Polymeric nanoparticles as cell-specific drug carriers

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Introduction: We have synthesized 2-methacryloyloxy-ethyl phosphorylcholine (MPC) polymers by mimicking biomembrane structure and clarified that MPC polymers reduce nonspecific protein adsorption and cell adhesion. Moreover, the nanoparticle covered with MPC polymers was not recognized from immunocytes, that is, the nanoparticle may be applied as exquisite drug carriers in the blood stream (1).

On the other hand, carbohydrates on the cell surface contribute most communications between cell and its environment, and are may be possible to design the material that interacts with the specific cells and the biological molecules. In this research, MPC polymer nanoparticles which can react with the carbohydrates of the specific cell is newly prepared to achieve novel drug carrier that interact with the specific cell.

Methods: Poly[MPC-*co*-*n*-butyl methacrylate (BMA)] (PMB) and poly[MPC-*co*-BMA-*co*-methacryloyl hydrazide (MH)] (PMBH) were synthesized by radical polymerization using 2,2'-azobisisobutyronitrile (AIBN) as an initiator (Figure 1) (2). These polymers were dissolved in purified water, and poly(L-lactide) (PLLA)/methylene chloride solution was added dropwise. The mixture was sonicated using a probe-type generator for 30 min and kept under reduced pressure for 2 h to completely evaporate the methylene chloride. The formed nanoparticles were fractionated by centrifuging at 10,300 g at 4 ℃ for 30 min. The particle size and ζ-potential were measured by a Dynamic Light Scattering measurement (DLS) and Laser Doppler Velocimetry (LDV). The surface condition of nanoparticle was analyzed with an x-ray photoelectron spectroscope (XPS). Human uterine cervical cancer (HeLa) cells with unnatural carbohydrates as cell-surface tags were harvested by treatment with *N*-levulinoylmannosamine (ManLev) by previously reported method (3). The nanoparticles containing hydrophobic fluorescence probe (Nile Red®) were incubated with ManLev-treated HeLa cells for a given time. The cells were rinsed with fresh medium to remove free nanoparticles and observed by fluorescence microscope.

Results / Discussion: MPC polymer nanoparticles were monodispersity with approximately 200 nm in diameter, and approximately 0 mV in surface potential (Figure 2). According to XPS analysis, spectra of phosphorylcholine and hydrazide groups were observed. On the other hand, spectra due to PLLA and Nile Red were not detected. These results suggested that the MPC copolymers completely covered surface of the nanoparticle. When the nanoparticles were in contact with ManLev-treated HeLa cells, they interacted with the cell surface (Figure 3). However, the nanoparticles did not observe on native HeLa cells (without unnatural carbohydrate). Hydrazide groups of the nanoparticles selectively reacted selectively to ketone groups of carbohydrates on membranal proteins.

Conclusions: Amphiphilic PMBHs are able to form the nanoparticle bearing hydrazide groups on its surface. The nanoparticles recognize ManLev-treated HeLa cells that express unnatural carbohydrates. It revealed that PMBH nanoparticles could function as nano-carrier that showed cellular specificity by carbohydrates recognition.

References:

(1) T. Konno et al., *TMRSJ* 2001;26:897
(2) Y. Iwasaki et al., *Bioconjugate Chem* 2005;16:567
(3) C. R. Bertozzi et al., *J Bio Chem* 2000;56:9515

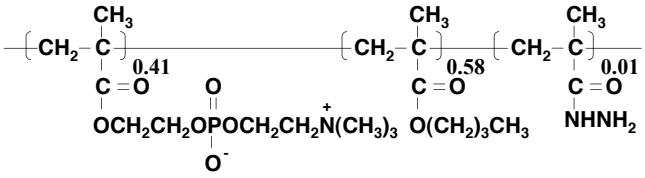

Figure 1 Chemical structure of PMBH50

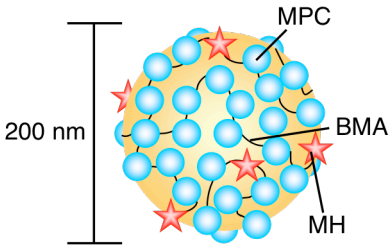

Figure 2 Illustration of a PMBH nanoparticle

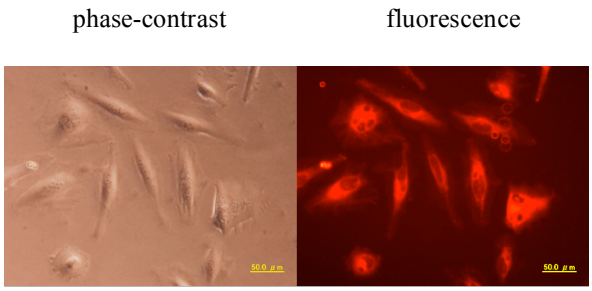

Figure 3 Fluorescence microscope images