Nanomedicine and Nanotechnology Journal

SCIENTIFIC LITERATURE

CASE REPORT

Recent Advances in the Glyco-Gold Nanoparticles of Different Shapes and its Potential Applications

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ARTICLE INFO

Received Date: September 28, 2017
Accepted Date: November 01, 2017
Published Date: November 09 , 2017

KEYWORDS

Carbohydrates;
Glyco gold-nanoparticles;
Nanoparticles;
Bacteria;
Zebrafish;
Homoglycodendron;
Heteroglycodendron

Citation this article: Chaudhary PM, Jaina P, Toraskara S, Sangabathunia S, Kikkeri R. Recent Advances in the Glyco-Gold Nanoparticles of Different Shapes and its Potential Applications. Nanomed Nanotechnol J. 2017; 1(1):112.

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ABSTRACT

Carbohydrates play a major role in many biological systems by their lectins which recognize them. Carbohydrate-Lectin Interactions (CLIs) are involved in expansively diverse biological processes which include cell-cell interaction, cell activation, cell adhesion, endocytosis, phagocytosis, inflammation, tumor cell metastasis, and apoptosis. One main drawback for investigating carbohydrate-lectin interactions is their weak affinity. Nature utilizes multivalent display of oligosaccharide to amplify the carbohydrate-protein interactions. In addition to multivalency, we have shown that shape of the multivalent probe also influences CLIs. In this review article, we have provided detail summary of the biological significances of glyco-gold nanoparticles of different shapes, ranging from bacterial, cellular to zebrafish model.

INTRODUCTION

Metallic Nanoparticles (NPs), such as gold, silver, iron, and CdSe are the class of multivalent probes found to have significant applications in biomedical systems ranging from imaging, sensing, drug delivery and gene targeting [1-3]. Being rigid systems, metallic NPs can also be easily synthesized in large quantities with different sizes, shapes and orientations and can also be easily decorated chemically and biologically [4-7]. Among these wide range of NPs gold is widely explored scaffold for their biomedical applications because of their excellent stability and solubility in biological medium, ease of obtaining different sizes and various morphologies (rod, sphere, star, cube and spindle) and tunable optical properties associated with surface plasma resonance [8,9].

Carbohydrate-Protein Interactions (CPIs) are one of the most significant and major events on cell surfaces [10-12]. Cell surface glycans recognizes different pathogens, toxic materials, and cells with high selectivity and sensitivity through cis/trans binding with the proteins. Therefore, carbohydrates are of central importance in the development of next-generation biomarkers. Generally, CPIs are found to be weak, which has been compensated by nature through the multivalent presentation of ligands. Major research efforts are put into mimicking the bio-events by replicating the multivalent scaffolds [13]. Glycan functionalized NPs provides versatile multivalent scaffolds, which could fine-tune CPIs by varying size, orientation and density of the sugars on their surfaces [14-20].

The outer topology of AuNPs can be easily functionalized with glycans of interest through the simple assembling of thiol-terminated sugars on the gold surface with the solid chemical compositions, which gives the multivalent presentation of glycans in a globular fashion almost mimicking the glycocalyx of the cell surface. Glyco-AuNPs could further increase the avidity of CPIs by tuning their optical and electrochemical properties. Being less toxic compared to other NP systems such as quantum, dots AuNPs have been thoroughly used to decorate more than one sugar for targeting HIV, bacteria, modulation of immune responses, and studying CPIs and carbohydrate-carbohydrate interactions [4-7]. Similarly, enormous effort has been put into developing gold nanodots and nanoclusters for the sensitive and selective detection of E. coli [21-24]. Similarly Au rods modified with aptamer switch probe was used successfully for multimodal cancer therapy [25]. In all these investigations, the shapes of AuNPs were kept constant to validate the binding with bacteria, cells or organs, limiting the assessment of the role of the different shapes of NPs involved in specific CPIs.

Recent studies have demonstrated that different shapes of the AuNPs influenced the cellular uptake, bio distribution, and immune response, making shape as one of the important factors for understanding the CPIs and developing new biomaterials [26]. Efforts have been taken in the direction of functionalizing different shapes of AuNPs with antibodies, peptides, aptamers to enhance their specificity for tumors, immune responses and bio sensing processes [27-30]. However, a systematic investigation of shape dependent CPIs with the same volume and sugar density and its potential applications have not been evaluated majorly. In this review, we summarized the work done by our group towards understanding the role of different morphologies of glycol-AuNPs on CPIs in a biological system. The complete account of various shapes of AuNPs functionalized with simple monomeric sugars, homo and hetero glycodendrons and their interactions in in vitro and in vivo systems along with bacterial detection are given in detail.

SHAPE-DEPENDENT GLYCO-GOLD NANOPARTICLES BACTERIAL ADHESION

To demonstrate the significance of shape-dependent glyco-AuNPs mediated biological interactions, we first reported the use of three distinct shapes of glyco-AuNps in bacterial recognition and inhibiting bacterial infection. Three different shapes (rod, sphere, and star) of gold nanoparticles coated with mannose and galactose sugar substrates and PEG were used to quantify the binding affinity with E. coli [31] (Figure 1). To profile the potential applications of the shape dependent CPIs, inhibition of E. coli infection of HeLa cells was quantified (Figure 1). Our studies showed that the rod-shaped AuNPs functionalized with mannose had substantial sensitivity compared to that of star-shaped and spherical shaped AuNPs. Factors such as self-assembly and effective surface contact are critical for sensitive adhesion. In a more general perspective, blockage of E. coli infection by rod mannose-AuNPs may open opportunities to develop efficient medicines for urinary or digestive tract infections.

EFFECT OF HOMO AND HETEROGLYCODENDRON FUNCTIONALIZED VARIOUS SHAPE GOLD NANOPARTIC LES ON BACTERIAL BINDING

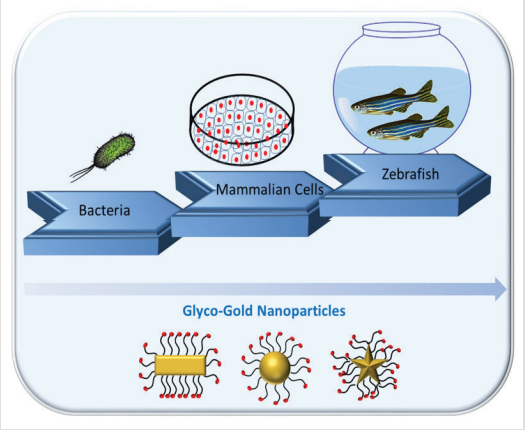
In addition to multivalency and shape, heterogeneity of carbohydrate scaffold is a crucial parameter which affects the avidity of CPIs [32]. To study the role of heterogeneity on glyco-AuNPs biological interactions. Homo and hetero glycodendrons of mannose and galactose were synthesized by stepwise addition of sugar unit to tripod active ester followed by fourth arm functionalization with thiol linker, which was then self-assembled on rod and spherical AuNPs [33]. Carbohydrate-lectin binding of Mannose homodendrons conjugated AuNPs showed a high affinity towards Con A lectin compared to heteroglycodendron. Further rod-shaped homodendron conjugated AuNps showed ~2 fold higher affinity towards Con A compared to sphere indicating the importance of homo-multivalency for lectin recognition. Similar kind of observations is found in case of binding studies with E. coli ORN 178 and 208. Rod-shaped homo mannose dendrons showed 5 to 10-fold higher bacterial aggregations compared to heteroglyco-dendron and sphere shaped homo and hetero glycol-dendrons (Figure 2). Finally, we conclude that homomultivalency with specific shape influence the CPIs predominantly, while heteromultivalency has very less impact (Figure 2).

IN VITRO SHAPE-DEPENDENT GLYCO-GOLDNPS UPTAKE

We next investigated the shape dependent uptake of Glyco-Gold Nanoparticles (G-AuNPs) in different cancer cell lines. Among all NPs only Mannose modified NPs showed inhibition Con A and DC-SIGN lectin binding, on top of this rod mannose NPs showed 3-fold potent inhibitions of lectins compare to sphere and star [34]. These NPs further in cellular internalization studies showed that mannose rod AuNPs internalized three-fold higher compared to sphere and star in DC-SIGN transfected HeLa cells while galactose and PEG NPs showed less internalization (Figure 3). In case of MDA-MB-231 cells which are expressing both mannose and galactose receptors showed more internalization of mannose and galactose rod NPs compared to other NPs. Uptake of mannose rod NPs was greater compared to galactose NPs, suggesting that mannose receptors are more active than galactose receptors on the cell Figure 3. In case of HepG2 cells expressing a high level of asialoglycan galactose receptors rod galactose, NPs internalized more compared to rest of NPs. These findings indicate cell surface carbohydrate receptors guided internalization was influenced by nano-rods. The probable reason for the highest internalization of rod-AuNPs may be because of high aspect ratio, a high contact area of rod-AuNPs with respect to external stimuli and self-assembly of rod-AuNPs. A further mechanism of uptake of these mannose rod NPs was evaluated using various inhibitors of endocytosis pathway by ICPMs and dark field imaging techniques. It was found that chlorpromazine treated DC-SIGN transfected HeLa cells showed lesser internalization of mannose rod NPs. These results proved that rod NPs internalized through energy-dependent, clathrin-mediated endocytosis (Figure 3).

SHAPE-DEPENDENT GLYCO-AUNPS BIODISTRIBUTION AND SEQUESTRATION

Finally, we investigated the bio-distribution of different shapes of glyco-gold nanoparticles (GAuNPs) in zebrafish system (Figure 4) [35]. In vivo experiments showed that rod-AuNPs exhibited the fast uptake, while, star-AuNPs displayed prolong sequestration, demonstrating its potential therapeutic efficacy in drug delivery (Figure 4). Collectively, these results revealed the benefits of different shapes in carbohydrate-mediated Figure 4. Interactions and also illustrate zebrafish as a potential in vivo system to study carbohydrate-mediated interactions in quick time (Table).



Nature utilizes multivalent display of oligosaccharide to amplify the carbohydrate-protein interactions. In addition to multivalency, shape of the multivalent probe also influences the binding avidity. In this review article we are providing detail account of biological significance of glyco-gold nano particles of different shapes ranging from bacterial, cellular to zebra fish model.

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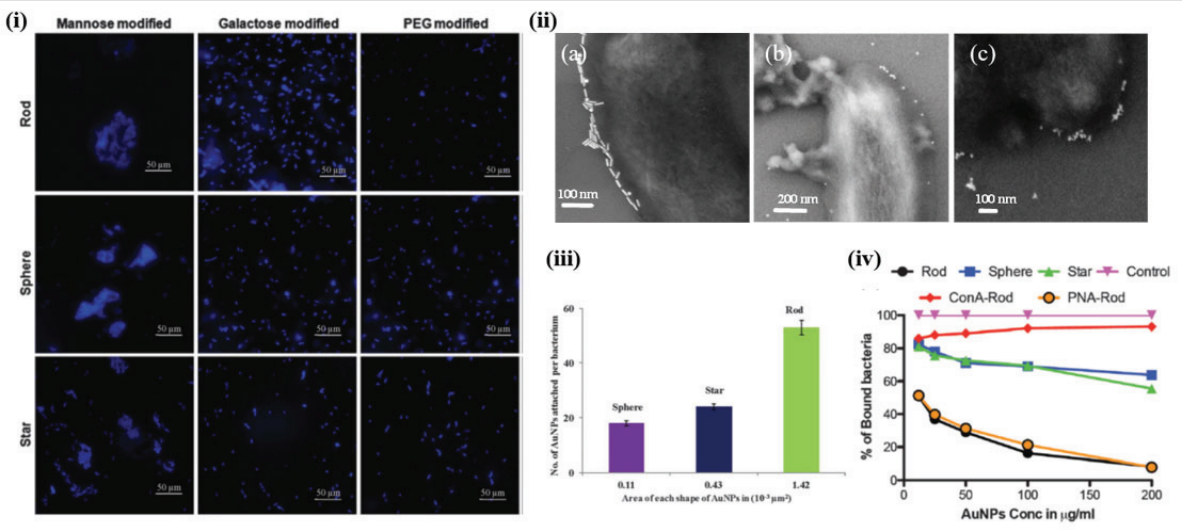

Figure 1: (i) E. coli strain ORN 178 aggregation using various shapes of glyco-AuNPs; (ii) SEM images of E. coli ORN 178 strain (a) Mannose-rods; (b) Mannose-sphere; (c) Mannose-star; (iii) Man-AuNPs (conc. 0.8 μg ml-1) bound to the surface of E. coli ORN 178 according to the surface availability; (iv) Inhibition of E. coli infection of HeLa cells.

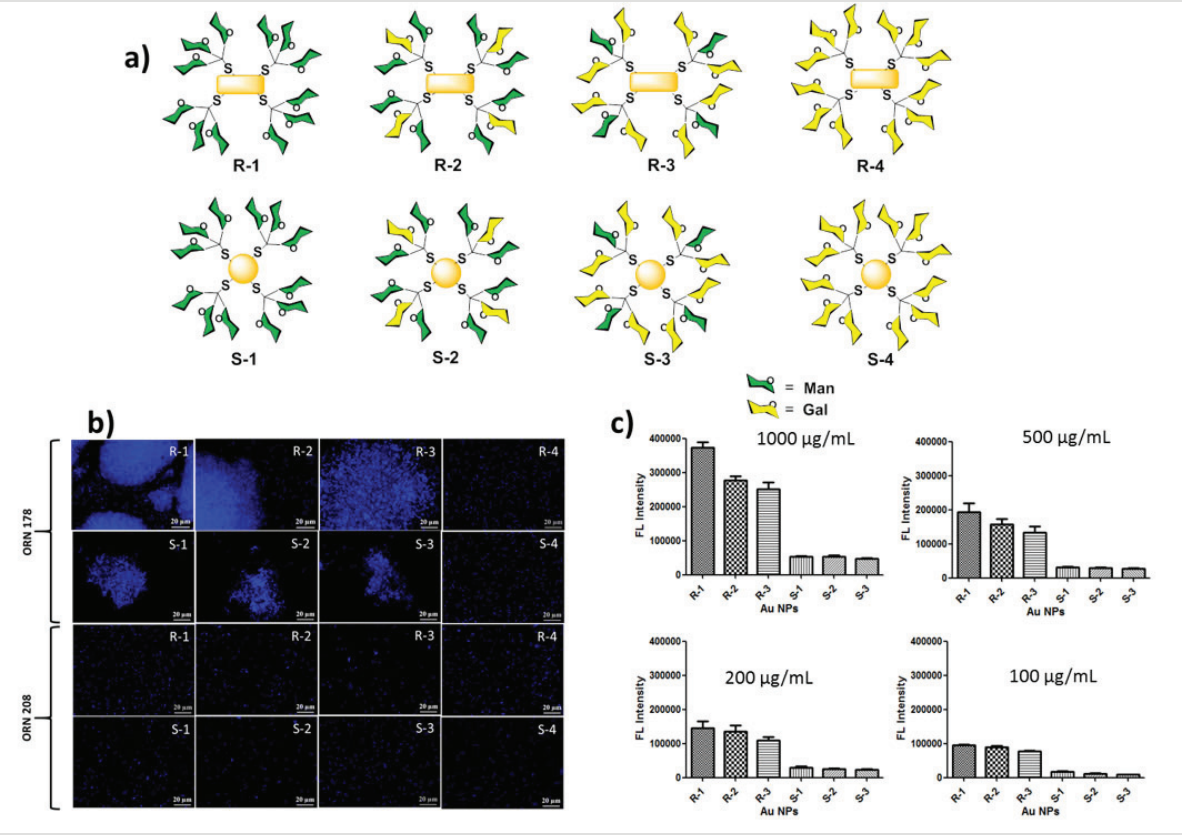

Figure 2: (a) Homo and Hetero glycodendron conjugated to different shapes of AuNPs; (b) Aggregation of E. coli strains ORN 178 and ORN 208 using Homo and Hetero glycodendron conjugated AuNPs; (c) Relative fluorescence intensity of bacterial aggregation at various AuNP concentrations.

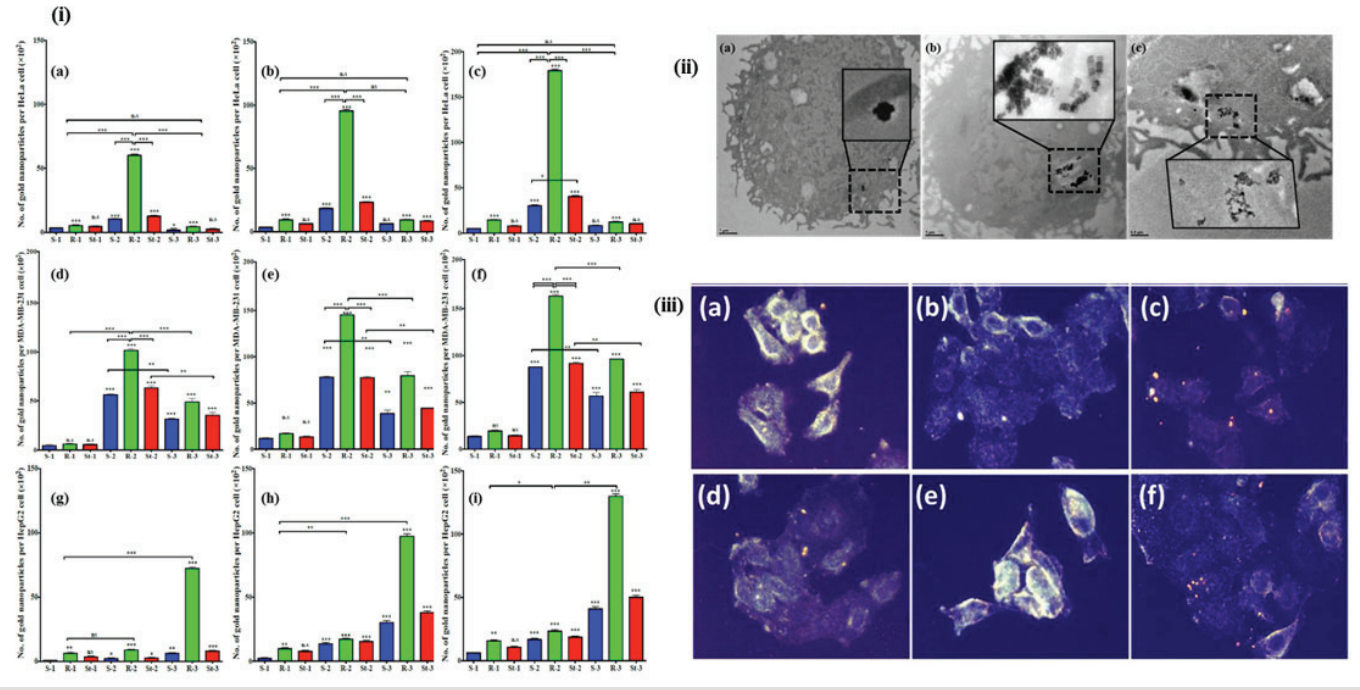

Figure 3: (i) Statistical analysis of ICP-MS data of HeLa (DC-SIGN transfected), MDA-MB-231 and HepG2 at different time intervals. (a) HeLa- 4 h; (b) HeLa- 24 h; (c) HeLa- 48 h; (d) MDA-MB-231- 4 h; (e) MDA-MB-231- 24 h; (f) MDA-MB-231- 48 h; (g) HepG2- 4 h; (h) HepG2- 24 h; (i) HepG2- 48 h. Data are presented as the mean ± SEM for three independent experiments (***P < 0.001, **P < 0.01 *P < 0.05 and n.s = not significant): (ii) TEM images of the HeLa cells containing (a) S-2; (b) R-2 and (c) St-2 after 24 h: (iii) Dark field microscopic images of the HeLa cells treated with inhibitor for 30 min followed by R-2 after 4 h. (a) Control R-2 after 4 h; (b) NaN3 (50 mM); (c) dynasore (50 µM); (d) chlorpromazine (25 µM); (e) Me-β-cyclodextrin (10mM); (f) mannose-9-glycan (50 mM).

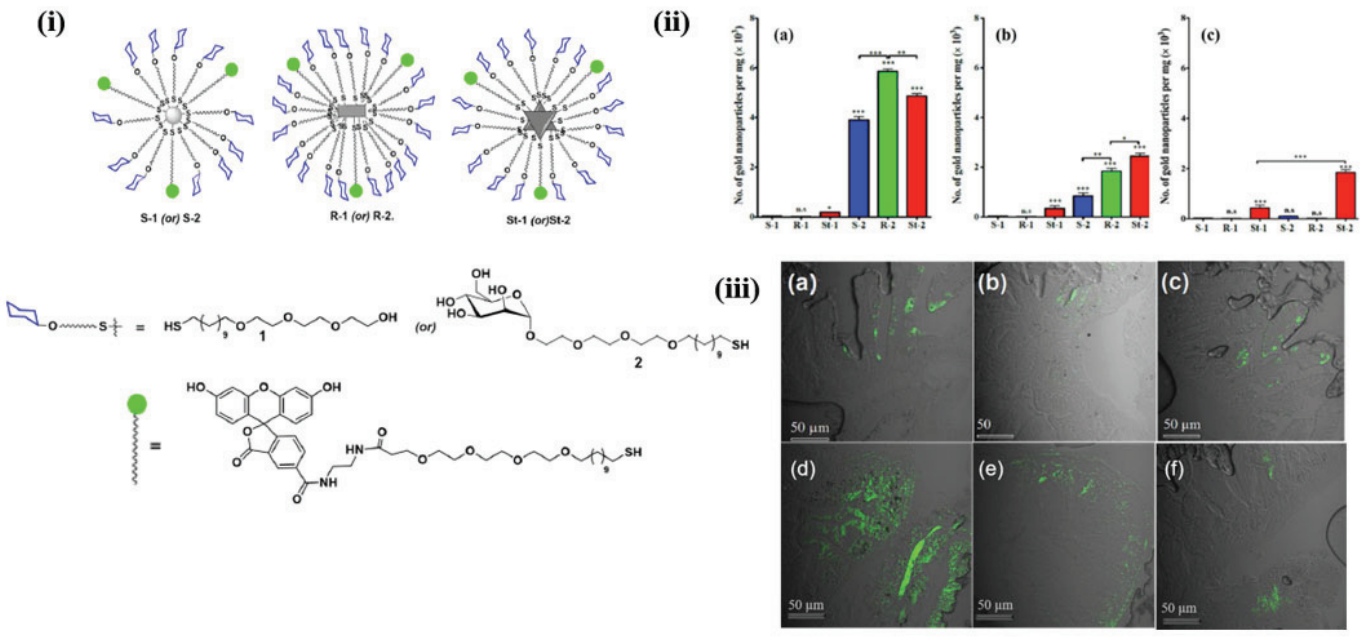

Figure 4: (i) Fluorescence conjugated glyco-AuNPs; (ii) Statistical analysis of ICP-MS data of Zebra fish digestive system after (a) 4 h; (b) 24 h; (c) 48 h; (iii) Con focal images of Zebra fish digestive system injected with Fluoresce in conjugated glyco-AuNPs (a) S-1, 4 h; (b) R-1, 4 h; (c) St-1, 4 h; (d) R-2, 4 h; (e) R-2, 24 h; (f) R-2, 48 h.

CONCLUSIONS

The results of this study permit the following conclusions and suggestion regarding the shape dependent glyco-gold nanoparticles interactions. (a) The bacterial adhesion with glyco-glyconanoparticles are sensitive to shape of the nanoparticles. Sensitivity is higher in rod-shaped gold-nanoparticles compared to spherical and star-shaped gold-nanoparticles. Similarly, in-vitro and in-vivo analysis indicated that shape indeed one of the crucial parameter to find tune the carbohydrate-protein interactions. Overall, an insight into how the particular shapes of the nanoparticles translate its information to the final carbohydrate-protein interactions generates the new set of rules to synthesize smart glycoprobes to target and imaging.

ACKNOWLEDGEMENT

Financial support from the IISER, DST is gratefully acknowledged. S. S. thanks CSIR-SRF and P. C. thanks DBT-Biocare for supporting their fellowships

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