

Synergistic antitumor effects of bisphosphonate and statin in human pancreatic cancer cell lines : An in vitro and viro studies

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論文名	Synergistic antitumor effects of bisphosphonate and statin in human pancreatic cancer cell lines: In vitro and vivo studies (ヒト膵がん細胞に対するビスホスホネートとスタチンの増殖抑制効果の増強作用に関する研究)
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論文審査の結果の要旨

【目的】又は【序論】

1. To examine the antitumor effects of both zoledronic acid, a nitrogen bisphosphonates, and fluvastatin, a statin, when used individually and in combination against pancreatic cell lines *in vitro* and *in vivo*.
2. To clarify the molecular mechanism underlying the synergistic antitumor effect of a combination treatment of zoledronic acid and fluvastatin.

【方法】

In vitro* study*Cell lines**

Human pancreatic ductal adenocarcinoma cell lines: Mia PaCa-2 and Suit-2 cell lines. Both cell lines were kindly obtained from National Kyushu Cancer Center (Fukuoka, Japan). The cell lines were stored at -80°C and thawed at room temperature. Cells were grown in RPMI-1640 media.

Reagents:

Zoledronic acid ([2-(imidazol-1-yl)-hydroxy-ethylidene-1, 1-bisphosphonic acid, disodium salt, 4.75 hydrate]. It was dissolved in sterile ddH₂O. Fluvastatin was diluted in 100% dimethyl sulfoxide and further diluted to reach the desired concentrations. All dilutions were freshly prepared before the experimental use. Mevalonate isoprenoid metabolites, farnesyl pyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP), both were used at a final concentration of 10 µM.

In vivo* study*Animals and Cells:**

Five-week-old male mice BALB/c (nu/nu) weighing 20-22g acclimatized for one week before being injected with cancer cells. The mice were raised in the standard care for specific pathogen free room (SPF room). All mice experiments were maintained and approved by the Ethics committee of Kyushu University. The human Pancreatic cancer cell line Mia PaCa-2 cells was suspended in phosphate buffer solution (PBS) and left to cool off to 5°C before the experiment use. Mice were injected subcutaneously (s.c.) into the right flank with 1x10⁷ Mia PaCa-2 cells.

Reagents:

ZOL and FLU were prepared as mentioned before. For *in vivo* use, ZOL and FLU (100 µg/kg once a week, 15 mg/kg three times a week respectively), were diluted in sterile PBS before being delivered to the animals.

【結果】

A single treatment of zoledronic acid and fluvastatin showed a significant antiproliferative effect against Mia PaCa-2 and Suit-2 cell lines, *in vitro*, in a time and dose dependent manner. Moreover, a potentiated and a clear synergistic antiproliferative effect of a combination treatment of zoledronic acid and fluvastatin against both pancreatic cancer cell lines compared to each single treatment

The synergistic antiproliferative effect exerted by the combination treatment of zoledronic acid and fluvastatin in both Mia PaCa-2 and Suit-2 pancreatic cancer cells were mainly due to the inhibition of FPP and GGPP. These results indicate that the interaction between zoledronic acid and fluvastatin is mainly mediated at least in part through the mevalonate pathway

The result for the *in vivo* study showed that a combination treatment of ZOL with fluvastatin (100 µg/kg once a week, 15 mg/kg three times a week respectively), induced a significant decrease in tumor size in *mice* bearing *Mia PaCa-2* human pancreatic cancer cells compared to each single treatment of zoledronic acid and fluvastatin. All treatments were remarkably well tolerated without any notable side effects on treated mice since no body weight loss or death due to toxicity were observed

【考察】

Combination treatment of zoledronic acid and fluvastatin could be a new approaching strategy for treatment of pancreatic cancer.

博士（創薬科学）の学位に値すると認める。