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

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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[1] (***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 ribonucreotides which exist abundantly and locally at cytoplasma. 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.

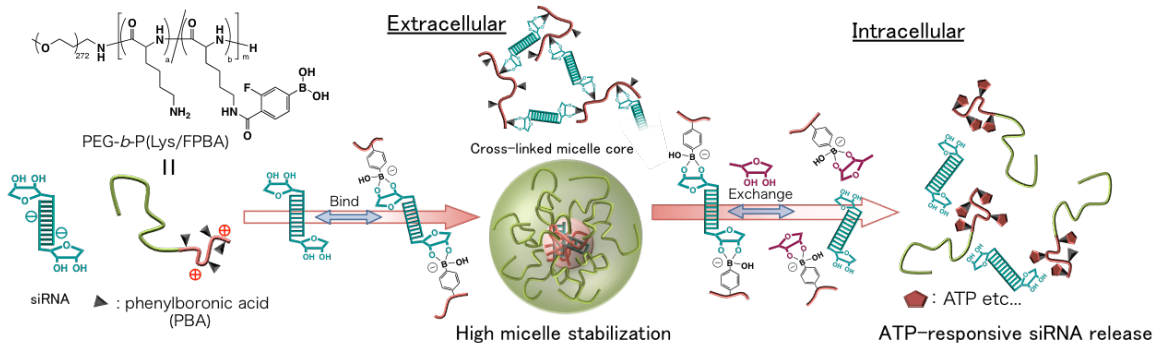

Figure 1. Schematic representation of PBA-assisted siRNA delivering strategy

[Result and Disucussion]

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 cytoplasma than in blood, whereas neither deoxiribonucreotides 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.

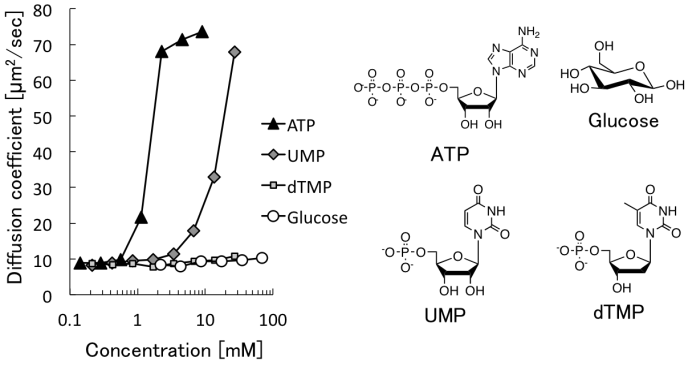

Figure 2. Ribose-specific siRNA release

[1] M. Naito et. al "A Phenylboronate-Functionalized Polyion Complex Micelle for ATP-Triggered Release of siRNA", ***Angew. Chem., Int. Ed,*** (2012), *51*, 10751-10755