEPES buffer (pH 7.4) with 10 mM or 0.01 mM $[Ca^{2+}]$ at different CRP concentration (13.6–217 nM). Reproduced with modifications from Ref. 33. © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

show that the CRP–PC interaction is Ca^{2+}-dependent, in agreement with stepwise uptake by CRP of two calcium ions at the PC binding site, mentioned earlier (Figure 2).[32] The dynamic range covers the physiological free calcium level of about 1.2 mM in human plasma. The observation that substituting Ca^{2+} by other cations in the surrounding aqueous system completely prevents this specific interaction shows that the calcium ions play a pivotal role in mediating the CRP–PC interaction by changing the free calcium concentration in the microenvironment (Figure 3). In addition, the CRP–PC affinity is enhanced by slight acidification of the solution pH. Damaged tissue or a tumor cause hypercalcemia and acidification,[34–36] and therefore, CRP can preferentially bind to the PC receptor expressed on the damaged plasma membrane. The biomimetic design of an interface using the MPC polymer classifies the physiological meanings of local hypercalcemia and/or acidification in a damaged tissue as a signal for activating CRP in blood circulation during the acute phase of inflammation. This opens up new applications of MPC unit in CRP recognition in addition to its previous applications in antifouling surfaces in biomaterials.

The above findings suggest numerous potential applications of MPC polymer, for example, as a biosensor for monitoring systemic CRP levels in combination with various transducers. Goda *et al.* determined systemic CRP levels in the presence of 10% human serum using the biomimetic PC surface and surface plasmon resonance (SPR).[33] A team of Iwasaki and Goda developed gold nanoparticles (∼10 nm in diameter) covered with MPC polymer in the form of a dense brush for direct colorimetric detection of CRP.[37] Nanocolloids undergo a spontaneous aggregation in the presence of CRP, which results in a red shift by the localized SPR effect. The color change is more pronounced in a buffer at pH 5.5 than at pH 7.4, indicating an enhanced affinity of CRP–MPC polymer unit under mild acidic conditions. Kitayama and Takeuchi determined CRP concentrations using gold nanoparticles wrapped in a thick MPC polymer brush layer (overall particle size ∼100 nm).[38] They successfully quantified CRP levels in the presence of 1% human serum, based on the protein repellency of the MPC polymer brush.

Synthetic molecules containing PC group can also serve as pharmaceutical blockers for systemic CRP in therapy for acute
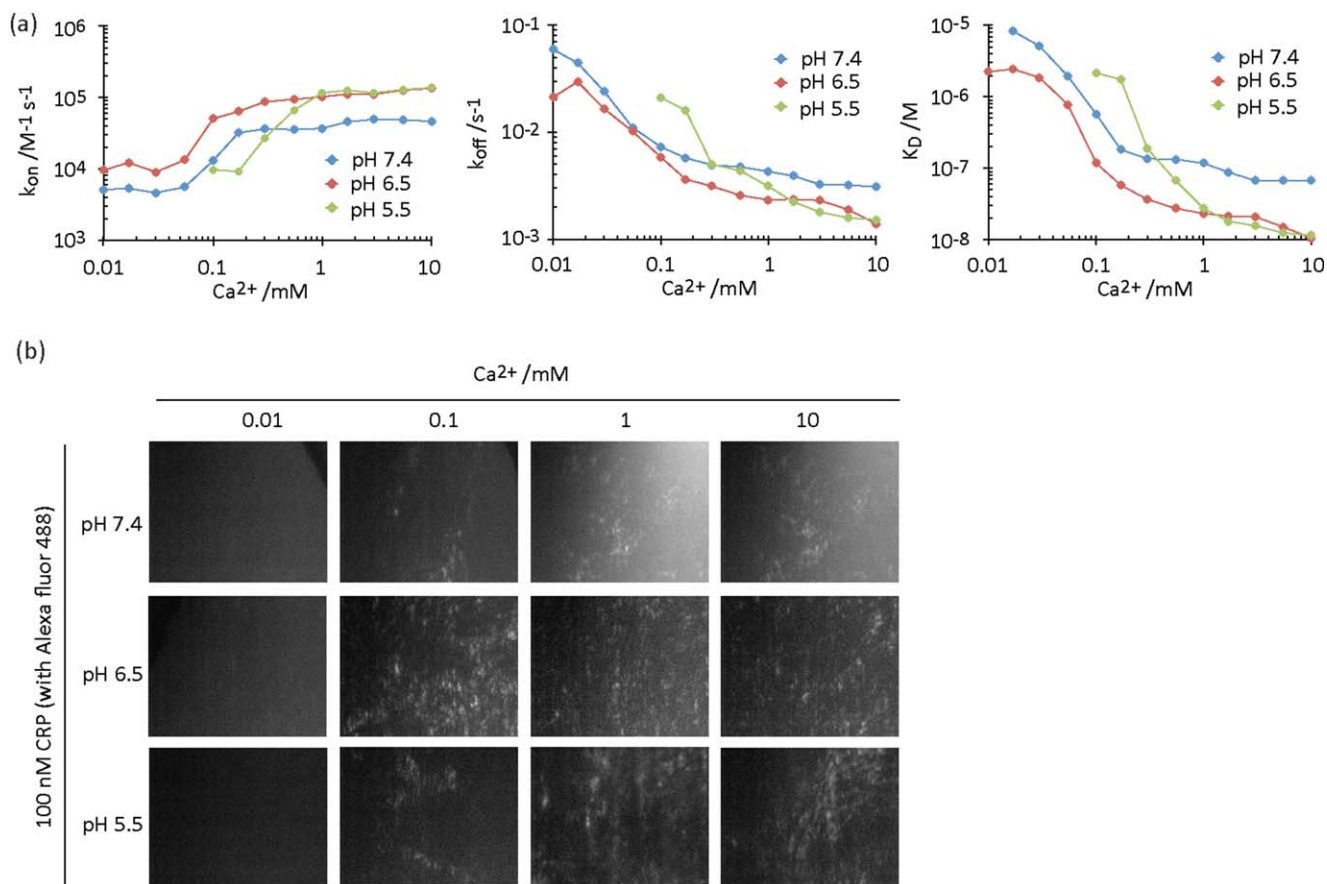
Figure 2. Calcium-dependent CRP activation of PC surface and effect of surrounding pH on binding kinetics. (a) Effects of Ca^{2+} and pH levels on apparent binding constants (k_{on}, k_{off}, and K_D) of CRP on PC surface. These constants were obtained by modeling the sensorgrams using the 1 : 1 Langmuir adsorption equation. (b) Total internal reflection fluorescence images (magnification: $100\times$) showing active binding of CRP–Alexa488 (100 nM) on PC surface at various Ca^{2+} and pH levels. Reproduced with modifications from Ref. 33. © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

myocardial infarction and atherosclerosis. It has been reported that overexpressed CRP in circulation binds to oxidized LDL; this causes antigenicity and increases the risk of atherosclerosis.[39] Disabling excess CRP in circulation with an inhibitor may therefore be an useful treatment. Pepys *et al.* designed a dumbbell-shaped synthetic molecule with a PC group at each end [1,6-bis(phosphorylcholine)-hexane] as a specific inhibitor for human CRP.[40] Five of the palindromic PC compounds are cross-linked with two pentameric CRPs to form a complex with two CRPs arranged face-to-face. Administration of the PC drug to rats inhibited CRP activity, thus preventing infarct and cardiac dysfunction. Blocking CRP with designer PC drugs may control the degree of complement activation for treatment of cardiovascular diseases, inflammation, infection, and other tissue-damaging conditions.

There has yet been no report of serious consequences of MPC polymer-based material implanted in humans. Some MPC polymer blends have been reported to reduce surface-induced inflammatory reactions *in vitro* using mouse fibroblasts.[41] However, current knowledge of specific CRP–PC interactions implies a potential risk of undesired activation of classical complement systems at implant sites during the acute phase of inflammation

and infection. An extended intravital study needs to be conducted to clarify the consequences of CRP recognition of MPC unit. Careful follow-up human clinical studies are therefore needed to determine the true safety of MPC polymer-based materials on challenge with organized host defense mechanisms in the use of artificial organs. In conducting *in vivo* studies, it should be kept in mind that the acute-phase proteins and innate immune mechanisms differ among animal species. A major increase in circulating CRP levels (>100-fold) linked to a systematic host defense mechanism in innate immunity only occurs for a limited number of species including humans, dogs, and nonhuman primates.[42] An animal study on the activities of MPC polymers against CRP may lead to different conclusions in the cases of mice, rats, rabbits, and other vertebrates. The administration of human CRP to rats may serve as an alternative model for investigating the reactions of endogenous human CRP with MPC polymer-based implants. Rat CRP does not activate rat complement, whereas human CRP activates both rat and human complement.[43]

DIRECT PENETRATION ACROSS PLASMA MEMBRANE

A eukaryotic cell protects its cytosolic compartment by physical separation from the surrounding environment by a plasma
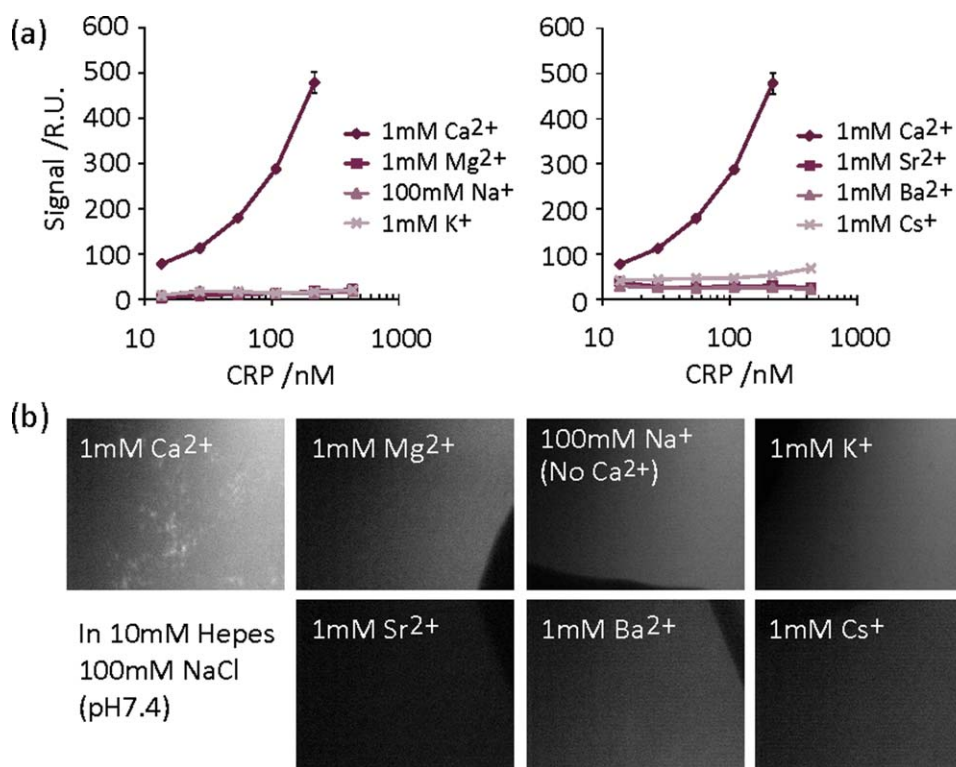
Figure 3. Effect of ionic species on CRP–PC interaction. (a) Amount of specifically bound CRP in terms of concentration was determined by SPR in HEPES buffer (pH 7.4). All plots show mean ± standard deviation ($n = 3$). (b) Total internal reflection fluorescence images on CRP–PC interaction in presence of 1 mM [Ca^{2+}] or other cations. Reproduced with modifications from Ref. 33. © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

membrane. The cell membrane, which consists mainly of a phospholipid bilayer, allows selective permeation to regulate the transport of molecules essential for homeostasis. The movement of substances across the membrane involves both passive processes, which occur via concentration gradients without cellular energy and active processes, which require the cell to consume chemical energy (i.e., adenosine triphosphate, ATP) for translocation. Relatively hydrophobic substances and gases (e.g., O_2 and CO_2) can move across the plasma membrane by passive diffusion. Sugars, amino acids, and water diffuse passively by transmembrane transporters, and ions are pumped actively against the concentration gradient by specific transmembrane protein channels. Large hydrophilic molecules generally cannot permeate the plasma membrane. Instead, cells take up large molecules and nanomaterials by endocytosis. The engulfed molecules are isolated by trapping in vesicular endosomes in the cytosol and are subjected to cell lysis.

In recent years, the interactions between nanomaterials and live cells have attracted much attention in bioengineering and biomedicine. The delivery of active therapeutic agent such as drugs and nucleic acids together with cargo molecules to the cytosolic machinery is essential for efficient cell therapy and cancer treatment by drug delivery system (DDS).[44] To achieve this, the well-organized security system of cells and the plasma membrane must be overcome without causing membrane disorder. Cationic polymers and nanoparticles are widely used for gene transfection. However, simple methods suffer from induced cytotoxicity, poor site selectivity, and relatively low transfection efficiency.[45–47] Several sophisticated approaches have been developed to improve this. The first example is the use of smart nanomaterials for efficient endosomal escape on stimulation by pH changes, heat, and light.[48] One major strategy is to introduce a pH-responsive cargo nanomaterial for endosomolysis by the proton sponge effect at a reduced pH at the late endosome stage.[49] Another approach is to conjugate a therapeutic agent with a functional ligand that has an intrinsic ability to penetrate into the cytoplasm across the plasma membrane originally discovered in viruses, for example, cell-penetrating peptides (CPPs).[50] CPP-conjugated nanomaterials can penetrate or fuse with the plasma membrane to enter the cytosol. CPPs achieve efficient translocation with minimum cytotoxicity based on well-arranged charge balance, hydrophobicity, polarity, and higher-order structures.[51] Surface-functionalized nanoparticles have been used for DDS and subcellular bioimaging. Oligonucleotide-modified spherical gold nanoparticles achieved intracellular gene regulation after engulfing by endocytosis, although the mechanism of efficient endosomal escape has not been identified.[52,53] Gold nanoparticles coated with subnanometer striations of alternating anionic and hydrophobic groups directly passed through the plasma membrane without apparent cytotoxicity.[54] Appropriate arrangement of amphipathic domains on nanoparticle surface is likely to permit nondisruptive fusion with plasma membranes and subsequent
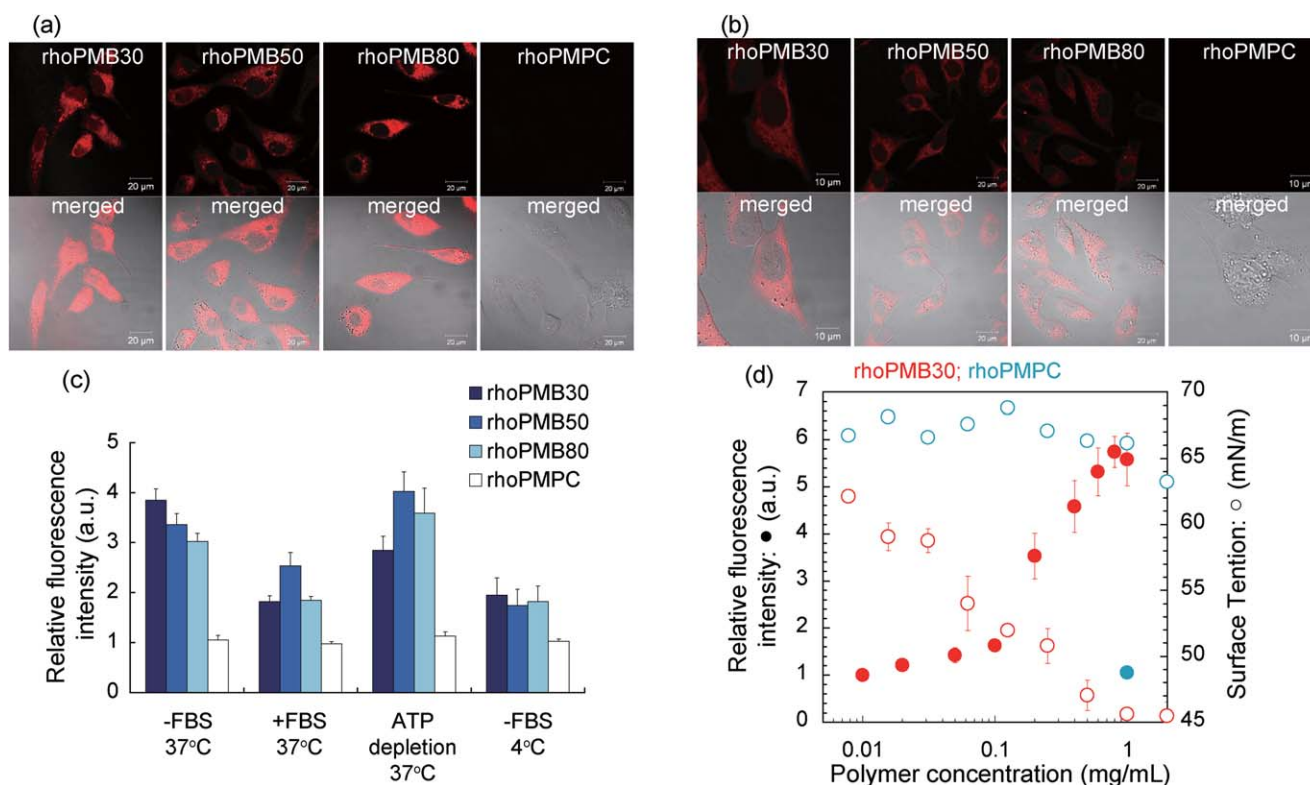
Figure 4. Amphipathicity of fluorescent polymers facilitates direct penetration into live HepG2 cells. (a, b) Confocal images of cells incubated with 1.0 mg mL^{-1} rhoPMB30, rhoPMB50, rhoPMB80, or rhoPMPC in serum-free medium for 30 min at 37°C (a) or at 4°C (b). All images were taken after rinsing the stained cells with PBS. (c) Quantitative comparison of rhodamine B fluorescence intensity of stained cells relative to autofluorescence intensity of untreated control cells using flow cytometry (1.0×10^4 cells, mean $\pm$ standard deviation). Cells were incubated with rhodamine B-tagged polymers (1.0 mg mL^{-1}) for 30 min in serum-free medium at 37°C, in serum-containing medium at 37°C, in ATP-depletion solution at 37°C, or in serum-free medium at 4°C. (d) Relative fluorescence intensity of cells (open symbols) and surface tension in solution (solid symbols) as function of rhoPMB30 (red) and rhoPMPC (blue) concentrations in serum-free medium. Surface tension was determined using the Wilhermy method. Data represent the mean ($n = 3$) $\pm$ standard deviation. Reproduced from Ref. 59, with permission from © Elsevier Ltd. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

translocation.[55,56] Computer simulations confirmed that the controlled hydrophobicity of nanoparticles enhances the direct permeability across the lipid bilayer.[57,58]

It has been identified for the first time as a synthetic macromolecule that amphipathic MPC polymers could passively diffuse across the plasma membrane without membrane damage and cytotoxicity. A water-soluble net-neutral random copolymer of MPC and BMA, that is, poly(MPC-co-BMA) (PMB), labeled with rhodamine B enters the cytoplasm within a few minutes confirmed by confocal laser scanning microscopy and fluorescence correlation spectroscopy.[59] The process is energy-independent, therefore, penetration proceeds under energy depletion condition or at 4°C, at which cell metabolism halts completely. The polymer flux is bidirectional across the plasma membrane, so PMB is able to escape from the cytosol in a concentration-dependent manner. As in the case of the aforementioned gold nanoparticles with a striped molecular pattern of anionic and hydrophobic groups,[54] the amphipathic nature of the MPC polymer is essential for direct penetration. The homopolymer of MPC, that is, poly(MPC), which is hydrophilic because of the absence of BMA units, fails to penetrate the plasma membrane directly (Figure 4). In addition, even PMB shows no cytosolic delivery at low concentrations (<0.01 mg

mL^{-1}) at which a hydrophobic domain is not formed as shown by fluorescent spectroscopy using pyrene as a hydrophobicity probe. Furthermore, water-insoluble PMBs of high molecular weight do not show direct penetration,[23] meaning that free mobility of hydrophobic units under aqueous conditions is required for interactions with the hydrophobic core in the lipid bilayer, followed by slipping into the cytosol.

The mechanism of direct penetration by an amphipathic polymer was confirmed using Monte Carlo simulations.[60,61] The results indicate that appropriate adjustment of the hydrophobicity of a polymer chain makes the fluctuating lipid bilayer transparent; namely, the relative hydrophobicities of the polymers are balanced so that both the solvent and the hydrophobic core in the membrane are equally poor environments for the chain. When the hydrophilicity is too high, the polymer fails to adsorb on the lipid bilayer and stays in a good solvent surrounding the cell. In contrast, a hydrophobic chain is strongly attracted and eventually trapped in the lipid bilayer core. The simulations also predict that perturbation of the membrane properties as a result of chain adsorption correlates with enhanced solvent permeability of the membrane close to the adsorption point; these results are not consistent with the experimental data on amphipathic MPC polymers. An extended experimental study of membrane
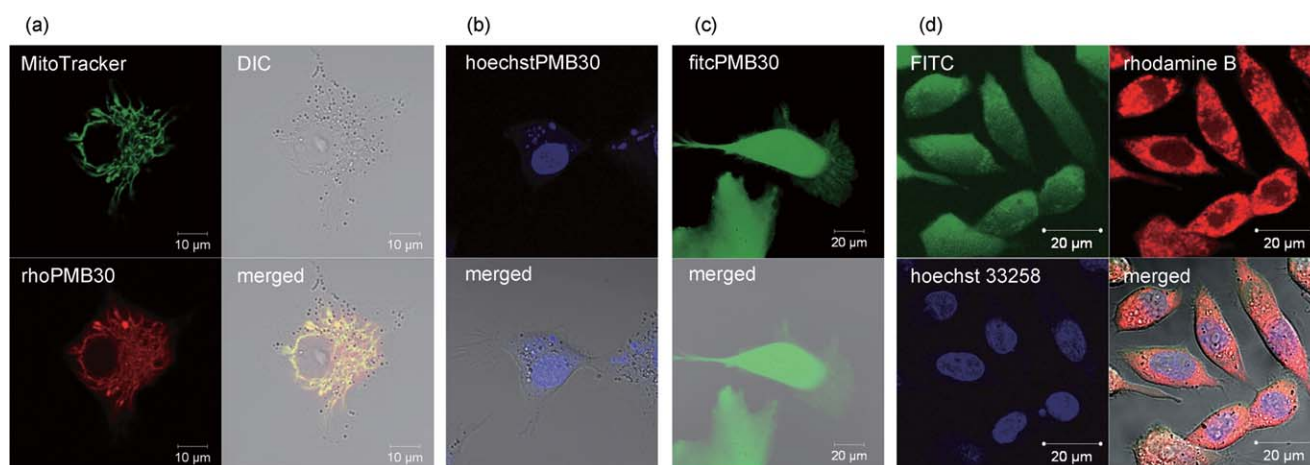
Figure 5. Rhodamine B-tagged PMB30 (rhoPMB30), Hoechst 33258-tagged PMB30 (hoechstPMB30), or FITC-tagged PMB30 (fitcPMB30) is distributed in subcellular compartments of live HepG2 based on the organelle specificity of the fluorescent dye after direct penetration. (a) Confocal images of cells treated with 100 nm MitoTracker green FM and 1.0 mg mL^{-1} rhoPMB30 in serum-free medium at 37°C using multitrack mode. (b, c) Confocal images of cells treated with 1.0 mg mL^{-1} hoechstPMB30 (b) or fitcPMB30 (c) in serum-free medium for 30 min at 37°C. (d) Confocal images of multiple color staining of live HepG2 cells incubated with rhoPMB30, hoechstPMB30, and fitcPMB30 (1 mg mL^{-1} each) in serum-free medium for 30 min at 37°C. All images were taken after rinsing the stained cells with PBS. Reproduced from Ref. 59, with permission from © Elsevier Ltd. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

disruption and facilitated permeation of the solvent surrounding the cells by direct penetration should therefore be performed on PMB. Such a study may elucidate the unique role of PC in the polymer in maintaining the ordered structure of a lipid bilayer.

Amphiphilic MPC polymers can target subcellular organelles with the aid of an affinity ligand after direct permeation across the plasma membrane.[59] Rhodamine B has an affinity with mitochondria, and therefore, PMB conjugated with rhodamine B (rhoPMB30) is localized in the mitochondria (Figure 5). Similarly, PMB tagged with Hoechst 33258 (hoechstPMB30) is enriched in the cell nuclei. PMB-fluorescein isothiocyanate (FITC) conjugates (fitcPMB) show no preferential orientation in the cytosol because PMB and FITC have no affinity with any subcellular compartments. Simultaneous administration of these PMB–fluorescence conjugates to cells achieves multiple staining of respective organelles by each polymer without mutual exclusion or cross talk. The findings also confirm that PMB is located in the cytoplasm rather than in endosomes, because the polymer has unlimited access to any organelle after internalization. These features are advantageous in the use of amphipathic MPC polymers for cell therapy and cell engineering. The direct penetration mechanism has been used for delivering polymer-conjugated molecular beacons to quantify intracellular mRNA expression directly.[62] Although the occurrence of direct penetration has not been confirmed, amphipathic MPC polymers and their derivatives improved treatments with drug, nucleic acids, proteins, and other therapeutic molecules in complexes.[63–75] Kitayama and coworkers reported that administration to nude mice of an anticancer drug, namely paclitaxel, solubilized with PMB, reduced the number of metastatic nodules and tumor volume, and therefore, significantly prolonged the survival time compared with a control.[76,77] This was accompanied by enhanced tissue permeation by the polymer–drug complex. Harashima and coworkers discovered that intracellular dissociation of plasmid DNA in primary hepatocytes was improved when the plasmid envelop was functionalized with a Glu-Ala-Leu-Ala (GALA) peptide conjugated with PMB, compared with the GALA peptide only.[78]

INTERFACE FOR FLUID FILM LUBRICATION

Articular cartilage in a natural joint shows low sliding friction and wear resistance because of the formation of a fluid thin film consisting of hydrated polyelectrolytes on hyaline cartilage. The polyelectrolytes, which consist of proteoglycan, glycosaminoglycan, collagen, and glycoprotein, can hold a large amount of tissue fluid and serve as a lubricant at the boundary. A thick hydrated film of the polyelectrolyte in the superficial zone of the cartilage causes a large separation of the two bearing surfaces, enabling fluid lubrication.[79] A surface with charged synthetic polymer brushes can replicate low frictional behavior in a dilute salt solution.[80,81] Preferential solvation of a surface-bound polymer brush and the repulsive forces between the brush and a mother substrate are important in mimicking biological lubrication.

A material surface modified with poly(MPC) through surface-initiated graft polymerization shows extremely low friction during lateral motion[82–89]; lubrication occurs even under a high contact pressure and physiological ionic strength.[90] These findings reflect the high mobility of water molecules surrounding the PC groups in poly(MPC) without induction of a salting out effect even under high ionic conditions.[10–13] Evaluation of the nanoscale contact force and tribology using atomic force microscopy shows that formation of a thick hydration layer around the poly(MPC) chains in a good solvent is required for producing facilitated lubrication.[91,92] The force curves indicate that steric repulsion from the poly(MPC) chains with retained hydration when challenged by contacting molecules is the origin of both lubrication and protein resistance at the interface.[93,94]
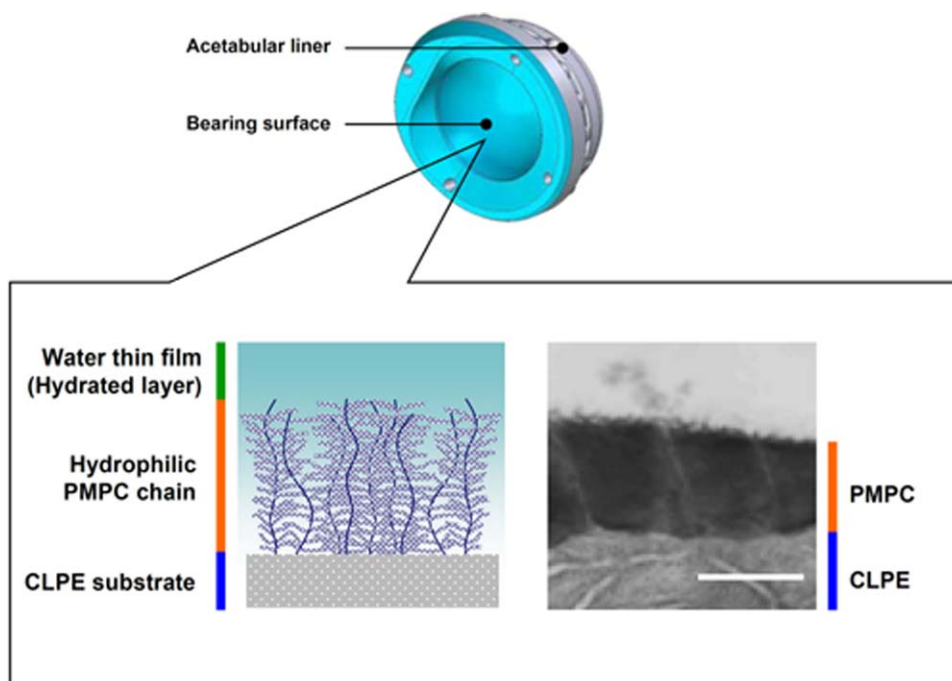
Figure 6. Schema of a total hip arthroplasty with cartilage-mimicking structure of poly(MPC)-grafted cross-linked UHMWPE liner. Poly(MPC) was covalently bound to the liner using photoinduced graft polymerization. A transmission electron microscopy image of the surface is shown on the right. Orange and blue lines indicate the poly(MPC) layer and the liner surface, respectively. Scale bar, 100 nm. Reproduced from Ref. 104, with permission from © Orthopaedic Research Society and Wiley Periodicals, Inc. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Moreover, the morphology with relatively unrestricted mobility of the graft chain of poly(MPC) in the modified thin layer is a key parameter for producing lubrication.[95–97] Consequently, poly(MPC) chains with free mobility without entanglements or contacts with an underlying substrate are important for producing macroscopic lubrication.

The mechanism of fluid film lubrication produced by MPC polymers has promising applications in joint replacement in orthopedic treatment. Moro *et al.* developed an artificial hip joint that had a surface modified with poly(MPC) chains via surface-initiated graft photopolymerization (Figure 6).[98–104] The modification of a cross-linked ultrahigh-molecular-weight polyethylene (UHMWPE) acetabular liner with poly(MPC) graft chains reduced sliding friction and wear at the boundary with a femoral head, and also prevented osteolysis induced by wear debris from the liner *in vivo*. The suppression of osteoclastic activity and inflammatory responses by surrounding tissue is attributed to the biological inertness of MPC polymers. Joint replacement using the poly(MPC)-modified cross-linked UHMWPE liners can prolong the lifetime of a prosthesis by preventing both mechanical wear and the biological responses.

CONCLUSIONS

This review highlights the newly discovered properties of MPC polymers, which are custom polymers mimetic with zwitterionic phosphatidylcholine. These properties extend the potential applications of MPC polymer-based materials in biomaterials and bioengineering, beyond their conventional uses based on their biological inertness. Its specific recognition of CRP enables the

use of MPC unit and its derivatives as biosensors and CRP inhibitors. Direct cell-penetrating ability of amphipathic MPC polymers without overt membrane disorder opens up applications in intracellular drug delivery and subcellular bioimaging. The biomimetic tribology of poly(MPC) graft surfaces under physiological conditions is now being used for joint replacements with long lifetimes in orthopedic surgery. The original bioinertness of the MPC unit is essential to these applications in biological environments.

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