

Review

FABRICATION AND BIOCOMPATIBILITY OF CELL OUTER MEMBRANE MIMETIC SURFACES*

Ming-ming Zong and Yong-kuan Gong**

Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, College of Chemistry and Materials Science, Northwest University, Xi'an 710069, China

Abstract The surface design used for improving biocompatibility is one of the most important issues for the fabrication of medical devices. For mimicking the ideal surface structure of cell outer membrane, a large number of polymers bearing phosphorylcholine (PC) groups have been employed to modify the surfaces of biomaterials and medical devices. It has been demonstrated that the biocompatibility of the modified materials whose surface is required to interact with a living organism has been obviously improved by introducing PC groups. In this review, the fabrication strategies of cell outer membrane mimetic surfaces and their resulted biocompatibilities were summarized.

Keywords: Surface modification; Phosphorylcholine; Cell membrane; Biocompatibility; Biomaterials.

INTRODUCTION

Various medical devices and artificial organs have been used in clinical applications. Although these devices are useful for improving the quality of life of patients, the performance of such artificial devices is quite limited due to the lack of biocompatibility. For example, most artificial liver and artificial lung were prepared from conventional polymeric materials such as polysulfone and polyurethane, polypropylene, nonspecific biofouling easily occurs on these polymer surfaces and induces various unfavorable bioreactions and reductions in the material function^[1].

Biomaterials and Biocompatibility

Biomaterials are predominantly applied to replace or restore the impaired organs and tissues. Biocompatibility including hemocompatibility and tissue compatibility is an essential property for biomaterials. Hemocompatibility of materials is that when they contact with blood, there is no unwanted reactions, such as the activation of the blood, the response of the immune system and the other tissue responses. The criterion to determine whether a material possesses biocompatibility is that when it contacts with living organism, there is no uncomfortable reactions, such as thrombus formation, inflammation and even canceration. Biocompatibility is usually evaluated by cytotoxicity, hemolysis, protein adsorption, and platelet adhesion and activation experiments. To date, there is no material possesses both excellent biocompatibility and good bulk properties. Since those unfriendly interactions are largely determined by the surface properties of the materials^[2], surface modification is the most promising approach to satisfy such requirements.

* This work was financially supported by the National Natural Science Foundation of China (Nos. 20774073, 20974087) and the Science and Technology Project of Shaanxi Province (No. 2010K09-04).

** Corresponding author: Yong-kuan Gong(宫永宽), E-mail: gongyk@nwu.edu.cn

Invited lecture presented at the International Symposium on Polymer Physics, 2010, Jinan, China

Received August 13, 2010; Revised August 27, 2010; Accepted August 30, 2010

doi: 10.1007/s10118-010-1019-1

Surface Modification Methods

When materials come into contact with living organisms, proteins are first adsorbed onto material surfaces. The interaction between protein and materials surface has been reviewed recently by Chen and her coworkers^[3]. The adsorbed protein layer will influence the subsequent biological reactions including platelet adhesion and activation, followed by thrombus formation^[4]. Hence, we can obtain an antifouling surface by suppressing the protein adsorption. The hydrophilicity, roughness and charge of the surface have critical influence on the protein adsorption. In general, a surface with high hydrophilicity, low roughness and neutral charge can reduce the protein adsorption effectively. There are several mechanisms to explain the suppression of the protein adsorption. First, water barrier theory: the materials attract large number of water to form a hydration shell, which essentially shield substrate from the nonspecific adsorption of proteins^[5]. This theory is often used to explain the biocompatibility of short chains of PEG polymers or zwitterionic polymers. Second, steric repulsion effect: the large structures of closely packed molecules on the surface initiate steric repulsion to inhibit the protein adsorption, which provides a deep understanding on the anti-biofouling surfaces containing PC polymers or long chains of PEG polymers^[6]. Third, maintain the native conformation of proteins, which means that polymer surface could not disrupt the protein structure. Fourth, surface charge: the surface and protein obey the law: same charges repel each other, opposite charges attract^[7].

According to the above mechanisms, three kinds of polymers have been introduced to surfaces to increase the biocompatibility of biomaterials. One is hydrophilic polymers, such as PEG^[8–10], PVP^[11–13], PHEMA^[14, 15] and PAA^[16–18]; next is bioactive macromolecules such as heparin^[3, 19, 20]. The third kind contains zwitterions, including phosphorylcholine^[4, 21, 22], sulfobetaine^[23–26] and carboxybetaine^[27].

List of Abbreviations

Nomenclature	Abbreviation
2-Bromoisobutryl bromide	BIBB
<i>n</i> -Butyl methacrylate	BMA
Choline methacrylate	CMA
2-(<i>N,N</i> -dimethylamino)ethyl methacrylate	DMAEMA
Poly(ethylene- <i>co</i> -vinyl alcohol)	EVOH
Human promyelocytic leukemia cells	HL-60
4-Methacryloxyethyl trimellitate anhydride	4-META
Methacryloyl hydrazide	MH
3-Methacryloylpropyltrimethoxysilane	MPS
Lauryl methacrylate	LMA
Poly(acrylonitrile- <i>co</i> -2-hydroxyethyl methacrylate)	PANCHEMA
Poly(<i>p</i> -xylylene)	Parylene C
Polyethylene	PE
Poly(ethyleneterephthalate)	PET
Poly(MPC- <i>co</i> -BMA)	PMB
Poly(MPC- <i>co</i> -BMA- <i>co</i> -MH)	PMBH
Poly(MPC- <i>co</i> -BMA-VPBA)	PMBV
Polymer possesses MPC unit having a diethylene oxide chain	PME02B
Poly(MPC- <i>co</i> -EHMA)	PMEH
Poly(MPC- <i>co</i> -2-ethylhexyl methacrylate- <i>co</i> -2-(<i>N,N</i> -dimethylamino)ethyl methacrylate)	PMED
Poly(MPC- <i>co</i> -glycidyl methacrylate)	PMG
1-Pyrenylmethylmethacrylate	PMM
Poly(methyl methacrylate)	PMMA
Poly(MPC- <i>random</i> -TFEMA)	(PMTF)
Poly(lactide- <i>co</i> -glycolide)	PLGA
Poly(vinyl acetate)	PVAc
Poly(vinylpyrrolidone)	PVP
Bis(trimethylsilyloxy)methylsilylpropyl glycerol methacrylate	SIMA
2,2,2-Trifluoroethyl methacrylate	TFEMA
Trimethoxysilylpropyl methacrylate	TSMA
4-Vinylphenylboronic acid	VPBA

Cell Membrane Mimetic Surface

In recent years, using zwitterion polymer to improve the biocompatibility of biomaterials has become one of the hottest research topics, especially the polymers bearing PC groups.

PC group which carries both a positive and a negative charge is the main composition of the blood cell outer layer membrane^[28]. A PC group can attract 22 water molecules around it, thus biomaterials bearing this groups have ability to shield the substrate from nonspecific, irreversible proteins adsorption^[29]. Inspired by the cell outer membrane structure, “biomimicry” was proposed by the groups of Nakabayashi and Chapman respectively in 1980s to obtain biocompatibility surface. Since this strategy essentially depends on the introduction of PC groups, it is also called “PC technique”. Research on surface modification of biomaterials with PC functionality has been expanding rapidly after publication of the synthetic procedure leading to 2-methacryloyloxyethyl phosphorylcholine (MPC), the monomer required to synthesize PC polymers^[30]. In most applications, MPC is copolymerized with methacrylates, yielding amphiphilic polymers employed to prepare biocompatible surfaces^[31–39]. The principle of making cell membrane mimetic surfaces with PC polymers is depicted in Fig. 1.

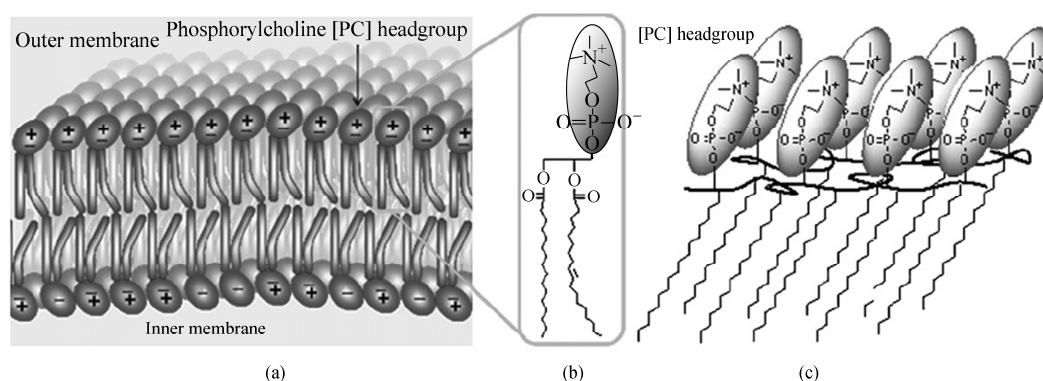


Fig. 1 Schematic structures of the cell membrane and the outer membrane mimetic polymeric assembly: (a) lipid bilayer of cell membrane, (b) phosphatidylcholine, (c) PMST assembly (Reprinted from Ref. [40] with permission from Elsevier B.V.)

After coating a biomaterial surface with an amphiphilic PC polymer, cell outer membrane mimetic structure can be formed automatically by contacting the surface with water. When an amphiphilic PC polymer is coated on a biomaterial surface, it forms a film with hydrophobic groups on its surface, morphology similar to the reverse structure of the cell outer membrane. Under certain conditions, the hydrophilic groups near the surface may migrate deeply inside the film, causing an irreversible change of the surface structure^[41]. To increase the stability of cell outer membrane mimetic structure, small molecules and polymers bearing PC groups are frequently grafted on the surface of biomaterials.

FABRICATION AND BIOCOMPATIBILITY OF CELL OUTER MEMBRANE MIMETIC SURFACES

Both chemical and physical methods are used to fabricate cell outer membrane mimetic surfaces. The chemical method includes grafting and self-assembly of a small molecule or polymer bearing PC groups. The physical method includes coating, blending and interpenetrating polymer networks with PC polymers. Each of the cell membrane mimetic techniques and the resulted biocompatibilities are summarized in the following subtitles.

MPC Graft Polymerization

Graft polymerization is frequently performed to fabricate a cell outer membrane mimetic structure on a substrate. This method can be divided into two types known as “grafting-to” and “grafting-from”^[42].

“Grafting to” is a method that the ready-made polymers bearing active groups react with the functional groups of the substrate. PC polymers containing carboxylic acid, hydroxyl or amino groups have been

synthesized for “Grafting to” surface modification. Table 1 lists some of the representative research works and the resulted biocompatibility. In general, due to the inherent complication in the reactive process, it is hard to reach a high density of the grafted polymer chains^[43, 44].

Table 1. Surface modification by “grafting-to” method with improved biocompatibility

Substrate	Surface bonding	Biocompatibility and references
Polyethylene and polypropylene	Photo-immobilization of MPC polymers containing azido groups	Platelet adhesion decreased from 1.13×10^3 cell/ μL^2 to 0.34×10^3 cell/ μL^2 . The adhesion of Mammalian which shows macrophage like properties was also inhibited ^[45] .
SiO ₂	The polymer bearing the trimethoxy silane react with SiO ₂	All of the MPC polymers with or without charged moieties showed the ability to suppress protein adsorption and cell adhesion. Pepsin and BSA adsorption decreased to 10%–20% ^[46] .
Glass	Covalent bonding between surface amino and PMA carboxylic groups	BSA and fibronectin adsorption decreased to 25% and 20%. MC-3T3 cell adhesion suppressed ^[47] .
Cellulose acetate and PMB30 blend hollow fiber membrane (HFM)	Covalent bonding between hydroxyl and PMA carboxylic groups	Good water and solute permeability, low cytotoxicity to the hepatocyte and antifouling property. RTH33 cells attached on the modified HFM surface showed part of the functions of livers ^[48] .

Table 2. Surface modification by “grafting-from” method with improved biocompatibility

Substrate	Surface bonding	Biocompatibility and references
TiAl ₆ V ₄	UV-irradiation of surface immobilized MPS	Contact angle (CA) decreased from 58.3° to 18.1°. Platelet adhesion decreased to 15% ^[51] .
Poly(ether-ether-ketone)	Self photo-induced surface grafting	CA decreased from 91° to less than 10°. BSA adsorption decreased to 10% ^[52] .
Cobalt-chromium-molybdenum alloy	UV-irradiation of surface immobilized 4-META	CA decreased from 81.6° to 20°. Friction coefficient decreased to less than 0.01. BSA, γ -globulins, and fibrinogen adsorption decreased to 20%, 35% and 10% respectively ^[53, 54] .
Silicone	Ozone-induced grafting	CA decreased from 102.9° to 43.2°. No platelet adhesion was observed ^[55] .
Cellulose membranes	ATRP initiated by surface immobilized BIBB	CA decreased from 47.6° to 20.3°. Protein adsorption decreased to about 45% and showed excellent resistance to platelet adhesion ^[56] .
Silicon wafer	ATRP initiated by surface immobilized oligomeric methoxy polyethylene glycol 2-bromoisobutyrate	Fibrinogen adsorption decreased to 1% ^[57] .
Parylene film	UV-irradiation of surface immobilized benzophenone	Advancing CA decreased from 91.7° to 70.9° and receding CA from 75.0° to 29.0°. Albumin and fibrinogen adsorption decreased to 27% and 22% respectively ^[58] .
PDMS	UV-irradiation of surface immobilized benzophenone	CA decreased from 120° to 25°. High oxygen permeability and low friction coefficient. Fibrinogen, γ -globulin and lysozyme adsorption decreased to 25%, 50% and 30% respectively ^[59] .
PE/PVAc	ATRP initiated by surface immobilized 2-bromoisobutryl bromide	Advancing CA decreased from 55° to 20°. The amount of BSA adsorption decreased with an increase in the chain length of poly(MPC) ^[60] .
PDMS	UV-irradiation of surface immobilized benzophenone	CA decreased from 120° to 60°. Albumin and fibrinogen adsorption decreased to 36% and 25% respectively ^[61] .
Polyethylene	UV-irradiation of surface immobilized benzophenone	CA decreased from 96° to 79°. Platelet adhesion and fibrinogen adsorption suppressed ^[62] .
Silicon wafer	ATRP initiated by surface immobilized 10-(2-bromo-2-methyl)propionyloxy-decyltrichlorosilane	CA decreased to 9.2°. Fibrinogen and lysozyme adsorption decreased to 8% and 4% respectively ^[63] .

“Graft from” is such a method that the monomers are initiated and polymerized from the surface. In general, initiators are immobilized on the surfaces by physical adsorption or chemical bonding. Table 2 summarizes some of the representative modifications and the resulted biocompatibility by “Graft from” technique. In order to obtain a high graft density on surface with a controlled length and narrow molecular weight distribution, living polymerization techniques, such as atom transfer radical polymerization (ATRP) and reversible addition-fragmentation chain transfer (RAFT), are frequently used to graft MPC polymers. Although ATRP is chemically versatile, compatible with various monomers and functional groups, the metal catalyst is difficult to remove and the residual traces of catalysts in the materials might have some unacceptable reactions for applications^[49]. RAFT is versatile and tolerates a wide range of functional groups, however the chain transfer agents are usually not commercially available and need to be prepared *via* several steps^[50].

Contact angle measurement is considered to be the most convenient way to evaluate the wetting characteristics of biomaterials, it mainly depends on surface hydrophilicity, generally, the lower the contact angle, the better the hydrophilicity of surface, such an increase in hydrophilicity may serve as a driving force for decreasing protein adsorption^[64]. After the surfaces are grafted with MPC polymers, the water contact angles are usually decreased obviously and the protein adsorptions are all decreased significantly. On the cell outer membrane mimetic layer, platelet adhesion and activation are decreased and cytotoxicity is reduced markedly. The degree of improvement in biocompatibility depends mainly on the surface density of PC groups. Therefore, the “grafting from” method has an advantage over the “grafting to” method in that it synthesizes a high-density MPC polymer brush.

PC Molecule Self-assembly

Self-assembly technique is an excellent method to fabricate thin films with a high degree of structural control. According to the number of layer, the self-assembly technique has been divided into two parts: self-assembly monolayers (SAMs) and layer-by-layer (LBL) self-assembly technique. Cell membrane mimetic surfaces have been fabricated by self-assembly techniques with both small molecules^[65–67] and polymers^[68–72] bearing PC groups.

Self-assembly monolayer is based on the reaction or deposition between the surfaces and PC group containing molecules. Because of the mutual ionic bonding among the zwitterionic PC groups, the molecules pack closely to form a PC-rich biomimetic surface^[68]. The covalently bonded monolayers have excellent stability to withstand the complicated biologic conditions. Unfortunately, the specific bonding requirement between the molecules and the surfaces limits SAMs technique applying to surfaces other than silver and gold.

In recent years, layer-by layer self-assembly technique has attracted a great deal of attention, which is based on the electrostatic interaction, covalent bonding or hydrogen bonding between the polymers. Through the molecular interaction between polycation and polyanion, cell outer membrane mimetic surface is conveniently fabricated with a PC containing polyelectrolyte^[70–72].

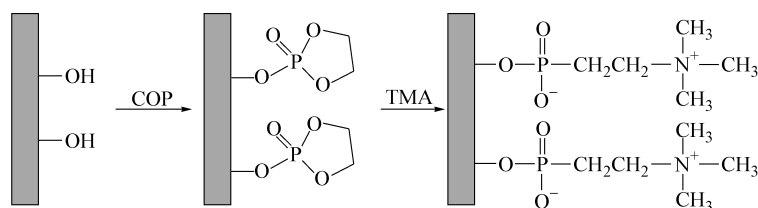
Table 3 summarizes the surface modifications and the resulted biocompatibilities by SAMs and LBL techniques. After the biomimetic surface modification, the water contact angles are decreased obviously, it suggests that the surface has a high density of PC groups. Protein adsorption and cell adhesion are reduced on both of LBL and SAMs modified surfaces. Compared with SAMs, LBL technique has more advantages, such as three dimensional structure, more functional groups, and easy adaptation into engineering processes^[69].

Surface Grafting with Small PC Molecules

Surface grafting with small PC molecules, a convenient way to fabricate a stable cell outer membrane mimetic surface, has attracted much attention in improving biocompatibility. Polymers bearing hydroxyl and amino groups on the surfaces have been grafted with PC molecules^[76–78]. A frequently used strategy of attaching PC groups is *via* the reaction of 2-chloro-2-oxo-1,3,2-dioxaphospholane (COP) as shown in Fig. 2. Table 4 shows the examples of grafting PC molecules on polymer and glass surfaces for improving biocompatibility. Similarly, the biocompatibility is enhanced obviously as the above mentioned techniques. As the biocompatibility is closely related to the surface density of PC groups, it is difficult to overcome the steric repulsion of molecules on surface to achieve a high graft density.

Table 3. Improvement of biocompatibility by PC molecule self-assembly

	Substrate	PC molecule	Biocompatibility and reference
Monolayer	Gold-coated surface	11-Mercaptoundecyl phosphorylcholine thiol	CA decreased to 28.0°. Fibrinogen adsorption decreased to 15%, neutrophil adhesion was also decreased ^[65] .
	Gold-coated surface	Bis(11-cholinyolphosphorylundecyl) disulfide	CA decreased to 10.1°. Albumin adsorption decreased to 36%. No platelets adhesion and lower toxicity toward 3T3 fibroblast ^[66, 73] .
	Gold-coated surface	11-Mercaptoundecyl-oligo-phosphorylcholine	The adsorbed amounts of fibrinogen, BSA, and Lyz were decreased to 0.003, 0.014, and 0.01 mg/m ² , respectively ^[67] .
Multilayer	Ti coated with octadecyltriethoxysilane	Covalent bonding of carboxylic groups in PMBV and hydroxyl groups in PVA	The CA of the 6th layer is zero, PMBV as the outmost layer could suppress protein adsorption and cell attachment ^[74] .
	Silicon wafer	Electrostatic self-assembly of cationic PC copolymer and negatively-charged c-myc anti-sense oligodeoxynucleotide (AS-ODN)	The multilayered films could control the loading and release of AS-ODN. The c-myc AS-ODN could reached the target c-myc mRNA then the proliferation cells was effectively blocked ^[69] .
	PET coated with poly(ethylenimine)	MPC was covalently attached on LBL self-assembled surface	CA decreased to 17°. Platelets adhesion on the outer layer bearing PC groups decreased to 1.6% ^[75] .

**Fig. 2** The routes of introducing PC groups on the surface by COP reactions (Reprinted from Ref. [79] with permission from Elsevier B.V.)**Table 4.** Improvement of biocompatibility by grafting with PC molecules

Substrate	Method	Biocompatibility and reference
EVOH microporous membranes	COP reacting with surface hydroxyl and then ring-opening with trimethylamine	The CA was decreased from 75° to 50°. BSA adsorption decreased to 34% ^[79] .
PE and PVAc blend	COP reacting with surface hydroxyl and then ring-opening with trimethylamine	Advancing CA decreased to 55°. BSA and BPF adsorption decreased to 22% and 29% respectively ^[80] .
PANCHEMA membranes	COP reacting with surface hydroxyl and then ring-opening with trimethylamine	Advancing CA decreased to 45°. BSA adsorption decreased to 23%, platelet adhesion inhibited ^[81] .
Glass coated with chlorodimethyl- <i>n</i> -octadecylsilane	2-Hydroxy-2-ethylphosphorylcholine bonded on surface through the linker of 1,6-diisocyanatohexane	Advancing CA decreased from 105° to 75°, receding CA decreased from 80° to 35°. BSA and BPF adsorption decreased to 31% and 64% respectively ^[82] .
Dendritic PAMAM	Michael addition of MPC and PAMAM	ECV304 viability increased to 99% ^[83] .

PC Polymer Blending

Polymer blend is defined as multi-component polymers. The polymers are dissolved in a common solvent which is then evaporated to form the blend. By mixing with a polymer containing PC groups, cell membrane mimetic structures can be formed on the surface of the polymer blend during contact with water^[36, 84, 85]. The blending methods and the resulted biocompatibility of several typical systems are listed in Table 5.

Table 5. Improvement of biocompatibility by blending with PC polymers

Substrate	Treatment	Biocompatibility and reference
Cellulose acetate hollow fiber membranes and PMB	Dry-jet wet spinning process	Kidney and liver cells adhered well on the surface. Albumin, γ -globulin, and fibrinogen adsorption decreased ^[86, 87] .
PMEH and SPU	Solvent evaporation technique	High permeability for insulin; fibroblast adhesion decreased to 44% ^[88–90] .
Poly(lactide-co-glycolide) and PMEH	Solvent evaporation technique	NIH/3T3 fibroblast cell adhesion decreased to 67%; inflammatory reaction also suppressed ^[84] .
PE and PMPC	Solvent evaporation technique	Good mechanical properties by thermal treatment; platelet adhesion suppressed ^[91] .
Cellulose acetate and PMB	Solvent evaporation technique	Good permeability, protein adsorption suppressed ^[85] .

Blending is mainly used in improving the biocompatibility of polymer membranes, such as SPU, PSf and cellulose acetate hollow fiber membranes, which are often applied in hemopurification therapy. When a small quantity of MPC polymer is introduced into these membranes by blending, the protein adsorption and blood coagulation are suppressed in a large extent. Although the process of blending is simple and the biocompatibility can be improved, the instability of the surface structure limits its application since a low entropy of the mixture may lead to phase separation. Hence, how to improve the stability of the blending is an important research subject.

Interpenetrating Polymer Networks (IPNS)

IPNS is a kind of polymer alloy, composed of two or more monomers which can crosslink or homopolymerize with themselves, all of the polymers have no chemical bonding to others^[92]. The surface modification by IPN formation is a good method to prepare polymeric materials possessing different characteristics. Semi-interpenetrating polymer network (semi-IPN) comprising one or more polymer networks and one or more linear or branched polymers, this is a simple method for obtaining a surface with different functional groups. Nobuyuki modified the surface of SPU with MPC by forming semi-IPN. MPC units were exposed on the surface confirmed by X-ray photoelectron spectroscopy, which mimicked the chemical structure of cell membranes resulted in a good biocompatibility. The mechanical property is not changed compared to the SPU membranes^[93].

Shimizu constructed IPNS composed of MPC and SiMA, compared with the copolymer with these two monomers, both of them showed good elasticity, optical transparency, high oxygen permeability, the difference is that the PSiMA-*ipn*-PMPC has a super-hydrophilic surface, the protein adsorption was about 0.18 $\mu\text{g}/\text{cm}^2$, while PMSi was 0.5 $\mu\text{g}/\text{cm}^2$ ^[94].

Liu fabricated extracellular matrix (ECM) mimetic interpenetrating polymeric networks with collagen and MPC, then they implanted the IPN hydrogels into mini-pigs. After twelve-month post-implantation the hydrogel showed regeneration of corneal tissue and no adverse inflammatory reactions were observed^[95].

PC Polymer Physical Adsorption

Up to now, the most convenient method of fabricating biomembrane mimetic surface is coating an amphiphilic polymer bearing PC groups on a substrate. The polymer is coated by dip, spin or spraying coating and immobilized on the substrate by physical adsorption.

Conventional coated surface

Since MPC homopolymer is too hydrophilic to be immobilized on a substrate surface under wet condition, various vinyl and methylacrylate hydrophobic monomers have been introduced to copolymerize with MPC, forming amphiphilic PC polymers. A large number of such polymers have been coated on biomaterials to improve the biocompatibility of the surfaces (Table 6).

As the physically adsorbed polymer layer may dissolve or decompose upon implantation in a complicated biological environment^[40], the instability of this coating is a big obstacle for the application. It is also demonstrated that the hydrophilic groups near the surface may migrate deeply inside the film under apolar conditions, causing an irreversible change of the surface structure^[96, 97]. In order to enhance the stability of the coating, Lewis^[98] and Ji^[99] groups introduced TSMA as crosslinker to stabilize the coating. However, the coating was crosslinked in a vacuum drying oven, and the hydrophobic segments/chains migrated onto the outermost surface, forming a structure opposite to the membrane outlayer^[41, 42].

Table 6. Improvement of biocompatibility by physical adsorption of PC polymer

Substrate	Method	Biocompatibility and reference
PMTF coated on glass	Dip-coating	Advancing CA was 60°. BSA, fibrinogen, and γ -globulin adsorption were decreased to 50%, 36%, and 30% respectively ^[100] .
PET coated with PMPC- <i>b</i> -PDMS	Dip-coating	CA was less than 20°, each of the block copolymer domain retain its own properties, the hydrophobic domain showed the property of protein adsorption, while the hydrophilic domain could inhibit protein adsorption ^[101] .
PET fibers coated with PMB or PMO2B	Dip-coating	PMO2B coated surface is more effective to reduce adhesion and activation of platelets than PMB: the recovery ratio of platelets passed through the PMEO2B surface was nearly 100%, while PMB was about 65% ^[102] .
PDMS coated with PMB or PMED	Dip-coating	BSA adsorption decreased from 18.6 mg/m ² to 4.7 and 4.2 mg/m ² on PMB and PMED respectively ^[103] .
PET coated with PMBL or PMB	Dip-coating	Serum protein adsorption on PMBA-coated surface was 0.68 $\mu\text{g}/\text{cm}^2$; PMBL-coated surface was 0.2 $\mu\text{g}/\text{cm}^2$, cell adhesion on PMB was reduced ^[104] .
PMMA coated with PC1036 or SB1036	Dip-coating	On PC1036 and SB1036-coated surfaces, bacterial adhesion decreased to 36%, 46% respectively; 3T3 mouse embryonic fibroblast adhesion decreased to 6% and 67% respectively ^[105] .
PET coated with PC1062	Dip-coating	The adhesions of mouse fibroblasts, rabbit corneal epithelial cells, human mononuclear cells and granulocytes were all increased with the increase of cationic groups ^[106] .
PMMA chips coated with PMB	Spin-coating	Platelets adhesion and BSA adsorption decreased obviously ^[107] .
Silicon wafer coated with PMG	Dip-coating	Excellent anti-fouling and good physical properties, <i>E.coli</i> adhesion was decreased to 10% ^[108] .
PET coated with PMBH	Dip-coating	Fibrinogen adsorption was about 0.4 $\mu\text{g}/\text{cm}^2$, which is lower than the extent of monolayer adsorption of albumin 0.9 $\mu\text{g}/\text{cm}^2$. HL-60 cells retained their native morphology and viability for 24 h of incubation ^[109] .

Immobilization of cell outer membrane mimetic surfaces

Currently, there are two strategies to immobilize the cell outer membrane mimetic structure on PC polymer coating surface. First, increase the glass transition temperature (T_g) of the polymers above room temperature, once the structure is fixed, it is difficult to mobile in mild conditions. Second, introduce chemical crosslinker into the polymer chain to covalently fix the membrane mimetic structure. When the crosslink degree is high enough, the chains and large groups can be immobilized completely.

Koji^[110] synthesized a copolymer of MPC and 2-vinylnaphthalene having high T_g . Once the phosphorylcholine was fixed on the coating surface, it is difficult to reorientate whether in polar or apolar environment. The PC surface showed hydrophilicity and protein-adsorption resistance on contact with protein

solutions.

For covalently immobilizing cell outer membrane mimetic structure on PC polymer coating surface, an amphiphilic random copolymer bearing phosphorylcholine (PC), stearyl and crosslinkable trimethoxysilylpropyl groups was synthesized by free radical copolymerization. The polymer was coated on glass coverslips by dip-coating. The coated films were treated in water allowing reorganization of the surface groups to mimic the structure of cell outer membranes. This tuned cell membrane mimetic surface was fixed by crosslinking of the trimethoxysilylpropyl groups linked to the copolymer chains^[40]. The process of this surface modification is shown schematically in Fig. 3. Recent report showed that this tuned and crosslinked cell outer membrane mimetic PC surface/interface had excellent resistance to platelet adhesion and protein adsorption^[111]. This novel technique may be of great significance in the surface modification of biomaterials and other related applications.

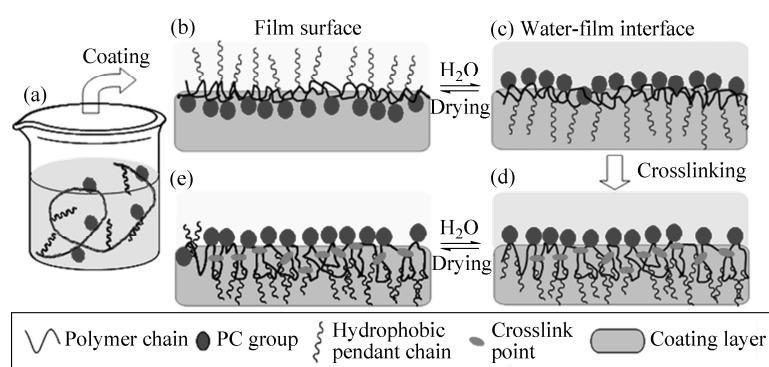


Fig. 3 Schematic structures of fabricating and crosslinking cell membrane biomimetic surface: amphiphilic PC polymer in solution (a), on the surface (b), at the solid–water interface (c), crosslinked interface (d) and crosslinked surface (e) (Reprinted from Ref. [39] with permission from Elsevier B.V.)

CONCLUSIONS

The most ideal biointerface is cell membrane. Surface modification of biomaterials with cell outer membrane mimetic structure is developing into one of the most promising strategies for satisfying the biocompatibility requirements. As PC moiety is the main composition of the blood cell outer layer membrane, various PC containing molecules, especially polymers are employed to improve biocompatibility. Six methods of fabricating cell membrane mimetic surfaces have been discussed. Among them, coating a substrate with a water insoluble PC polymer is the simplest way, while surface graft polymerization can obtain most stable and highest density of PC polymer surface. By combining the advantages of different techniques, such as the simplicity of coating and the stability of surface grafting, an easily performable new method is desirable from the view point of applications.

In order to improve the biocompatibility of biomaterials for a specific purpose, biologically functionalized biomimetic modification is indispensable. For example, the application of specific ligands bound to the cell outer membrane mimetic surfaces may be extremely useful for a variety of biomedical engineering applications. The combination of cell membrane mimetic surface and specific interactions may induce only the desired reaction that will be accepted by the biological environment in which it is placed. This ultimate goal requires joint research in two main areas: the fabrication of perfect cell outer membrane mimetic surfaces by chemical modification, and the use of specific ligands to induce the anticipated cell responses. In the near future, such a well developed cell outer membrane mimetic technique is expected to solve most of the biocompatibility problems in clinical applications.

REFERENCES

- 1 Iwasaki, Y., Takami, Y., Sawada, S. and Akiyosh, K., *Appl. Surf. Sci.*, 2008, 255: 523
- 2 Tirrell, M., Kokkoli, E. and Biesalski, M., *Surf. Sci.*, 2002, 500: 61
- 3 Chen, H., Yuan, L., Song, W., Wu, Z.K. and Li, D., *Prog. Polym. Sci.*, 2008, 33: 1059
- 4 Anderson, J. M., *Ann Rev., Mater. Res.*, 2001, 31: 81
- 5 Raschke, T. M., *Struct. Biol.*, 2006, 16: 152
- 6 Jeon, S.I. and Lee, J.H., Andrade J.D., *J. Colloid Interface Sci.*, 1991, 142: 149
- 7 Lee, J.H., Khang, G. and Lee J.W., *J. Biomed. Mater. Res.*, 1998, 40: 180
- 8 Morra, M., *J. Biomater Sci. Polym. Ed.*, 2000, 11: 547
- 9 Zhang, M., Li X.H., Gong, Y.D., Zhao, N.M. and Zhang X.F., *Biomaterials*, 2002, 23: 2641
- 10 Xua, Z.K., Nie, F.Q., Qu, C., Wan, L.S., Wu, J. and Yao K., *Biomaterials*, 2005, 26: 589
- 11 Higuchi, A., Shirano, K., Harashima, M., Yoon, B.O., Hara, M. and Hattori M., *Biomaterials*, 2002, 23: 2659
- 12 Wetzels, G.M.R. and Koole, L.H., *Biomaterials*, 1999, 20: 1879
- 13 Wan, L.S., Xu, Z.K., Huang, X.J., Wang, Z.G. and Wang, J.L., *Polymer*, 2005, 46: 7715
- 14 Martins, M.C.L., Wang, D., Ji, J. and Feng, L., Barbosa, M.A., *Biomaterials*, 2003, 24: 2067
- 15 Joshi, J.M. and Sinha, V.K., *Polymer*, 2006, 47: 2198
- 16 Gupta, B., Plummer, C., Bisson, I., Frey, P. and Hilborn, J., *Biomaterials*, 2002, 23: 863
- 17 Vermette, P. and Meagher, L., *Langmuir*, 2002, 18: 10137
- 18 Combellas, C., Fuchs, A., Kanoufi, F., Mazouzi, D. and Nunige, S., *Polymer*, 2004, 45: 4669
- 19 Morra, M., *J. Biomater Sci. Polym. Ed.*, 2000, 11: 547
- 20 Sanchez, J., Elgue, G., Riesenfeld, J. and Olsson, P., *J. Biomed. Mater. Res.*, 1997, 37: 37
- 21 Parker, A.P., Reynolds, P.A., Lewis, A.L., Kirkwood, L. and Hughes, L.G., *Colloids Surf. B: Biointerfaces*, 2005, 46: 204
- 22 Xu, F.M., Xu, J.P., Ji, J. and Shen, J.C., *Acta Polymerica Sinica(in Chinese)*, 2008, (10): 1006
- 23 Willis, S.L., Court, J.L., Redman, R.P., Wang, J.H., Leppard, S.W. and O'Byrne, V.J., *Biomaterials*, 2001, 22: 3261
- 24 Yuan, J., Hou, Q.F., Liu, B.L., Shen, J. and Lin, S.C., *Colloids Surf. B: Biointerfaces*, 2004, 36: 19
- 25 Arasawa, H., Odawara, C., Yokoyama, R., Saitoh, H., Yamauchi, T. and Tsubokawa, N., *React. Funct. Polym.*, 2004, 61: 153
- 26 Wang, L.J., Su, Y.L., Zheng, L.L., Chen, W.J. and Jiang, Z.Y., *J. Membr. Sci.*, 2009, 340: 164
- 27 Zhang, Z., Chen, S. and Jiang, S., *Biomacromolecules*, 2006, 7: 3311
- 28 Zwall, R.F., Comfurius, P. and Vandeenen, L.L., *Nature*, 1977, 268: 358
- 29 Ishihara, K., Nomura, H. and Mihara, T., *J. Biomed. Mater. Res.*, 1998, 39: 323
- 30 Ishihara, K., Ueda, T. and Nakabayashi, N., *Polym. J.*, 1990, 22: 355
- 31 Nakabayashi, N. and Williams, D.F., *Biomaterials*, 2003, 24: 2431
- 32 Ishihara, K., *Sci. Technol., Adv. Mater.*, 2000, 1(3): 131
- 33 Zhang, Z.Q., Cao, X.C., Zhao, X.B., Withers, S.B., Holt, C.M., Lewis, A.L. and Lu, J.R., *Biomacromolecules*, 2006, 7: 817
- 34 Sibarani, J., Takai, M. and Ishihara, K., *Colloids Surf. B*, 2007, 54: 88
- 35 Okajima, Y., Saika, S. and Sawa, M., *J. Cataract. Refract. Surg.*, 2006, 32: 666
- 36 Watanabe, J., Nederberg, F., Atthoff, B., Bowden, T., Hilborn, J. and Ishihara, K., *Mater. Sci. Eng. C*, 2007, 27: 227
- 37 Watanabe, J. and Ishihara, K., *Biomacromolecules*, 2005, 6: 1797
- 38 Murphy, E.F., Lu, J.R., Brewer, J., Russell, J. and Penfold, J., *Langmuir*, 1999, 15: 1313
- 39 Ye, S.H., Watanabe, J., Takai, M., Iwasaki, Y. and Ishihara, K., *Biomaterials*, 2006, 27: 1955
- 40 Gong, M., Yang S., Ma, J. N., Zhang, S.P. and Gong, Y.K., *Appl. Surf. Sci.*, 2008, 255: 555
- 41 Yang, S., Zhang, S.P., Winnik, F.M., Mwale, F. and Gong Y.K., *J. Biomed. Mater. Res.*, 2008, 84A: 837
- 42 Zhao, B. and Brittain, W.J., *Prog. Polym. Sci.*, 2000, 25: 677
- 43 Barbey, R., Lavanant, L. and Paripovic, D., *Chem. Rev.*, 2009, 109: 5437

- 44 Ma, I.Y., Lobb, E.J. and Billingham, N.C., *Macromolecules*, 2002, 3: 9306
- 45 Konno, T., Hasuda, H. and Ishihara, K., *Biomaterials*, 2005, 26: 1381
- 46 Xu, Y., Takai, M. and Ishihara, K., *Biomaterials*, 2009, 30: 4930
- 47 Jang, K., Sato, K. and Mawatari, K., *Biomaterials*, 2009, 30: 1413
- 48 Ye, S.H., Watanabe, J.J., Takai, M. and Ishihara, K., *Biomaterials*, 2006, 27: 1955
- 49 Ma, I.Y., Lobb, E.J. and Billingham, N.C., *Macromolecules*, 2002, 3: 9306
- 50 Boyer, C., Bulmus, V. and Davis, T.P., *Chem. Rev.*, 2009, 109: 5402
- 51 Ye S. H, Johnson Jr, C.A., Woolley, J.R. and Ishihara, K., *Colloids Surf. B: Biointerfaces*, 2009, 74: 96
- 52 Kyomoto, M., Moro, T., Takatori, Y., Kawaguchi, H., Nakamura, K. and Ishihara, K., *Biomaterials*, 2010, 31: 1017
- 53 Kyomoto M., Iwasaki, Y., Moro T. and Ishihara, K., *Biomaterials*, 2007, 28: 3121
- 54 Kyomoto M., Moro T., Saiga K.I. and Ishihara, K., *Biomaterials*, 2010, 31: 658
- 55 XU, J.M., Yuan, Y.L., Shan, B., Shen, J. and Lin, S.C., *Colloids Surf. B: Biointerfaces*, 2003, 30: 215
- 56 Liu, P.S., Chen, Q., Wu, S.S., Shen, J. and Lin, S.C., *J. Membr. Sci.*, 2010, 350: 387
- 57 Feng, W., Brash, J.J. and Zhu, S.P., *Biomaterials*, 2006, 27: 847
- 58 Goda, T., Konno, T., Takai, M. and Ishihara, K., *Colloids Surf. B: Biointerfaces*, 2007, 54: 67
- 59 Goda, T., Konno, T., Takai, M., Moro, T. and Ishihara, K., *Biomaterials*, 2006, 27: 5151
- 60 Hoshi, T., Matsuno, R., and Sawaguchi, T., *Appl. Surf. Sci.*, 2008, 255: 379
- 61 Goda, T., Mstuno, R., Konno, T., Takai, M. and Ishihara, K., *Colloids Surf. B: Biointerfaces*, 2008, 63: 64
- 62 Ishihara, K., Iwasaki, Y. and Ebihara, S., *Colloids Surf. B: Biointerfaces*, 2000, 18: 325
- 63 Feng, W., Zhu, S.P., Ishihara, K. and Brash, J.L., *Langmuir*, 2005, 21: 5980
- 64 Gong, Y.K. and Nakanishi, F., Abe K., *Mol. Cryst. Liq. Cryst. Sci. Technol*, 1999, A 327: 123
- 65 Vassiliki, A. and Tegoulia, Rao W.S., *Langmuir*, 2001, 17: 4396
- 66 Chuang, Y.C., Chiu, Y.H., Wu, Y.W. and Tao, Y.T., *Biomaterials*, 2005, 26: 2313
- 67 Chen, S.F., Liu, L.Y. and Jiang, S.Y., *Langmuir*, 2006, 22: 2418
- 68 Choi, J., Konno, T., Takai, M. and Ishihara, K., *Biomaterials*, 2009, 30: 5201
- 69 Zhang, Z.Z., Cao, X.C., Zhao, X.B. and Holt, C.M., *J. Controlled Release*, 2008, 130: 69
- 70 Tto, T., Iwasaki, Y., Narita, T., Akiyoshi, K. and Ishihara, K., *Colloids Surf. B: Biointerfaces*, 2005, 41: 175
- 71 Mansouri, S., Fattison, J., Miao, Z., Merhi, Y., Winnik, F.M. and Tabrizian, M., *Langmuir*, 2009, 25: 14071
- 72 Kujawa, P., Schmauch, G., Viitala, T., Badia, A. and Winnik, F.M., *Biomacromolecules*, 2007, 8: 3169
- 73 Chen, S.F., Zheng, J., Liu, L.Y. and Jiang, S.Y., *J. Am. Chem. Soc.*, 2005, 127: 14473
- 74 Choi, J., Konno, T., Matsuno, R., Takai, M. and Ishihara, K., *Colloids Surf. B: Biointerfaces*, 2008, 67: 216
- 75 Xu, J.P., Wang, X.L., Fan, D.Z., Ji, J. and Shen, J.C., *Appl. Surf. Sci.*, 2008, 255: 538
- 76 Huangfu, P.B., Gong, M., Zhang, C.F., Yang, S., Zhao, J. and Gong, Y.K., *Colloids Surf. B: Biointerfaces*, 2009, 71: 268
- 77 Gong, Y.K. and Francoise, M.W., *Acta Chimica Sinica(in Chinese)*, 2005, (7): 643
- 78 Tiera, M.J., Qiu, X.P., Bechaouch, S., Shi, Q., Fernandes, J.C. and Winnik, F.M., *Biomacromolecules*, 2006, 7: 3151
- 79 Zhou, J., Meng, S., Guo, Z., Du, Q.G. and Zhong, W., *J Membr. Sci.*, 2007, 305: 279
- 80 Hoshi, T., Sawaguchi, T., Konno, T., Takai, M. and Ishihara, K., *Polymer*, 2007, 48: 1573
- 81 Huang, X.J., Xu, Z.K., Wan, L.S., Wang, Z.G. and Wang, J.L., *Langmuir*, 2005, 21: 2941
- 82 Lv, J.A., Ma, J.N., Huangfu, P.B., Yang, S. and Gong, Y.K., *Appl. Surf. Sci.*, 2008, 255: 498
- 83 Jia, L., Xu, J.P., Ji, J. and Shen, J.C., *Acta Polymerica Sinica(in Chinese)*, 2008, (11): 1108
- 84 Iwasaki, Y., Sawada, S.I., Ishihara, K., Khang, G. and Lee, H.B., *Biomaterials*, 2002, 23: 3897
- 85 Ye, S.H., Watanabe, J.J., Iwasaki, Y. and Ishihara, K., *J. Memb. Sci.*, 2002, 210: 411
- 86 Ye, S.H., Watanabe, J.J., Takai, M., Iwasaki, Y. and Ishihara, K., *Biomaterials*, 2005, 26: 5032
- 87 Ye, S.H., Watanabe, J.J., Takai, M., Iwasaki, Y. and Ishihara, K., *J. Membr. Sci.*, 2005, 249: 133
- 88 Uchiyama, T., Watanabe, J.J. and Ishihara, K., *J. Membr. Sci.*, 2002, 208: 39
- 89 Morimoto, N., Watanabe, A., Iwasaki, Y., Akiyoshi, K. and Ishihara, K., *Biomaterials*, 2004, 25: 5353
- 90 Uchiyama, T., Watanabe, J.J. and Ishihara, K., *J. Membr. Sci.*, 2002, 210: 423

- 91 Ishihara, K., Nishiuchi, D., Watanabe, J.J. and Iwasaki, Y., *Biomaterials*, 2004, 25: 1115
- 92 Utracki, L.A., "Polymer alloy and blends", Carl Hanser, Munich FRG, 1989
- 93 Morimoto, N., Iwasaki, Y., Nakabayashi, N. and Ishihara, K., *Biomaterials*, 2002, 23: 4881
- 94 Shimizu, T., Goda, T., Minoura, N., Takai, M. and Ishihara, K., *Biomaterials*, 2010, 31: 3274
- 95 Liu, W.G., Deng, C. and McLaughlin, C.R., *Biomaterials*, 2009, 30: 1551
- 96 Frank, J.H. and Miguel, F.R., *Mater. Res.*, 1975, 9: 315
- 97 Kitano, H., Sudo, K., Ichikawa, K., Ide, M. and Ishihara, K., *J. Phys. Chem. B*, 2000, 104: 11425
- 98 Andrew, L.L., Zoie, L.C., Hind, H.G., Laura, C.K., Lee, A.T. and Peter, W.S., *Biomaterials*, 2001, 22: 99
- 99 Fan, D.Z., Yan, X.H., Bian, H.J., Cai, C.S., Sun, F.Y., Xu, J.P., Jin, J., Shen, J.C., Qiu, H. and Gao, R.L., *J. Clin. Rehab. Tissue Eng. Res.*, 2009, 13: 4109
- 100 Inoue, Y., Watanabe, J.J. and Ishihara, K., *J. Colloid Interface Sci.*, 2004, 274: 465
- 101 Seo, J.H., Matsuno, R., Takai, M. and Ishihara, K., *Biomaterials*, 2009, 30: 5330
- 102 Iwasaki, Y., Yamasaki, A. and Ishihara, K., *Biomaterials*, 2003, 24: 3599
- 103 Sibarani, J., Takai, M. and Ishihara, K., *Colloids Surfaces B: Biointerfaces*, 2007, 54: 88
- 104 Iwasaki, Y., Takami, U., Shinohara, Y., Kurita, K. and Akiyoshi, K., *Biomacromolecules*, 2007, 8: 2788
- 105 West, S.L., Salvage, J.P., Lobb, E.J., Armes, S.P., Billingham, N.C., Lewis, A.L., Hanlon, G.W. and Lloyd, A.W., *Biomaterials*, 2004, 25: 1195
- 106 Rose, S.F., Lewis, A.L., Hanlon, G.W. and Lloyd, A.W., *Biomaterials*, 2004, 25: 5125
- 107 Bi, H.Y., Zhong, W., Meng, S., Kong, J.L., Yang, P.Y. and Liu, B.H., *Anal. Chem.*, 2006, 78: 3399
- 108 Chae, K.H., Jang, Y.M., Kim, Y.H., Sohn, O.J. and Rhee, J.I., *Sens. Actuators B*, 2007, 124: 153
- 109 Iwasaki, Y., Tabata, E., Kurita, K. and Akiyoshi, K., *Bioconjugate Chem.*, 2005, 16: 567
- 110 Futamura, K., Matsuno, R., Konno, T., Takai, M. and Ishihara, K., *Langmuir*, 2008, 24: 10340
- 111 Yang, S., "Synthesis and Application of Biomembrane Mimetic Polymers", Thesis, Northwest University, 2009