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大阪府立大学博士（応用生命科学）学位論文

Drug delivery system for poorly water-soluble anti-tumor drug
by using intravital transporter protein

生体内輸送蛋白質を用いた
難水溶性抗癌剤に対するドラッグデリバリーシステム

(論文要約)

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Most synthesized compounds in the drug discovery process, especially anti-tumor drug, are generally water-insoluble and have severe side effects. Some common approaches to improve the solubility of anti-tumor drugs are the chemical modification of drugs and the usage of solubilizers such as organic solvents, surfactants, and pH modifiers. However, the chemical modification of drugs decreases their potency in many cases. The usage of solubilizers is limited due to their toxicity and tendency to cause drug instability. In addition, anti-tumor drugs inhibit the rapid growth of normal cells, such as bone marrow and gastrointestinal tissue, and lead to the undesirable side effects due to their inability to differentiate between normal and tumor tissue. Therefore, these compounds are limited the clinical use, and dropped from development in the preclinical stage in many cases. Under the circumstances, a drug delivery system (DDS) is focused as a novel approach to overcome the poor solubility and severe side effects of anti-tumor drugs. Different types of nano-sized delivery vehicle, such as liposome, polymer micelle and dendrimer, have been studied widely. However, these delivery vehicles have many problems, such as immunogenicity, hemolysis and targeting property of the delivery vehicles. Therefore, it is essential to develop a novel and safe delivery vehicle possessing tumor-targeting property.

Lipocalin-type prostaglandin D synthase (L-PGDS) is known to be a multifunctional protein acting as a PGD₂-producing enzyme, a scavenger of reactive oxygen species, and a secretory transporter protein for several small lipophilic molecules. L-PGDS has a typical lipocalin β -barrel fold, and the interior of this barrel forms a hydrophobic cavity that can bind a large variety of lipophilic ligands within it. The previous study demonstrated that L-PGDS improved the solubility of various poorly water-soluble

drugs.

In this study, the aim is to construct a novel tumor-targeting DDS by using human L-PGDS as a delivery vehicle for the poorly water-soluble anti-tumor drugs. In chapter 1 of this thesis, the feasibility of a DDS using human L-PGDS for 7-ethyl-10-hydroxy-camptothecin (SN-38), poorly water-soluble anti-tumor drug, was evaluated. In the presence of 2 mM L-PGDS, the concentration of SN-38 increased to 1.7 mM, which was 1,130-fold as compared with that in PBS. The intravenous administration of SN-38/L-PGDS complexes resulted in a pronounced anti-tumor activity without the typical side effects of SN-38 such as intestinal mucositis. In addition, human L-PGDS did not show any anaphylaxis responses in mice, thus considering that L-PGDS would be a non-immunogenic and safe drug delivery vehicle.

In chapter 2, in order to develop the tumor-targeting DDS, the tumor-targeting peptides (iRGD or CRGDK) were introduced into L-PGDS at a C-terminal region. L-PGDS-iRGD and L-PGDS-CRGDK were purified by simple methods such as affinity and gel filtration chromatography. These proteins showed same CD spectra as L-PGDS in the far- and near-UV regions. In addition, in the presence of 2 mM L-PGDS-iRGD and L-PGDS-CRGDK, the concentration of SN-38 increased to 1.7 mM. Furthermore, *in vitro* cellular uptake and *in vivo* fluorescence imaging revealed that L-PGDS-iRGD and L-PGDS-CRGDK accumulated in tumor tissue, and internalized into cancer cells.

These results, taken together, demonstrated that the complex formulation using human L-PGDS makes it possible to use SN-38, poorly water-soluble anti-tumor drug, for cancer treatment. In addition, it is considered that L-PGDS introducing the tumor-targeting peptide is a potent delivery vehicle for anti-tumor drugs.