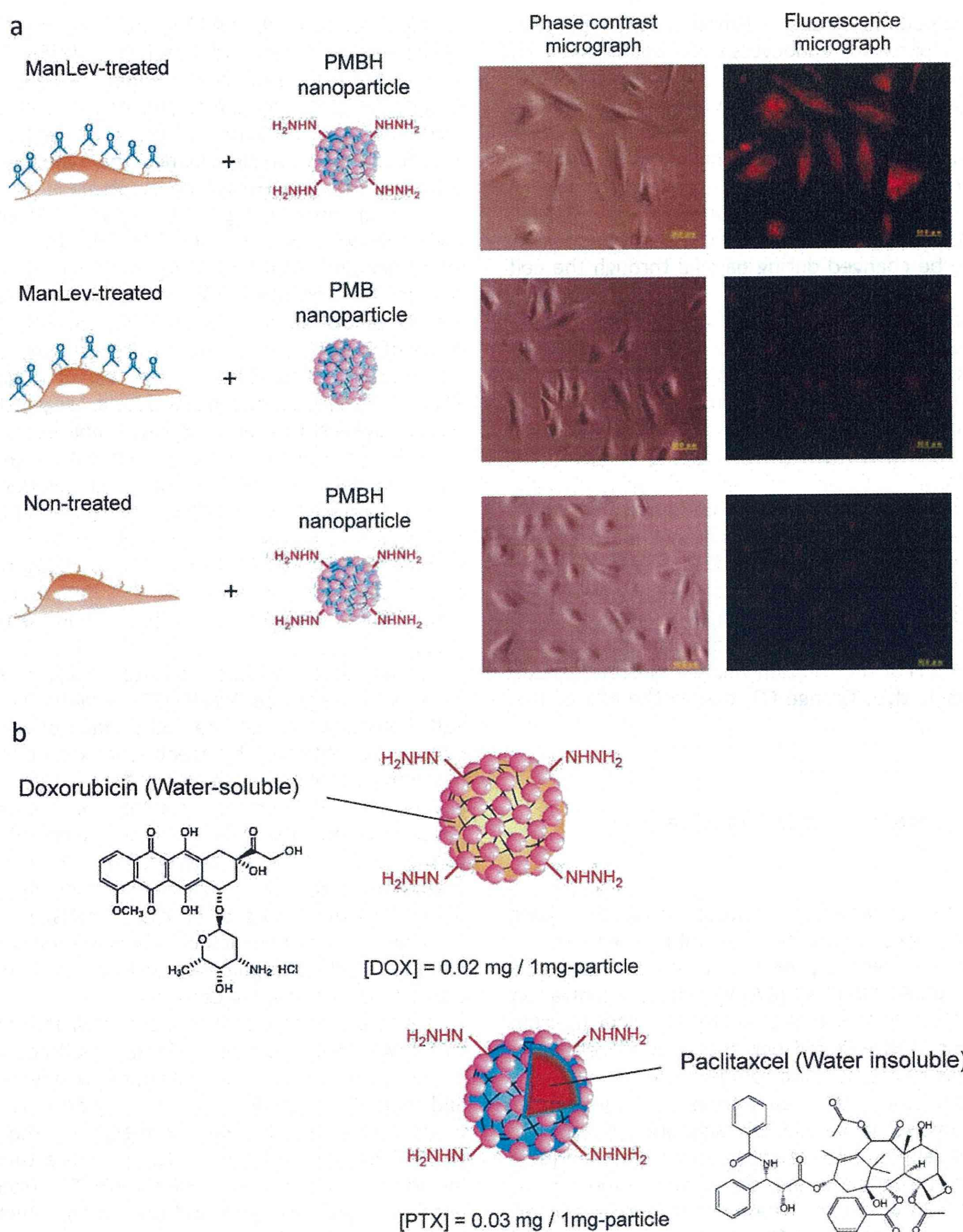

Figure 5 Cell-specific function of polymer nanoparticles covered with the hydrazide group modified MPC polymer (PMBH) [77]. (a) Specific interaction of PMBH with ketone group generated cells. (b) Schematic representation of anticancer drug-immobilized nanoparticles.

the specific transfer of genes into human hepatocytes [85]. The specific expression of sFlt-1 or GFP by PMDN conjugated to HBs containing plasmid (HBs-PMDN/plasmid), PMDN containing plasmid (PMDN/plasmid), plasmid only, and PBS were assessed in HepG2 and WiDr tumor cells *in vitro* and *in vivo*. The sFlt-1 and GFP expression was observed only in HepG2 cells transfected with sFlt-1 or HBS-PMDN/GFP. These results suggest that HBs-PMDN can function as a human hepatocyte-specific gene delivery vector without serious side effects.

Armes et al. reported a structural study of DNA condensation induced by poly(MPC-*block*-2-(*N*,*N*-dimethylaminoethyl methacrylate (DMA)) and poly(MPC-*block*-DEA) as a non-virus vector for gene delivery [86—88]. The cationic amino groups in the side chain interact with the anionic DNA molecules. The incorporation of an MPC moiety into the DEA polycation provides steric stabilization of the DNA polyplexes and reduces their non-specific cellular association *in vitro*. Poly(FA-MPC-*block*-DEA) was applied to a targeting gene delivery vector via folate receptor-mediated endocytosis

[89]. In MCF-7 and KB cells overexpressing folate receptors, the conjugated systems undergo folate-specific association and achieve significantly enhanced transfection efficiency, relative to the FA-nonconjugated control, with dramatically reduced nonspecific cellular association. On the other hand, the level of cellular association of FA-MPC-DEA was not statistically increased in A549 cells that have an undetectable level expression of folate receptors, relative to nonconjugated control. Targeting of ligand-immobilized or capped MPC polymer can also be used as an active targeting gene carrier. Additionally, MPC polymers with other cationic units such as N-(3-dimethylaminopropyl) acrylamide (DMAPAA) [90] or 2-[(2-(*N*,*N*-dimethylamino)ethylmethylamino)ethyl methacrylate (DAMA) [91], were synthesized for development of DNA vectors.

Multifunctional envelope-type nanocolloids

An integration system using a multifunctional envelope-type nano device (MEND) has significantly higher transfection activity relative to conventional gene delivery systems [92]. Harashima and coworkers have reported that modification of cholesteryl glutamic acid-alanine-leucine-alanine (GALA) peptide on the surface of MEND enhances fusion with the endosomal membrane and cytoplasmic release of encapsulated macromolecules [93]. It was recently reported that an additional coating of GALA-modified liposomes with PMB50 produces an enhancement in the transfection activity of encapsulating plasmid DNA, which is two orders of magnitude higher [94]. The MPC polymer coating decreases the zeta potential of GALA-modified liposomes. This suggests that the polymer coating assists in the functional display of negatively charged GALA on the cationic liposomes by providing shielding from mutual electrostatic interactions.

Polymeric nanoparticles covered with phospholipid polymers and immobilized biomolecules

To determine the amounts of specific molecules using biodevices within a biological environment, a molecular recognition reaction is required. The most useful method for this purpose is to employ biospecific molecular reactions such as antibody/antigen and enzyme/substrate reactions. The surfaces of the biodevices require effective immobilization of biomolecules, and maintenance of the activity of the biomolecules. Concurrently, non-specific binding of the target molecules should be inhibited. The excellent applicability of PMBN has been demonstrated in an ELISA system, a microchip immunoassay system and an immunosensor system as a blocking agent [95–97]. The coating of the MPC polymer for the large detection area of the sensor causes a decrease in noise level, which is attributed to non-specific binding and an increase in signal level. Thus, a high signal/noise (S/N) ratio is obtained. We provide a description of diagnosis probes, which employ polymer nanocolloids covered by the MPC polymer in an aqueous medium. The PMBN was easily deposited onto the surface of the polymer nanoparticles by the solvent evaporation method. Table 4 summarizes the immobilization of biomolecules on PMBN nanoparticles and applications in diagnosis.

Goto et al. evaluated the retention of the reactivity of antibody, which is immobilized on the nanoparticles and the selectivity with respect to the protein mixture [98]. The affinity binding of the BSA and anti-BSA antibody on the PMBN particles with poly(L-lactic acid) (PLA) core was examined as a model antigen/antibody interaction. The stability of antigen/antibody complexes with the antibody immobilized on PMBN/PLA-NP is the same as that in solution. This value is 100 times higher relative to the values measured for the antibody immobilized on conventional polystyrene nanoparticles. The selective binding of BSA as an antigen from a protein mixture, BSA, γ-globulins, and human plasma fibrinogen was found to be high relative to that observed with conventional antibody-immobilized polymer nanoparticles due to the effects of phosphorylcholine groups on the suppression of protein adsorption.

Watanabe et al. prepared polymer nanoparticles for sequential enzymatic reactions by combining PMBN with a polystyrene core with a diameter of ca. 360 nm [99]. For the sequential enzymatic reactions, acetylcholine esterase, choline oxidase, and horseradish peroxidase-labeled IgG were individually immobilized onto the nanoparticles. Acetylcholine chloride, choline chloride, and tetramethylbenzidine were added as substrates to the suspension of the nanoparticles. The acetylcholine chloride was converted to choline chloride. The choline chloride was oxidized by choline oxidase, and then hydrogen peroxide was formed as an enzymatic degradation product. The hydrogen peroxide was used for a subsequent enzymatic reaction involving oxidization of tetramethylbenzidine by the peroxidase. The rates of the sequential enzymatic reactions taking place on the nanoparticles via hydrogen peroxide were significantly higher than the corresponding reaction rates in the enzyme mixture. This indicates that the diffusion pathway of the enzymatic products, and the localization of the immobilized enzyme are important aspects of these reactions.

Bimolecular recognition for instantaneous determination using a fluorescence resonance energy transfer (FRET) system-installed PMBN particle was also investigated [101]. C-reactive protein (CRP) and osteopontin (OPN) were used as the target biomarkers for the instantaneous determination. The resulting fluorescence intensity correlated well with changes in the concentrations of the target molecules. The immunoassay protocol simply involves mixing of FRET-installed NPs and target molecules such as CRP and OPN antigens. Additionally, these immunoassays were found to be capable of detecting the existence of interfering molecules.

Konno et al. prepared two types of enzyme co-immobilized particles and applied them in the development of a microdialysis biosensor [100]. The PMBN was used as an emulsifier and a surface modifier to prepare the PLA nanoparticles with diameter of ca. 200 nm. Both acetylcholine esterase and choline oxidase were co-immobilized (dual-mode conjugation). The enzymatic reactions on the nanoparticles were followed using a microdialysis biosensor system with a microtype hydrogen peroxide electrode in the probe. The nanoparticles enabled detection of acetylcholine chloride as hydrogen peroxide, which is a product of the continuous enzymatic reactions occurring on the surface of the nanoparticles in the probe. It was concluded that

Table 4 Function of nanoparticles covered with PMBN for diagnosis probe.

Core	Immobilized biomolecules	Contents and applications	Diameter (nm)	Ref.
PLA	Anti-albumin antibody	High affinity separation system for proteins	<290	[98]
PSt	Acetylcholinesterase, choline oxidase, and horseradish peroxidase-labeled IgG	Sequential enzyme reaction	ca. 360	[99]
PLA	Acetylcholine esterase and choline oxidase	Microdialysis biosensor	ca. 200	[100]
PSt	Alexa Fluor 488-labeld anti-CRP-IgG, and Alexa Fluor 555-labelded anti-OPN-IgG	Biomolecular recognition system by FRET	190	[101]
PLA	Anti-CRP monoclonal antibody	CRP-detection system	205—654	[102]
PLA	Luciferase	Microdialysis biosensor	ca. 200	[103]
PLA	Anti-IgG antibody, alkaline phosphatase	Medical treatment agent	ca. 200	[104]

PLA: poly(L-lactic acid), PSt: polystyrene, CRP, C-reactive protein, OPN: osteopontin, IgG: immunoglobulin G, FRET: fluorescence resonance energy transfer.

the nanoparticles are a promising tool for development of a highly sensitive microdiagnostic system.

Ito et al. investigated dual mode reactions on PMBN particles [104]. Both an anti-mouse IgG antibody and an alkaline phosphatase enzyme were immobilized on the nanoparticles and the antigen/antibody reaction and enzymatic reaction, were both observed. When an antigen was added to the suspension of the nanoparticles, aggregation and precipitation of the nanoparticles occurred. The enzymatic reaction proceeded efficiently when the enzyme substrate was added to the suspension. The novel polymer nanoparticles could be used for nano-/micro-scaled diagnostic and medical treatment systems. In addition, a diagnosis probe using PMBN was applied to a C-creative protein-detection system [102], and a microdialysis biosensor [103].

Functionalization of quantum dots with phospholipid polymer

The development of bioimaging technologies for medicine, pharmacology, and biology is an important research area. Fluorescence imaging with an adaptable fluorescence probe is widely used in life sciences because of it is non-invasive. As described above poly(MPC) has excellent protein adsorption resistance and cell adhesion resistance. Consequently, a bioimaging probe with a stable and highly sensitive fluorescence probe covered by poly(MPC) is incapable of penetrating into cells by itself. To facilitate penetration, the probe has been integrated with cell-penetrating peptides and embedded with QDs. In the next section, we discuss bioimaging probes using poly(MPC).

Direct modification of QDs

QDs ranging in size between 2 and 6 nm have unique optical properties. Their emission spectra are material- and size-dependent, and their absorption spectrum is wide. They have high quantum yields, exhibit simultaneous multicolor emissions, and have excellent resistance to photo-bleaching. In biological applications, QDs have been widely used for *in vitro* applications such as cell labeling [105,106], tracking cell migration [107,108], and fluorescence resonance energy transfer [109,110] and for *in vivo* applications such as contrast agents of tumor-tissue sections [111], imaging of prostate cancer [112], and sentinel-lymph-node mapping in pigs [113]. Obviously, to obtain a stable and highly sensitive bioimaging fluorescence probe without cytotoxicity under cell culture medium, the surface of the QDs must be coated by biomolecules or water-soluble polymers because the QD surface is generally covered by hydrophobic ligands such as trioctylphosphine oxide (TOPO) [114].

Matsuno et al. reported a poly(MPC) grafted onto a QD (CdSe/ZnS) surface using a new strategy involving the use of a double functional RAFT agent to develop a biocompatible polymer modification method [115]. As the first function, the RAFT agent has surface activity that forms a micelle in aqueous solution and solubilizes the TOPO-coated QD into the solution. As the second function, the RAFT agent has chain transfer agent ability that synthesizes a poly(MPC)-grafted QD in an aqueous medium. The RAFT polymerization initiates at the surface of QDs treated with the RAFT agent. The MPC polymer chains formed are immobilized stably at the surface. The poly(MPC)-modified QD has good biocompatibility based on the poly(MPC) properties and was able to suppress uptake by HeLa cells despite the fact that the diameter of the poly(MPC)-modified QD was approximately 12 nm.

QDs embedded in polymeric nanoparticles covered with phospholipid polymer

Goto et al. prepared PMBN nanoparticles with embedded QDs with diameters of ca. 20 nm [116,117]. When the surface of the PMBN/PLA nanoparticles is reacted with glysine through active ester group in the MEONP unit, the polymer nanoparticles without cell-penetrating peptides showed resistance to cellular uptake from HeLa cells owing to the nature of the phosphorylcholine groups. On the other hand,

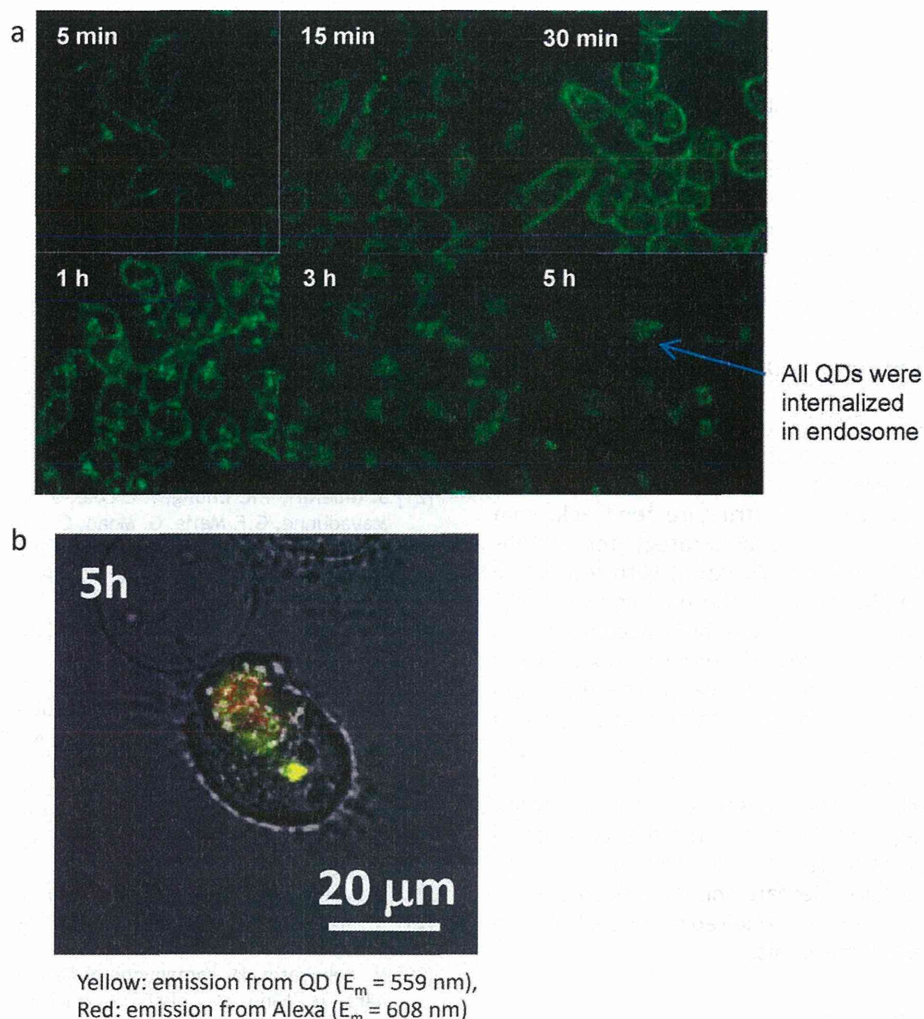

Figure 6 Cellular uptake of the MPC polymers-modified QDs as imaging probe. (a) Real-time confocal microscopic image of R8-PMBN/PLA nanoparticles embedding QDs in HeLa cells through endocytosis process [117]. (b) pH imaging by FRET between MPC polymer-immobilized QD and fluorescence dye probe in HeLa cells [118].

when arginine octapeptide (R8) was immobilized at the surface of the nanoparticles through an active ester in MEONP, the nanoparticles were able to penetrate the membrane of HeLa cells effectively without cytotoxicity through the process of endocytosis shown in Fig. 6(a). This indicates that the function of immobilized R8 was not affected by surrounding MPC polymers.

Recently, Masuda et al. prepared a fluorescence probe, which exhibits a combination of pH response and changes in fluorescence spectra for detection of cellular pH responses [100]. The nanoparticles were composed of a QD core and a block-type water-soluble poly(MPC) with a pH-responsive poly(DEA) segment as a shell. After Alexa 594 cadaverine dye was immobilized via MEONP located on the outer surface, the FRET efficiency between the QD core and Alexa was observed in aqueous media at pH 7.4 and pH 5.5. These pH values initiate the process of endocytosis as a result of the proton sponge effect. The fluorescence spectra undergo changes between pH 7.4 and pH 5.5 because the distance between QD and Alexa changes according to the pKa 7.1 of the poly(DEA) chain. Thus, when the distance between the QD core and Alexa is within several nm at pH 7.4, FRET arises from QD as a donor to Alexa as an acceptor. This produces an increase in fluorescence intensity of Alexa with a red color. When the distance is far at pH 5.5 due to protonation, independent fluorescence of QD and Alexa are observed. A color change of the poly(MPC) nanoparticles resulting from the arrest of endocytosis was observed after injection into HeLa cells, which were cultured for 5 h (Fig. 6(b)). Yellow and red colors indicate emissions from QD (E_m = 559 nm) and from Alexa (E_m = 608 nm), respectively. According to the process of endocytosis, the red color indicates arrest of endocytosis in the endosome at pH 5.5 to the cytosol at pH 7.4.

Future perspectives

Fortunately, when poly(MPC) is synthesized, there is no need to worry about reduction of the biocompatibility over a wide range of molecular weights because the biocompatibility of poly(MPC) is independent of molecular weight. Therefore, many kinds of MPC polymers have been designed and synthesized to have flexibility for use in several applications. As described in this paper, it has been demonstrated that

poly(MPC) provides the means to control nanodevices using nanocolloids. The representative PMB, PMBN, and poly(MPC-*block*-cationic unit) polymers are useful for applications including delivery of biomolecules, and development of diagnosis probes and bioimaging probes using nanocolloids. Poly(MPC) concentrated on nanodevices surface provides the high shielding effect required for protein adsorption without interruption to provide immobilized biomolecules on the surfaces. The arrangement is a key to achieving a biointerface. New investigations have indicated that effective integration with amphiphilic MPC polymers and other devices produced good results. In one example, the combination of GALA-modified MEND with PMB50 resulted in enhancement of the transfection activity of encapsulating plasmid DNA by two orders of magnitude. The integration is expected to identify new fields of research.

The structure of MPC is inspired from a part of the phospholipid structure. This structure feedback from biomolecules represents a rational strategy for obtaining new biocompatible material. However, with respect to biocompatibility, phospholipids are the only known useful compounds existing in nature. There is thus a need for development of new material to provide different feedback. Over past decade, research has been active on the hydration states of biomaterials. It has been revealed that possession of a common hydration state is important for biocompatible polymers as well as proteins. Thus, as a first step toward obtaining new materials, ''mechanism feedback'' from the hydration state is required. Presently, the hydration state cannot be assessed with respect to biocompatibility on the basis of chemical structure. Research on the biocompatibility of the hydration state will be required to obtain the next generation of ''feedback materials.''

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生体親和性材料によるナノ表面処理を用いた画期的な人工膝関節の開発に関する研究

平成２３～２５年度　総合研究報告書

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