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Receptor-Mediated Gene Delivery Using Chitosan Derivatives

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Chitosan has been considered to be a good candidate for gene delivery system, since it is already known as a biocompatible, biodegradable, and low toxic material with high cationic potential. However, low specificity and low transfection efficiency of chitosan need to be overcome prior to clinical trial. In this study, we focused on the chemical modification of chitosan for enhancement of cell specificity and transfection efficiency and we investigated the potential of clinical applications. To induce the receptor-mediated endocytosis into liver cells having asialoglycoprotein receptor (ASGP-R), water-soluble chitosan was coupled with lactobionic acid (LA) bearing galactose group as the specific ligand to ASGP-R of liver cells. Also, mannosylated chitosan (MC) was prepared by coupling water-soluble chitosan with mannopyranosylphenylisothiocyanate bearing mannose group to induce the receptor-mediated endocytosis into dendritic cells (DCs) having mannose receptor. And their physicochemical properties, morphology, cytotoxicity, and transfection efficiency of the complexes *in vitro* and *in vivo* were studied. The potential of antitumor effect *in vivo* by using mannosylated chitosan for delivery of IL-12 genes was also evaluated.

Galactosylated chitosan (GC) was successfully prepared and transfection efficiency into HepG2 which has ASGP-R was higher than that into HeLa without ASGP-R. MC was successfully prepared and its potential as a targeting gene delivery system to DCs was evaluated. It had low cytotoxicity and exhibited much enhanced gene transfer efficiency on the macrophage cell lines compared with chitosan itself. Increased IL-12 production by DC induced increase of IFN-γ production. *In vivo* study shows that intratumoral delivery of IL-12 genes using MC is an effective method of generating antitumor immunity.

In conclusion, it is expected that relatively non-toxic GC and MC is suitable for repeated administration to maintain sustained gene expression, thereby opening the possibility for cancer gene therapy.