Precise Design of Star Polymers for Controlling the Interactions with the Target Biomolecules

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In living systems, biomacromolecules play an important role as one of the components in organized molecular systems. One of the goals of polymer science is to produce functional nanomaterials that are comparable with biomacromolecules such as DNA and proteins. The functions of these biomacromolecules are based on their well-defined polymer structures. The homogeneous and predictable molecular structures of DNA and peptides enabled to form synthetic nanostructures (Figure 1). However, in contrast to the biomacromolecules, the structures of synthetic polymers are heterogeneous in terms of their molecular weight, monomer sequence. Recently, controlled polymerization techniques including living radical polymerization have provided synthetic polymers with well-defined structures.[1] Herein, we demonstrate the design of synthetic polymers using the living radical polymerization to control their biological function (biomolecular recognition). The target biomolecule is hemagglutinin (HA) of the influenza virus, which binds to carbohydrates on cell surfaces through the three binding pockets on their surfaces. To realize multivalent interaction with HA, a tri-arm star polymer with the optimal structure was designed.

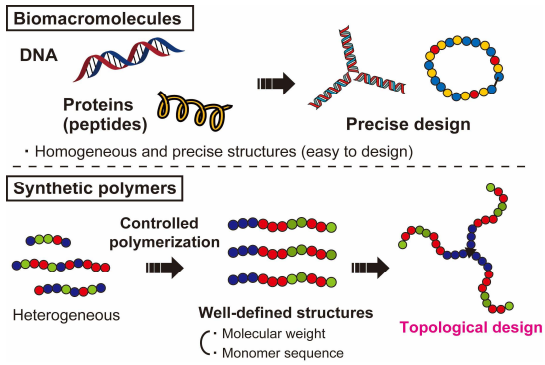

Figure 1. Comparison of biomacromolecules and synthetic polymers.

Prior to the synthesis of the star polymers, the degree of polymerization (DP) required to achieve multivalent binding to the three pockets of HA was estimated using classical

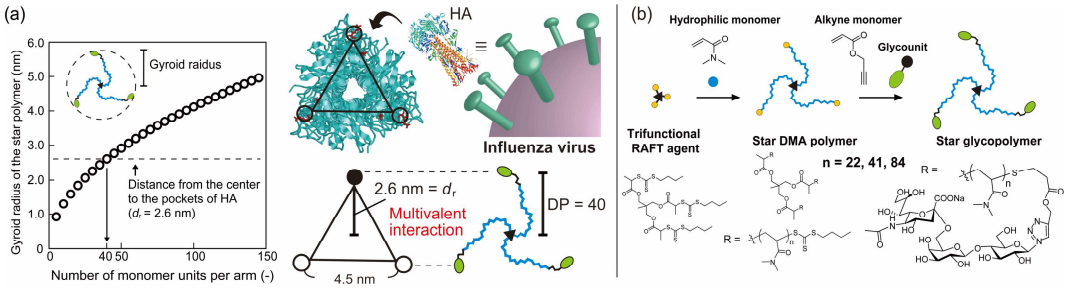

Figure 2. (a) Illustration of hemagglutinin and the designed star polymer. (b) Schematic illustration of the synthesis of star polymers by RAFT polymerization and functional modification onto the polymer terminals.

theoretical polymer models. The three binding pockets of HA are located at the vertices of the triangle formed on the HA surface (Figure 2). The distance from the center of the triangle to the pocket (d_r) is 2.6 nm. The relationship between the number of monomer units of the polymer arm and the gyroid radius is shown in Figure 2a. The theoretical prediction suggested that a star polymer with a DP of 40 would have a comparable gyroid radius to the arrangement of pockets on the HA surface.

The star polymer was designed with 6'-sialyllactose (6'-SALac) at the terminals of the polymer arms. The hydrophilic star polymer with trivalent arms was synthesized by reversible addition-fragmentation chain transfer (RAFT) polymerization of DMA with a trifunctional RAFT agent (the polymer is abbreviated to **SD** below). The DP of the **SD** polymer was calculated to be 41 from the ^{1}H NMR measurement (**SD$_{41}$**). As control samples, **SD** polymers with different DP (**SD$_{22}$** and **SD$_{84}$**) were synthesized. The terminal trithiocarbonate groups of the SD polymers were converted to alkyne groups in a one-pot procedure. 6'-SALac azide was conjugated to the alkyne terminals of the polymer arms (**SD$_n$G**). To evaluate the precision of the molecular design of the glycopolymers, their hydrodynamic radii (R_h) in phosphate buffer saline solution were measured using dynamic light scattering. The R_h of the star glycopolymers were 2.0, 2.8, and 3.9 nm for **SD$_{22}$G**, **SD$_{41}$G** and **SD$_{84}$G**, respectively (Figure 3a). The R_h of the synthesized glycopolymers increased with the DP of the polymer arms, and the R_h of **SD$_{41}$G** was close to the distance from the center of the triangle to the CRD of HA (d_r = 2.6 nm) as expected in the Gaussian model calculated before the synthesis. The interaction of the star polymer with the influenza virus was evaluated by the hemagglutination inhibition test (Figure 3b). As anticipated, the star polymer with optimal length of polymer arms (the degree of polymerization = 41) showed the strongest interaction with the virus among the synthesized polymers, demonstrating that precise design of synthetic polymers enables to control the biological function.

Reference: (1) J.-F. Lutz et al., *Nat. Rev. Mater.* **2016**, *1*, 16024.

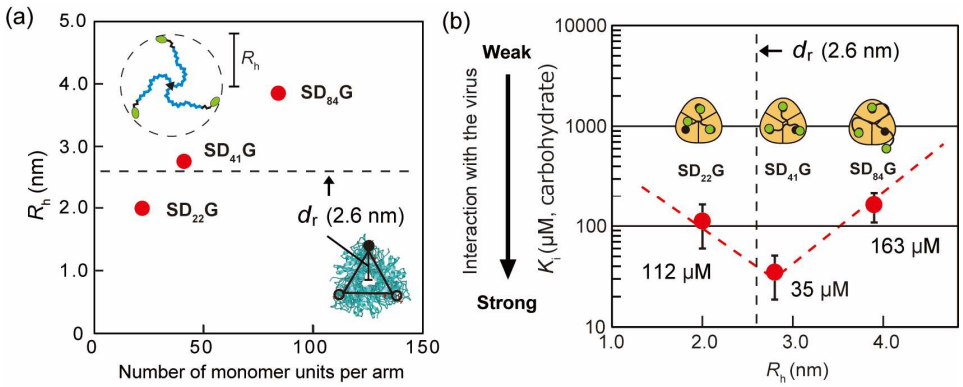

Figure 3. (a) Hydrodynamic radius (R_h) of star glycopolymers with different numbers of monomer units per polymer arm. (b) K_i against hydrodynamic radius (R_h).