Hyaluronic Acid - Gold Nanoparticle/Interferon α Complex for Targeted Treatment of Hepatitis C Virus Infection

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Statement of Purpose: Gold nanoparticles (AuNPs) have been widely investigated as drug delivery carriers due to their biocompatibility, simple synthesis, facile surface modification, and versatile conjugation with biomolecules. Meanwhile, hyaluronic acid (HA) is a biocompatible, biodegradable, non-immunogenic, non-toxic, negatively charged, and limear polysaccharide in the body [1]. HA has antifouling effect on the prevention of protein adsorption and opsonization, and can be delivered target-specifically to liver tissues with HA receptors such as HARE and CD44 [2]. Here, instead of nonspecific polyethylene glycol (PEG) conjugated interferon α (IFNα) for the clinical treatment of hepatitis C virus (HCV) infection, a target-specific long-acting delivery system of IFNα was successfully developed using the hybrid materials of AuNP and HA.

Methods:

Preparation of HA-AuNP/IFNα complex: The HA-AuNP/IFNα complex was prepared by chemical binding of thiolated HA and physical binding of IFNα to AuNP.

Quantification of IFNα accumulated in the liver: After single intravenous injection of HA-AuNP/IFNα complex to mice, the amount of IFNα in the liver tissue was determined by ELISA.

Hepatocellular distribution: After single intravenous injection of HA-AuNP/IFNα complex, the hepatocellular distribution was analyzed by ICP-AES and TEM.

Quantification of OAS1 expression levels in the liver: The *in vivo* antiviral activity of HA-AuNP/IFNα complex was assessed from the elevated expression levels of OAS1 in the Western blot analysis.

Results: Figure 1 shows a schematic representation for the target specific HA-AuNP/IFNα complex. After single intravenous injection, native IFNα and PEGintron were not detected in 7 days because of the rapid clearance. However, HA-AuNP/IFNα 110 complex showed the highest level of IFNα remaining even after 7 days (Figure 2A). The hepatocellular distribution of HA-AuNP/IFNα complex was investigated using ICP-MS and TEM. As shown in Figure 2B, TEM clearly visualized the well dispersed HA-AuNP/IFNα 110 complexes uptaken to liver sinusoidal endothelial cells (LSECs). HA-AuNP/IFNα complex drastically enhanced the expression level of OAS 1. The OAS 1 is a protein induced by IFNα which participates in innate immune responses to viral infection. HA-AuNP/IFNα 110 complex was the most effective for the production of the OAS 1, followed by AuNP/IFNα 120, HA-AuNP/IFNα 75, PEG-Intron, and native IFNα 7 days post-injection (Figure 3). HA might be effective to reduce the uptake by RES and prevent enzymatic degradation of IFNα, making possible the target specific delivery of the complex to the liver tissue [3].

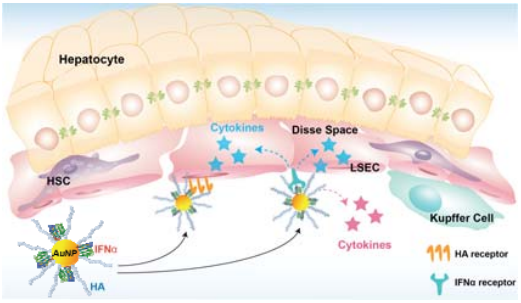

Figure 1. Schematics of HA–AuNP/IFNα complex.

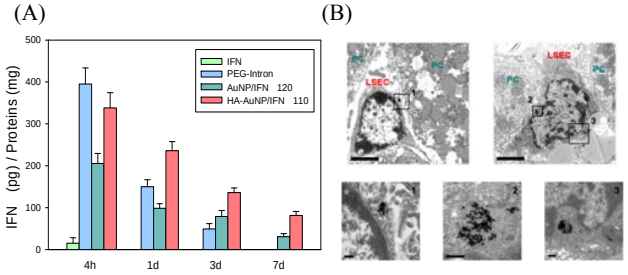

Figure 2. (A) IFNα content accumulated in the liver tissue 4 h, 1, 3 and 7 days after intravenous injection. (B) TEM images of HA–AuNP/IFNα complexes in representative LSECs in the liver tissue.

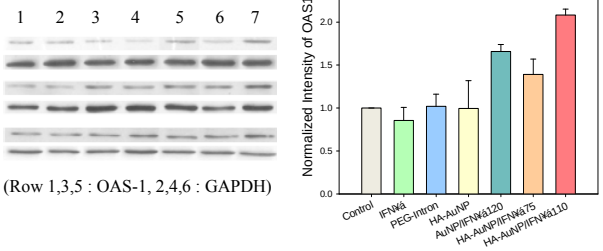

Figure 3. (A) Western blots of OAS 1 in mouse liver tissues 7 days post-injection. (B) Quantification of the expressed OAS 1 level by densitometric analysis (n = 3).

Conclusions: HA–AuNP/IFNα complex was successfully developed for target-specific treatment of HCV infection. HA–AuNP/IFNα complex was effectively delivered to the liver by HA receptor mediated endocytosis promoting the IFNα-induced cytokine release. Furthermore, the HA-AuNP was thought to be effectively exploited to prepare a diverse protein complex for target-specific systemic treatment of various liver diseases.

References:

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