Anti-Tumor Effect of Heparin-Taurocholate Conjugate to Various Kinds of Orthotopic Pancreatic Cancer Animal Model

Hee Jeong Jeong1, Youngro Byun2, Dong Yun Lee1,*

1Department of Bioengineering, College of Engineering, Hanyang University, Seoul 133-791, Republic of Korea
2Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, and College of Pharmacy, Seoul National University, Seoul 151-742, Republic of Korea
dongyunlee@hanyang.ac.kr

ABSTRACT SUMMARY

Pancreatic cancer is classified as an incurable disease because it has the lowest life rate among other types of cancer. In general, heparin is known as anti-coagulant drugs, but has been reported that heparin can have anti-cancer effect. Recently, we developed heparin-taurocholate derivative for improving half-life of heparin in blood stream. Here we evaluated whether the heparin-taurocholate conjugate could have anti-tumor effect on various types of orthotopic pancreatic cancer animal model. Collectively, Heparin-taurocholate conjugate (LHT7) could attenuate the tumor growth of 3 types of pancreatic cancer (from PANC1, MIAPaCa2, RINm cell line) and also reduce the formation of neovascularization in those tumor tissues.

INTRODUCTION

Pancreatic cancer is one of the most incurable diseases because it is very hard to do early diagnosis and has the lowest life rate among other cancers. Surgery, chemotherapy and radiotherapy have been used for the treatment of pancreatic cancer, but it cannot bring any effective result. Therefore, it is required that develop another new method.

Recently, we newly synthesized heparin-taurocholate conjugate (so-called to LHT7) and reported that could significantly suppress tumor growth of Squamous-cell carcinoma (SCC) cancer cells1. So, we hypothesized that LHT7 would inhibit the growth of pancreatic cancer. To confirm this hypothesis, we treated LHT7 to three kinds of orthotopic pancreatic cancer animal model using PANC1, MIAPaCa2 and RINm caner cell lines.

EXPERIMENTAL METHODS

Pancreatic ductal adenocarcinoma cell lines (PANC1 and MIAPaCa2) and pancreatic islet tumor cell (RINm) were purchased from the American Type Culture Collection (ATCC, USA). All cells were cultured in DMEM containing 10% heat-activated fetal bovine serum and 1% antibiotics. All cells were cultured at 37°C in humidified 95% air atmosphere and 5% CO2. 5-week-old male BALB/c nu/nu nude mice were purchased from Nara-Bio Company (Seoul, Korea). All animal studies were approved by the Institutional Animal Care and Use Committee (IACUC, 11-084A) of Hanyang University.

Orthotopic injection and orthotopic implantation technique were carried out with minor modification2,3. 5-week-old male nude mouse were anesthetized with intraperitoneal injection (1 μL/g body weight) of Zoletil 50 (Virbac, France) and Rompun (Bayer Korea, Korea). 3 types of cell lines were detached from the plate and suspended in 50 μL PBS solution (5 × 10⁶ cells/50 μL). Then they were slowly injected into the body of pancreas organ of nude mice. This injection was repeated 2 weeks after first injection for making orthotopic model perfectly. 4-6 weeks after first orthotopic injection, tumor tissues were harvested from the mice and then minced at same size outer parts of the tumor tissues. Single tumor tissue fragment (36 mg, 20 mm³) was implanted into the body of pancreas of recipient nude mice. Then LHT7 (5 mg/kg b.w.) or vehicle (PBS buffer solution) was intravenously injected into the tumor tissue-implanted mice (Q2D × 15, n = 10) for 30 days. Thirty days after initial injection of drug, mice were sacrificed and tumor tissues were dissected. Then tumor tissues weighed and confirmed histologically.

RESULTS AND DISCUSSION

Thirty days after LHT7 injection to 3 kinds of pancreatic cancer orthotopic model, tumor growth of all tumor tissues was significantly attenuated when compared to each control group (Fig. 1). In the case of PANC1 tumor, the average tumor weight of control group was 136.20 ± 7.83 mg, whereas that of LHT7-treated group was 72.10 ± 12.21 mg (Fig 1). For MIAPaCa2 tumor, the average weight of tumor tissue in control group was 145 ± 98.58 mg, whereas that of LHT7-treated group was 84.67 ± 23.54 mg (Fig 2). For RINm tumor, the average weight of tumor tissue in control group was 5537.83 ± 747.84 mg, whereas that of tumor tissue in LHT7-treated group was 2837.92 ± 328.14 mg (Fig 2). By the administration of LHT7, tumor growth of PANC1, MIAPaCa2 and RINm was significantly attenuated (~ 53%, 58% and 51%, respectively). From these results, we found that the injected LHT7 could attenuate the tumor growth regardless of tumor types in pancreatic cancer (specially ductal adenocarcinoma and islet tumor cells in this stud). As on-going work, we are doing the histological evaluation to confirm the inhibition of neovascularization in tumor tissue.
CONCLUSION

Heparin-taurocholate conjugate (LHT7) could affect the tumor growth of 3 kinds of pancreatic cancer (PANC1, MIAPaCa2, RINm cell line) and show anti-tumor effect. Therefore, LHT7 could be a potential drug for pancreatic cancer therapy.

REFERENCES


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