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H. 知的財産権の出願・登録状況
特になし。

様式19

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機関名　国立大学法人東京大学

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整形外科領域におけるバイオマテリアルー人工膝関節について	増田裕也, 茂呂徹	バイオマテリアル 32 (4), 327-329, 2014	2014.1	国内
A critical update on 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer science.	Goda T, Ishihara K, Miyahara Y	J Appl Polym Sci 132(16): 41766, 2015	2015.1	国外

SPECIAL TOPICS

医療の現場が求めているバイオマテリアル

整形外科領域におけるバイオマテリアル
～人工膝関節について～

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運動器の障害は，生活機能の低下，QOL(quality of life)の低下をきたし，生命予後にもわるい影響を与える．その影響は患者個人にとどまらず，患者周囲の家族にも及び，さらには社会への経済的負担ともなるものである．2007年に日本整形外科学会は，運動器障害のために移動能力の低下をきたして要介護になったり，あるいは要介護になる危険の高い状態のことを“ロコモティブシンドローム”と提唱し，以後予防啓発を行っている．ロコモティブシンドロームの五つの要因として，バランスの低下，筋力の低下，変形性膝関節症，腰部脊柱管狭窄症，骨粗鬆症があげられており，これらの要因が複合して運動機能が低下していきロコモティブシンドロームとなる．このことからも変形性膝関節症の予防・加療は今後来るであろう超高齢化社会において喫緊の重要課題であるといえる．

膝関節の関節面は軟骨に覆われており，それにより滑らかな関節運動が可能となっている．加齢や過負荷により，関節軟骨とその土台になっている骨(軟骨下骨)の変性が生じ，軟骨の摩耗や骨の増殖性変化を引き起こされる．これらの組織の破綻により膝関節の疼痛や拘縮が生じた状態を変形性関節症とよび，多くの患者において日常生活活動制限の原因となっている．大規模コホート調査によると，日本における変形性膝関節症の患者数はおよそ2,530万人(男性860万人，女性1,670万人)であると推定されており，今後もその数は増加すると予測されている[1)]．

人工膝関節全置換術(TKA)

変形性膝関節症を発症した際には，体重コントロール，膝周囲筋の筋力トレーニング，抗炎症剤の投与，ヒアルロン酸の関節内注射などが行われるが，それらの保存療法が奏功しない場合はTKA(total knee arthroplasty)の適応となる．

人工関節の歴史は長く，1950年前後には現在の人工膝関節の原型ともいえる金属を使用した人工膝関節の報告がされている．その後の60年以上を経てTKAも徐々に進歩し，現在では変形性膝関節症手術のgolden standardとなっている．現在のTKAは大きく分けると，後十字靭帯を温存するcruciate retaining(CR)型と，後十字靭帯も取り除き人工関節自体で関節の安定性を図るposterior stabilized(PS)型の二つに分類される．いずれも後十字靭帯の働きを残存あるいは代償させることで人工膝関節の安定性を確保し，良好な術後成績を得ているといえる．現時点でも安定した術後成績を得られているTKAであるが，今後さらなる向上を目指す課題として，人工関節の形状の改善と人工関節材料の改善があげられる．

“Biomaterials for orthopedic surgery”
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人工関節の形状

TKAは人工関節自体の進化と手術手技の進歩によって安定して良好な術後成績を得られるに至っている．特に術後の疼痛の軽減，日常生活への早期の復帰については非常に満足度の高い手術となっている[2]．しかしながら特に若く活動性の高い患者においては，TKA後の満足度はやや低下してしまう傾向にある[3]．活動性の高い患者の半数近くが深屈曲位での活動性に不満を感じており，人工関節の形状やTKA後の関節の不安定性が原因と考えられている[4]．

膝関節が十分屈曲するためには，膝を屈曲していくにしたがって大腿骨外側顆が脛骨外側の関節面を後ろにスライドする必要がある(roll back)．また，十分筋力を作用させるためには，膝の最終伸展時に脛骨が大腿骨に対して軽度の外旋運動をする必要がある(screw home movement)．しかしながら現在一般的に使用されている人工膝関節においては，このroll backとscrew home movementという生理的に重要な動作を正確に行うことがなかなかできておらず，そのことが上記の不満を生じる原因となっていると考えられている[5]．

TKA後にもこれらの動作を可能とするためにはCR，PSの機種で行われているように後十字靭帯の機能を残存させるだけでは十分とはいえず，いままでは比較的軽視されていた前十字靭帯の機能も残存させることが必要である[6]．

そこでroll back, screw home movementといった生理的な動作をスムーズに行えるように新たに考案されたのがbi-cruciate stabilized(BCS)という新しい概念の人工膝関節である．このBCS TKAは人工関節の形状をもともとの解剖学的な形状(関節面は水平ではなく，やや内反，脛骨関節面の形状は内外側非対称，大腿骨の内外側顆部の形状も非対称)に近づけ，さらにポスト・カム機構部の形状を工夫することでPCL(posterior cruciate ligament)だけでなくACL(anterior cruciate ligament)の機能も代償するように設計されており，そのことよりTKA後の生理的な動作を可能としている[7]．

Iliotibial band traction syndromeや膝蓋大腿関節症の亢進などの合併症の報告もみられるが，長期成績に関しての報告が待たれるところである．この両十字靭帯の機能を残存させたBCS TKAの理論をさらに推し進めた人工膝関節として現在開発中といわれるのが両十字靭帯そのものを残存させるという人工膝関節である．手術前の時点で両十字靭帯が残存している必要があり，適応となる患者は限定されることとなるが，TKAをさらに進化させる可能性のあるものとして期待されている．

人工関節の材料

TKAの長期成績に大きく関与する因子としては，人工関節のゆるみがあげられる．一般的に人工膝関節では大腿骨側・脛骨側のimplantの間に超高分子ポリエチレン(ultrahigh molecular weight polyethylene, UHMWPE)を挿入し，スムースな関節運動を可能としているが，このUHMWPEの摩耗粉が骨とimplantの隙間に入り込み骨融解を引き起こすことが人工関節のゆるみの主な要因と考えられている[8]．このことより，UHMWPE以外のさまざまな材質によるものが開発されてきたが，それぞれの成績は芳しいものとは言い難く歴史とともに消えていった．UHMWPEを用いたlinerの形状や作製方法も様々なtry and failが繰り返されてきた．形状に関しては，以前は摺動面が平らなlinerが用いられていたが，linerの摩耗が多いことが明らかとなり，現在では摺動面にもすこし彎曲をかけて大腿骨implantとの適合性を高めた形状が一般的である[9]．

作製方法に関してもさまざま考慮されてきており，近年の進歩に大きく寄与したのがクロスリンクという処理方法である．UHMWPEにγ線あるいは電子線を照射することで分子間結合を促進して，摩

耗に対する耐性を強くすることを可能とした．クロスリンクを行う際には同時にfree radicalが生じ，これがlinerの酸化を促進することで摩耗を逆に増加させるという報告もあり[10]，現在ではクロスリンクを行ったうえでfree radicalの発生を抑制する処置(熱処理，γ線処理)が行われている．酸化予防の手段として抗酸化作用の強いvitamin Eが添加されているlinerなども使用されており，長期経過の報告が待たれるところである[11]．

PE(polyethylene)の摩耗を減少させる新しい手段として現在注目されているのは，合成リン脂質材料である2-メタクリロイルオキシエチルホスホリルコリン(MPC)ポリマーを関節摺動面に一層構成することで，摩擦を軽減するだけでなく摩耗も大幅に減少させるという技術である[12]．人工股関節においてはすでに製品化がなされており，同様な技術が人工膝関節においても適応となることが待望されている[13]．

まとめ

TKAは歴史も深く，現在では安全で効果的な治療法として確立されているといえる．しかし，活動性の高い患者や若い患者においてはまだ改善の余地が大きく残されており，人工関節の形状や材料の分野において更なる開発・進歩が期待されるところである．

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REVIEW

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.

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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 lysophosphatidylcholine 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

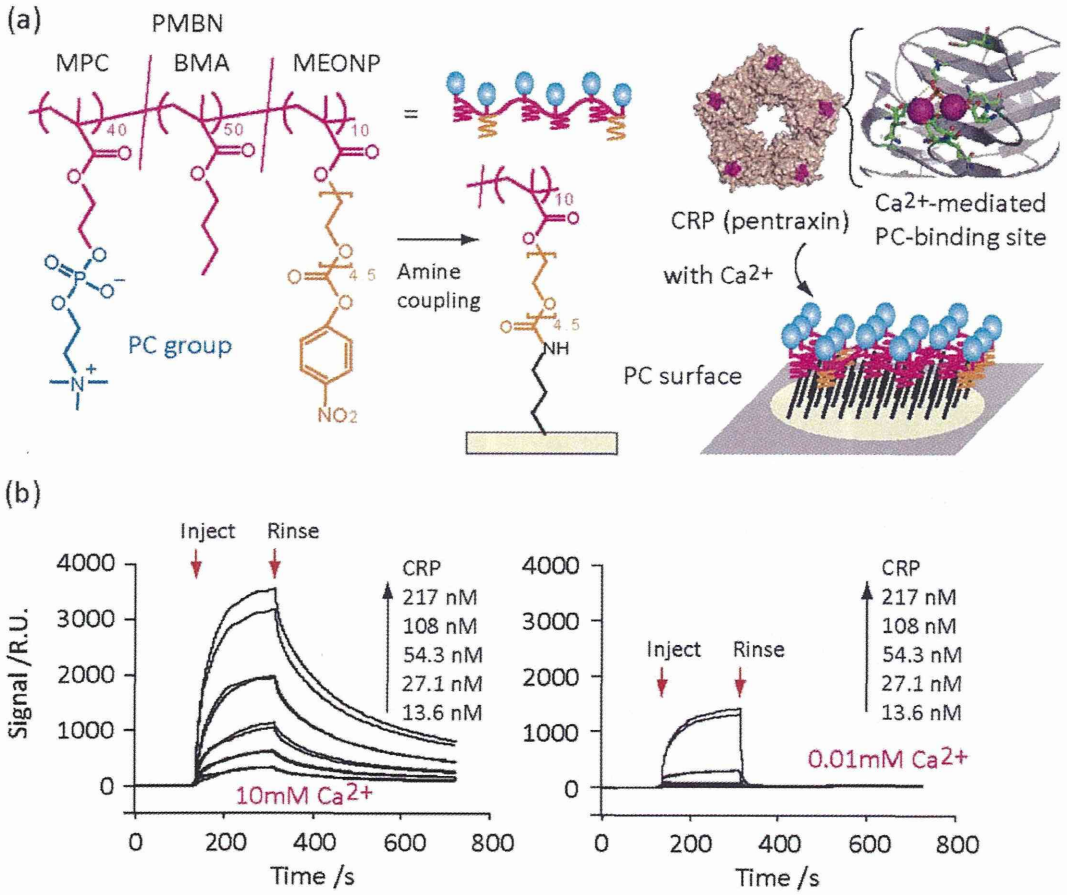

Figure 1. (a) Schematic diagram of covalent deposition of biomimetic MPC polymer (PMBN) monolayer on amine SAM-formed substrate for investigating binding kinetics of CRP on PC surface mediated by Ca^{2+}. (b) SPR sensorgrams showing a sharp contrast of association and dissociation processes of CRP adsorption onto the PC surface in HEPES buffer (pH 7.4) with 10 m*M* or 0.01 m*M* [Ca^{2+}] at different CRP concentration (13.6–217 n*M*). 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 m*M* 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