Biotin-conjugated Block Copolymeric Nanoparticles for Tumor-targeted Drug Delivery System

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Statement of Purpose: Although there have been significant progress in the development of new anticancer agent and anticancer technology, cancer is still one of major cause of death. Currently used chemotherapeutic drugs are systemically active and are not selective for cancer cells. Thus, high systemic dosages are required to reach therapeutically effective concentration at the tumor site, resulting in severe side effects. One approach that overcomes this limitation is the active targeting of tumors with particulate drug carriers [1,2]. Polymeric nanoparticles can be delivered to specific sites by size-dependent passive targeting or by active targeting through conjugation of targeting molecules [3]. Nanoparticles conjugated with targeting molecules (e.g., antibody, sugar and vitamins) could achieve a high degree of selectivity to a specific organ and enhance the internalization of drug into target cells [4]. Especially, rapidly dividing cells such as those present in solid tumor cancers requires great amount of certain vitamins, such as folate, vitamin B_{12} and vitamin H, and as a consequence the receptors involved in uptake of the vitamins are over-expressed on the surface of cancer cells [5]. Therefore, in this study, we focused on the biotin-conjugated block copolymeric nanoparticles for tumor-targeted drug delivery system.

Methods: The main objective of this study is to prepare biotin-conjugated poly(ethylene glycol)/ poly(ε-caprolactone) (PEG/PCL) amphiphilic block copolymeric nanoparticles and investigate their feasibility as ligand-mediated drug carrier for targeting anticancer therapy. Biotin-conjugated PEG/PCL block copolymers were characterized by FT-IR, ^{1}H-NMR, 2,4,6-trinitrobenzene sulfonic acid (TNBS) assay and GPC measurements. The particle size, surface characteristics and loading efficiency of anticancer were also investigated. The in vitro release kinetics of anticancer drug from the biotin-conjugated PEG/PCL nanoparticles was determined depending on the molecular weight of copolymers. In addition, in vitro cytotoxicity study was performed using normal and cancer cells, and compared their biotin ligand-dependent cytotoxicity.

Results/Discussion: Biodegradable PEG/PCL amphiphilic nanoparticles conjugated with biotin ligand were prepared as targeted chemotherapy for cancer treatment. For biotin-conjugated PEG/PCL block copolymers, the size of nanoparticles formed was about 87~117 nm depending on the molecular weight of the block copolymers. As shown in Figure 1 the particles exhibited sub-micron size with spherical shape. However, the size of particles observed by FE-SEM was smaller than those obtained by light scattering. It is because the diameter of block copolymeric nanoparticles with micelle structure measured by light scattering reflected the hydrodynamic diameter of micelles, which swelled in aqueous solution, while that observed by FE-SEM was the diameter of dried micelles.

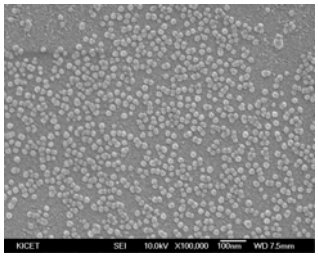

Figure 1. Biotin-conjugated PEG/PCL nanoparticles observed by field emission scanning electron microscopy (FE-SEM).

The loading efficiency of the hydrophobic anticancer drug paclitaxel was influenced by the chain length of hydrophobic PCL segment and feed weight ratio of drug/copolymer. The release of paclitaxel from biotin-conjugated PEG/PCL nanoparticles showed no initial burst effect and sustained release kinetics. From the cytotoxicity study, biotin-PEG/PCL nanoparticles itself exhibited relatively high cell viability (more than 85%) at 0.005~1.0 μg/ml of concentration (Figure 2)

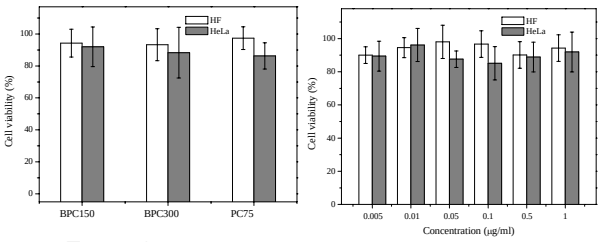

Figure 2. In vitro cytotoxicity of biotin-conjugated/ nonconjugated amphiphilic block copolymers.

To evaluate the targeting property into cancer cells of biotin-conjugated nanoparticles, the viability of human fibroblasts and HeLa cells was also determined using paclitaxel-loaded nanoparticles with/without biotin ligand. Paclitaxel-loaded PEG/PCL nanoparticles with biotin group exhibited higher and selective toxicity for cancer cells, whereas the paclitaxel-loaded nanoparticles without biotin group showed similar cytotoxicity regardless of normal or cancer cells.

Conclusions: These results suggested that the biotin-conjugated PEG/PCL nanoparticulate drug carriers could be selectively delivered into cancer cells through biotin-receptor mediated endocytosis.

References:

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