Poster

[P26-9] P26-9: Oncologic drugs (5): Pharmacokinetics, TDM practice

Chair: Kiyoshi Mihara, Japan

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[P26-9-3] Dihydromyricetin inhibits human osteosarcoma cells metastasis by suppressing uPA activation through the ERK1/2 signaling pathway

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Keywords: Metastasis, Dihydromyricetin, Osteosarcoma

Background

Osteosarcoma is the most common and high-grade primary malignant tumor of bone. The age at presentation ranges from 15 to 19 years of teenagers, is the most common tumor in bone of child. The clinical observation of a shift from benign tumor to malignant neoplasm with the survival rate decrease as the result of metastasis. From extensive studies for metastasis, it is well known that proteinases like MMPs and uPA can destroy the ECM and promote cancer metastasis. Dihydromyricetin is the main components of flavonoids, isolated from the classical Chinese herb Ampelopsis grossedentata. Dihydromyricetin was reported to have various pharmacological activities such as antioxidation, anti-inflammation, and anticancer effects. Recently, reference showed that Dihydromyricetin inhibits migration and invasion of hepatoma cells through regulation of MMP-9 expression. However, the effect of Dihydromyricetin on human osteosarcoma metastasis and the underlying mechanisms has not been studies yet.

Methods

A wound healing model and Boyden chamber assays in vitro were used to determine the effects of Dihydromyricetin on the migration and invasion of human Osteosarcoma cells. Western blot analysis, casein zymography, RT-PCR, real-time PCR and promoter assays were used to evaluate the inhibitory effects of Dihydromyricetin on uPA expression in these cells.

Results

Our results from wound healing and modified Boyden chamber assays revealed that a treatment of Dihydromyricetin (0, 25, 50, 75, 100 μM) significantly inhibited the abilities of migration and invasion. In addition, human protein array found treatment with Dihydromyricetin its uPA expression was decreased than not treatment with Dihydromyricetin. Moreover, we use casein zymography, western blot, RT-PCR, and real-time PCR to confirm that Dihydromyricetin can effectively inhibit osteosarcoma cell lines secreted u-PA enzyme capacity and reduced protein level and mRNA expression. Western blot result also showed that Dihydromyricetin reduced phosphorylation of ERK in a dose-dependent manner. Furthermore, treatment with DHM led to a decrease in uPA promoter activity in a dose-dependent manner.

Conclusions

Dihydromyricetin possesses the anti-metastatic activity of osteosarcoma cells by transcriptionally repressing uPA via ERK signaling pathways. This may be potentially useful as anti-metastatic agents for osteosarcoma chemotherapy.