Phenylboronate functionalized polyion complex micelles as ATP-sensitive smart delivery system of siRNA

Mitsuru Naito, Takehiko Ishii, Akira Matsumoto, Kanjiro Miyata, Yuji Miyahara and Kazunori Kataoka

1) Department of Materials Engineering, 2) Department of Bioengineering, 3) Division of Clinical Biotechnology, Center for Disease Biology and Integrative Medicine, The University of Tokyo, 4) Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University

Short interfering RNA (siRNA) offers great potential as a research tool and a therapeutic agent because of its ability of gene-silencing in a sequence-specific manner. However, siRNA is easy to be decomposed by RNase and eliminated rapidly from blood through a renal clearance, results in an impediment to clinical use. Polyion complex (PIC) micelle encapsulating siRNA that formed through the molecular self-assembly of the electrostatic complex consists of negatively charged siRNA and positively charged synthetic block copolymers is one of the most promising approach for protection from enzymatic degradation, though there is a room for improvement of the structural stability of the PIC micelle during circulating in blood stream.

Very recently, we reported a completely new approach for environment-responsive siRNA delivery carrier. Our system capitalizes solely on phenylboronate functionality, which, nonetheless, renders the micelle stabilization with intracellular sensitivity (Figure 1). Phenylboronic acid (PBA) introduced to the side chain of polycation can form reversible covalent esters with ribose at both 3’-ends of siRNA and the intermolecular binding among polymers and siRNAs can lead PIC micelle to high stabilization. Advantageously enough our system can also release the encapsulated-siRNA easily by exchanging with ribonucleotides which exist abundantly and locally at cytoplasm. In this study, as illustrated in Figure 1, we used poly(ethylene glycol)-block-poly(L-lysine) modified with fluorine substituted phenylboronic acid (FPBA) (PEG-b-(PLys/FPBA)) as a siRNA carrier and examined the stability and the responsivity to release siRNA.

[Result and Discussion]

PEG-b-P(Lys/FPBA) formed more stable PIC micelle compared with PBA-unmodified PEG-b-PLys and released siRNA in response to increased concentration of ribonucleotides, especially, adenosine triphosphate(ATP) existing more abundantly in cytoplasm than in blood, whereas neither deoxiribonucleotides nor glucose the most abundant polyol in the blood, having lower binding constant with PBAs caused no significant destabilization (Figure 2).

In summary, PBA-functionalized PIC micelle system can be used for intracellular ATP-triggered release of siRNAs and has a great potential for in vivo siRNA delivery.