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Synthesis of Target-Directed Nanogel Carriers with Glycopolymers and Their Application to Immunotherapy †

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Abstract: This study describes the preparation of a core-shell nanogel system for active-targeted delivery of antigenic proteins to dendritic cells (DC cells), which play a critical role in inducing cytotoxic T lymphocytes (CTL) for effective immune response against cancer and infectious diseases. Mannose-type glycan block copolymers were synthesized and modified onto hydrophilic silica nanoparticles to create mannose-presenting nanoparticles (SiNP-Man), which were shown to selectively bind to lectin and inhibit aggregation in the presence of free mannose. This nanogel system has potential as an effective and stable antigen delivery method for CTL induction. Thus, the newly designed mannose block copolymer would have promising property to install nature of active-targeting towards mannose specific c type lectin on DC cells.

Keywords: nanogel carrier; protein delivery; cancer immunotherapy

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1. Introduction

Immunotherapy to induce antigen-specific immunity is expected to be an effective and safe treatment for cancer and infectious diseases, and induction of cytotoxic T lymphocytes (CTL) is particular important for the treatment of these diseases [1]. For effective CTL activation, antigen-presenting cells (APC) such as macrophages and dendritic cells must take up antigenic proteins/antigen peptides, through degradation them intracellularly, and present the generated peptide fragments on MHC class I molecules [2]. Although various antigen administration methods have been studied to induce CTL efficiently, conventional techniques have not been sufficiently effective. The main reasons for this are low translocation of their antigens to APC and protein instability during in vivo delivery. In this study, we prepared a core–shell mannose-installed nanogel with a suitable aqueous environment for a protein stabilization that can be active-targeted to dendritic cells in vivo. Targeting of the nanogel to dendritic cells with mannose receptors was confirmed by aggregation inhibition experiments of silica particles mimicking nanogel structures. For higher sensitivity, gold nanoparticles grafted with mannose-glycopolymers were synthesized, and the specific binding to lectin was analyzed from the surface plasmon changes. In addition, inhibition experiments were also conducted to investigate the binding mode in more detail.

2. Experiment

Mannose-type glycan block copolymers (pManEMA-b-pMAA, Man) were synthesized by RAFT polymerization using the monomer consisting of D(+)-Mannose and 2-hydroxyethyl methacrylate (ManEMA) and methacrylic acid (MAA). Next, the surface of a hydrophilic silica nanoparticle (SiNP) was modified with pManEMA-b -pMAA via a silane coupling agent with an amino group at the end. The specificity of mannose-presenting SiNP (SiNP-Man) to the receptor protein was evaluated from the inhibition experiment by the addition of free mannose as an inhibitor.

3. Results & Discussion

The structure of the synthesized glycopolymers was confirmed by ^{1}H-NMR spectra and GPC measurements. Competitive inhibition of SiNP-Man aggregation by lectin was confirmed by the addition of free mannose as an inhibitor. When concanavalin A (ConA), mannose specific lectin was added to the SiNP-Man solution, particles aggregated due to the specific interaction at the low inhibitor. However, when excess amount of inhibitor was added, the binding site of the lectin was competitively suppressed and the particles did not aggregate. These results confirm the active target property of the mannose-modified nanoparticles.

Supplementary Materials: The material is available at https://www.mdpi.com/article/10.3390/ASEC2022-13764/s1, Conference Poster: Synthesis of Target-Directed Nanogel Carriers with Glycopolymers and Their Application to Immunotherapy.

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