



Synthesis and bio-applications of carbohydrate–gold nanoconjugates with nanoparticle and nanolayer forms

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ABSTRACT

Carbohydrate-conjugated gold nanoparticles (GNPs) and gold nanolayers (GNLs), which have recently attracted increasing attention as innovative nano-biomaterials, were successfully synthesized using carbohydrate thiosemicarbazones in an aqueous *N*-methylmorpholine *N*-oxide (NMMO) system. This system can dissolve various types of carbohydrates including structural polysaccharides, e.g., cellulose. We observed that oxidative NMMO solvent unexpectedly promoted the immediate reduction of $[\text{Au}^{\text{III}}\text{Cl}_4]^-$ species to nanosized metallic Au^0 , that is GNP. One possible mechanism is that the chloride ligand was oxidized to chlorate *via* the formation of a hypochlorite intermediate. Site-selective S-labeling of sugar reducing ends with thiosemicarbazide may have enabled regulated self-assembly immobilization to the surfaces of GNPs and GNLs. The carbohydrate–gold nanoconjugates possess unique nanoarchitectures and biofunctions for carbohydrate–cell interactions. Novel and simple approaches for the structural design of carbohydrate-decorated GNPs and GNLs in the NMMO system have potential to inspire a new phase in glyco-biomaterials engineering.

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1. Introduction

1.1. Gold nanoparticles and bio-applications

Gold nanoparticles (GNPs) possess unique physicochemical properties because of their quantum-size effects that contribute to various optical, electromagnetic and catalytic characteristics, and have become a center of attraction in advanced nano- and bio-engineering fields [1–4]. In particular, the surface plasmon resonance (SPR) signals dependent on the size variation of GNPs have been utilized as a high-sensitive biosensor [5]. Surface modification of GNPs is also essential for further practical applications; thus, methodological studies on the synthesis of GNPs conjugated with various molecules have been carried out actively [6–9]. Currently, GNPs are commonly conjugated with a variety of biomolecules, e.g., nucleic acids and oligopeptides, for applications in bioanalytical and biomedical fields [10–12]. Carbohydrates have become a major target due to their specific molecular recognition and various actions in most living systems [13]. Many types of carbohydrate-related GNP conjugates, mannose, galactose, dextran and others, have been reported [14–17]. Biosensing and bioimaging *via* carbohydrate–protein/cell interactions would enable physiological control and manipulation of living cells.

However, there have been few reports on conjugation with structural carbohydrates, e.g., cellulose and chitin, because of their poor solubility and low reactivity in common synthetic processes, resulting in considerable difficulties in an effective conjugation with GNPs at a molecular level. Structural carbohydrates, such as cellulose, have unique self-assembling properties and form hierarchical organizations from nano- to micro-architectures *via* regular intra- and inter-molecular hydrogen bonding systems [18]. Such molecular features are expected to provide high potentials for controlling the surface density and alignment of bioactive moieties on solid materials, aimed at achieving the clustering effect of carbohydrates that is essential for success in glyco-biomaterials engineering.

1.2. Sugar-decorated biointerfaces

In the biomedical fields, a diverse array of scaffold materials for tissue engineering has been reported with a view to stimulating cellular responses [19–21]. To design matrix functions, many researchers have made great efforts to control the surface properties, e.g., chemical composition, charge, topography and wettability, of layer-state materials [22–24]. Various types of substrates have been used for surface biomodifications; in particular, gold nanolayers (GNLs) are widely applied because gold is bio-inert and easily modified by various approaches. Bio-derived molecules are recognized as fascinating candidates for novel biomaterials, and successful preparations of bioactive interface materials composed of biomolecules have

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been reported [25,26]. As such, glycoconjugation is gaining increased attention in the surface modification of biomaterials [27–29] due to the critical role of carbohydrates that are anchored to cell surfaces for biological interactions of cells with extracellular signal components and adjacent cells [30]. To overcome the weak, monovalent carbohydrate-mediated interactions, clustering of carbohydrates on a material surface has been a significant approach for the design of biomimetic, biofunctional glycoconjugates.

1.3. Cellulose and bio-applications

Cellulose, a β -1,4-linked D-glucopyranose polymer, is the major constituent of plant cell walls and a typical structural polysaccharide with biodegradability and eco-compatibility [18]. Cellulosic repeating units have unique amphipathic and self-assembling properties via the formation of regular intra- and inter-molecular hydrogen bonds, and eventually various crystalline polymorphs are present in stable forms, e.g., I $_{\alpha}$ (parallel, triclinic), I $_{\beta}$ (parallel, monoclinic), II (anti-parallel), III $_{\beta}$, III $_{\alpha}$ and IV [31–33]. Thus, we expect that such molecular features and nanoarchitectures possess a high potential for clustering functional sugar moieties onto GNP and GNL surfaces.

To date, cellulose and its derivatives have been widely used in not only traditional papermaking and textile fiber industries, but also in pharmaceutical and biomedical fields [18,34–36]. Cellulosic polymers have been frequently used as a hemodialysis membrane composed of regenerated cellulose or cellulose acetate due to their blood-protein hindrance properties [35]. In current biomedical fields, bacterial cellulose (BC, I $_{\alpha}$ -rich), which is biosynthesized by bacteria such as *Acetobacter*, *Acanthamoeba* and *Achromobacter* spp. [18], has attracted much attention as a promising cellulose-based biomaterial for wound dressings, artificial blood vessels and scaffold materials for tissue culture because of its favorable material properties that are attributed, in part, to the specific nanosized structures [18,34–36]. Additionally, chemical modifications, e.g., phosphorylation and sulfation, of BC have been actively investigated to improve the bioactivity of BC-based cell culture scaffolds [37,38]. At any rate, not only the chemical properties but the nanostructures, e.g., crystalline structure and nanomorphology, of the surface layers of glyco-materials have great impacts on their biofunctionality.

1.4. Contents

In this short review article, we present our recent achievements of the preparation and bio-applications of carbohydrate-decorated nanomaterials that are glycoconjugates with GNPs and GNLs. First, we describe a novel route for GNP synthesis in an aqueous *N*-methylmorpholine *N*-oxide (NMMO) solution and its unique auto-redox mechanism. This GNP synthesis protocol was allowed to conjugate *in situ* with various sugars including structural carbohydrates and an application of bioactive sugar-decorated GNP conjugates was introduced. Second, surface modification and characterization of GNLs with cellulosic carbohydrates are presented. Self-assembly chemisorption of selectively S-labeled sugar chains provides new types of cellulosic layers with a parallel chain alignment. The specific properties of carbohydrate-GNLs, e.g., crystallographic structure, surface wettability and biointerface functions are also reviewed.

2. Experimental

2.1. Preparation and characterization of carbohydrate-GNPs

Sulfur–gold interaction (S–Au bond) has often been utilized for the versatile design of self-assembled monolayers (SAMs) in nanomaterials engineering. In a series of our studies, the reducing end of carbohydrates were functionalized with thiosemicarbazide (TSC) *via* reductive amination to form thiosemicarbazones (Fig. 1) in the good

solvents for each target sugar [39] to promote spontaneous chemisorption of carbohydrate-TSCs onto GNP surfaces. Carbohydrate–GNP conjugates were prepared by a one-step GNP synthesis and simultaneous *in situ* surface glyco-modification in the NMMO/H₂O solvent system. An outline is summarized as follows: a dilute aqueous solution of tetrachloroauric acid (HAuCl₄) was added dropwise to a carbohydrate-TSC solution of 80% NMMO/20% H₂O mixture at 70–100 °C with stirring [39]. Carbohydrate-free GNPs were synthesized in a similar manner whereby an aqueous HAuCl₄ solution was added to a hot carbohydrate-free NMMO/H₂O solution. The characterization of GNP conjugates and a mechanism study of GNP formation were carried out by UV–vis spectrometry, transmission electron microscopy (TEM), nuclear magnetic resonance (NMR) analysis, quartz crystal microbalance (QCM) analysis, capillary electrophoresis (CE) and others [39].

2.2. Preparation and characterization of carbohydrate-GNLs

Carbohydrate nanolayers were architecturally designed on a flat gold surface by spontaneous chemisorption of TSC-modified cellulose or its water-soluble derivatives [40–42]. An outline is schematically illustrated in Fig. 1. Gold-coated silicon wafer was treated with cellulose-TSC/NMMO/H₂O/dimethylsulfoxide solution, followed by a thorough rinse with hot NMMO solvent [40]. In the case of cellulose derivatives, distilled water was used as a solvent [41,42]. For cell culture scaffolds, transparent glass plates were used. The cellulosic SAMs were stably formed on the gold substrate through vectorial chain immobilization of cellulosic polymers whose one termini (reducing ends) were covalently fixed on the substrate surface. The surface morphology, crystalline structure and wetting property of obtained carbohydrate-GNLs were investigated by TEM, electron diffractometry (ED), X-ray diffractometry (XRD), X-ray photoelectron spectroscopy (XPS) and atomic force microscopy (AFM); and their biofunctionality was evaluated by a cell culture assay.

3. Results and discussion

3.1. Synthesis and bio-applications of carbohydrate-GNPs

3.1.1. NMMO-mediated synthesis of GNPs

The first scientific paper of GNPs was reported by Faraday in 1857 [43]; however, the reddish color of GNPs has been utilized as a dye for a long time. The synthesis of GNPs is achieved by reducing aurate chloride (Au^{III}) to metallic gold (Au⁰) in water using reductants, such as citric acid [44]. This method is still used to effectively modify GNPs with functional molecules in an aqueous system [10,14,15]. Additionally, there are numerous approaches to synthesize GNPs using ascorbic acid, ethanol, formaldehyde and sodium borohydride both in aqueous and nonaqueous systems [45].

In this review, we present a novel preparation route of GNPs and *in situ* conjugation with cellulose and other sugars in an NMMO/H₂O system, which is a well-known, good solvent for structural polysaccharides [46]. A conventional two-step approach, *i.e.* GNP synthesis by the citrate-reduction method and then conjugation with water-soluble biomolecules in aqueous media [10,14,15], was not allowed for water-insoluble cellulose. Fortunately, we found that GNPs can form immediately in a hot NMMO solution without any reductant through an extraordinary redox procedure, which is the focus of the present study. Sequential procedures of GNP synthesis and glycoconjugation are outlined below [39].

A dilute aqueous HAuCl₄ solution was added dropwise to an 80% NMMO/20% H₂O mixture, changing the solution immediately from a light-yellow to a reddish-purple color (Fig. 2a), without any particular treatment. The UV–vis spectrum clearly showed a maximum adsorption at 530 nm, which was presumably attributed to the SPR signal of the well-dispersed GNPs. This is a strong indication that GNPs

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