

Supramolecular Design of Polyrotaxanes as Advanced Nano-Biomaterials

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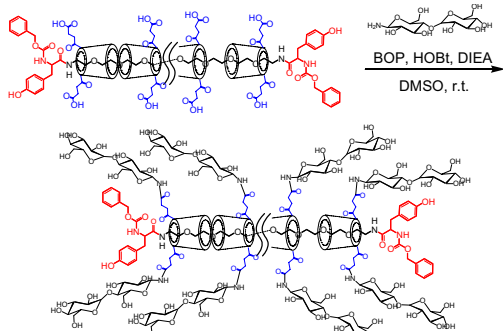
Abstract

Supramolecular architectures have been extensively studied in the last decade [1]. In particular, polyrotaxanes have been much interested as a novel class of molecular assemblies, in which cyclic compounds are threaded onto a linear polymeric chain capped with bulky end-groups. We have systematically studied a variety of biodegradable polyrotaxanes consisting of many cyclodextrins such as α -cyclodextrins (α -CDs) and a polyether such as poly(ethylene glycol) (PEG) and their hydrogels aiming at carriers for drug delivery or scaffolds for tissue regeneration. For instance, hydrolyzable polyrotaxane hydrogels have been designed as a scaffold for cartilage regeneration [2]. Here the hydrolysis of our designed polyrotaxane hydrogels is well controlled by inclusion complexation of ester groups located at the terminal of the PEG in the polyrotaxanes, and the time to complete hydrogel erosion varies from a few days to more than two year in spite of their highly swollen states in physiological conditions [3]. Alternatively, we have proposed a new idea on using such polyrotaxanes: multiple copies of ligands can be incorporated into our polyrotaxanes in order to enhance multivalent bindings with biologically active proteins. Here, the ligands are covalently bound to α -CDs threaded onto a PEG chain capped with bulky amino acid (tyrosine) via biodegradable spacer. In our previous studies, biotin-polyrotaxane conjugates were designed and their multivalent binding with streptavidin-fixed surface was clarified by

surface plasmon resonance spectroscopy [4]. Also, oligopeptide-polyrotaxane conjugates were designed aiming at inhibitors of intestinal human peptide transporter 1 (hPEPT1) and their inhibitory effect was clarified using hPEPT1 expressing HeLa cells in vitro and rats in vivo [5]. These studies have demonstrated an important aspect of our designed polyrotaxanes as new nano-biomaterials which can bind biologically active molecules in a multivalent manner.

Such multivalent interaction with biological systems is an important issue not only for new drug design but also for controlling intercellular signal transduction in cultured cells. Multivalency is widely accepted as the way to achieve strong attachment and interaction of two or more binding sites on a certain biological molecule with multiple receptor sites on another cell surface, and such multiple binding interactions between ligands and receptors are of much interest in the rational design of new drugs. However, previous studies using polymeric architectures have been not so successful because ligand introduction into a polymeric backbone is thermodynamically unfavorable. Thus, one can imagine that polyrotaxanes with mobile ligands are a promising candidate for functional biomaterials: the cellular functions may be well enhanced through this approach. Recently, it has been found that maltose-polyrotaxane conjugates (Mal-PRXs, Scheme 1) have a unique function for recognizing a binding protein, Concanavalin

A (Con A) due to the multivalent interaction. In this paper, the effect of ligand mobility along the polyrotaxane structure on multivalent interaction was examined by using maltose-Con A interaction [6].



Scheme 1. Synthesis of Mal-PRXs.

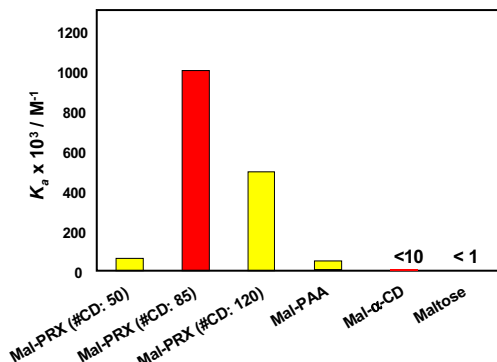


Fig. 1. Association constant (K_a) of each Mal-conjugates.

The K_a values of Mal-PRXs and Mal-polyacrylic acid conjugate (Mal-PAA) were from 1st to 4th power of ten as high as those of Mal- α -CD and maltose, indicating their excellent multivalent effect. It is noted that the Mal-PRX (#CD: 85) showed the highest K_a value with Con A even in the same number of maltose (ca. 240) per one polymeric backbone (Fig. 1). This conjugate was found to exhibit the highest mobility of maltose in terms of T_2 of maltose C(1) proton NMR measurement and the highest magnitude of the relative index of water clusters obtained by Raman scattering measurement [7]. The ΔH value of the Mal-PRX showed a large negative

value in comparison with the other conjugates. The negative enthalpy change is interpreted as an enhanced interaction between maltose and the binding site of Con A, due to high mobility of maltose in the Mal-PRX and preserving ordered structure of the bulk water clusters surrounding the Mal-PRX. These features of the Mal-PRX were enthalpically advantageous for multivalent interactions.

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