

Drug Delivery System for Poorly Water-soluble Anti-tumor Drug SN-38 Utilizing L-PGDS

Masatoshi Nakatsuji, Haruka Inoue, Masaki Kohno, Mayu Saito, Syogo Tsuge, Shota Shimizu, Osamu Ishibashi

Osaka Prefecture University, Graduate School of Life and Environmental Sciences
1-1 Gakuen-cho, Nakaku, Sakai, Osaka 599-8531, Japan
st201031@edu.osakafu-u.ac.jp; inoueharuka@bioinfo.osakafu-u.ac.jp; sr202016@edu.osakafu-u.ac.jp;
st201022@edu.osakafu-u.ac.jp; su201027@edu.osakafu-u.ac.jp; sv201025@edu.osakafu-u.ac.jp;
ishibashi@biochem.osakafu-u.ac.jp

Takashi Inui

Osaka Prefecture University, Graduate School of Life and Environmental Sciences
1-1 Gakuen-cho, Nakaku, Sakai, Osaka 599-8531, Japan
inuit@bioinfo.osakafu-u.ac.jp

Extended Abstract

Lipocalin-type prostaglandin D synthase (L-PGDS) is a multi-functional protein that acts as not only a PGD₂-synthase but also a reactive oxygen species scavenger and a secretory transporter protein for several small lipophilic molecules. We recently reported that the drug delivery system (DDS) utilizing L-PGDS as a delivery vehicle could facilitate the pharmaceutical development and clinical usage of poorly water-soluble drugs.

7-ethyl-10-hydroxy-camptothecin (SN-38) is an active metabolite of an anti-tumor agent, irinotecan hydrochloride (CPT-11). SN-38 exhibits 1,000-fold more potent anti-tumor activity as compared with CPT-11. However, the poor solubility of SN-38 prevents clinical usage of this molecule.

Here, we report the development of the DDS utilizing L-PGDS which enables a direct clinical usage of SN-38. The solubility of SN-38 in PBS with 2 mM L-PGDS was 1.7 mM which was 1,100-fold higher than that without L-PGDS. Calorimetric analysis revealed that the dissociation constant of SN-38 for L-PGDS was 59.2 μ M, and that L-PGDS formed a 1:2 complex with SN-38.

Next, we evaluated the anti-tumor activity of SN-38/L-PGDS-complex using human colorectal, breast and prostate cancer cell lines such as Colo201, MDA-MB231, and PC-3. Both SN-38/L-PGDS-complex and CPT-11 reduced the cell viability in a concentration-dependent manner, and the IC₅₀ values were 72 nM and 28 μ M for Colo201 cells, 800 nM and 35 μ M for MDA-MB231 cells, and 11 nM and 9.8 μ M for PC-3 cells, respectively. Thus, the inhibitory effects of SN-38/L-PGDS-complex on cell growth were 44- to 891-fold more potent than those of CPT-11.

Furthermore, we examined the tissue distribution and anti-tumor activity of SN-38 after intravenous administration of SN-38/L-PGDS-complex in human xenograft tumor model (nude mice) bearing colorectal cancer. The concentration of SN-38 in the liver increased to 26 μ g/g tissue at 5 min after the administration of the complex, then afterward decreased in a time-dependent manner and came down to 1.4 μ g/g tissue at 6 h after the administration. In contrast, the concentration of SN-38 in the small intestine was not detected at 5 min, but transiently increased thereafter with a peak at 1 h (8.9 μ g/g tissue). These results suggested that SN-38 in the liver was excreted with the bile into the small intestine. The concentration of SN-38 in the tumor tissue was 0.27 μ g/g tissue at 30 min. This concentration level was maintained thereafter for more than 6 h, possibly due to the lack of lymphatic drainage in the tumor tissue. The anti-tumor activity of SN-38 after the administration of SN-38/L-PGDS-complex was

evaluated by measuring tumor volume. SN-38/L-PGDS-complex (2 mg/kg/d), CPT-11 (4 mg/kg/d) or PBS was intravenously administrated once every other day for 2 weeks. As a result, SN-38/L-PGDS-complex showed a pronounced anti-tumor effect, while did neither CPT-11 nor PBS significantly.

In summary, we showed that L-PGDS could improve the solubility of SN-38, and provided evidence that this drug could exert a potent anti-tumor effect on xenograft tumor model in vivo. Thus, we believe that L-PGDS is a novel and valid DDS carrier for SN-38.