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Suppression of Rat Stellate Cell Activation and Liver Fibrosis by a Japanese Herbal Medicine, Inchinko-to (TJ135)

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Introduction

Herbal medicine has been recognized as one of useful treatments for chronic liver diseases. Inchinko-to (TJ135) consists of *Artemisia Capillaris Spike*, *Gardenia Fruit* and *Rhubarb Rhizome*. *Artemisia Capillaris Spike* and *Gardenia Fruit* promote bile secretion [1,2]. *Rhubarb Rhizome* is used for constipation. *Rhubarb Rhizome* contains anthraquinone derivatives, such as aloe emodin and emodin. TJ135 is used for cholestasis, primary biliary cirrhosis [3] and hepatitis C [4] in Japan. Although therapeutic benefit of TJ135 was recently reported on acute liver injury induced by Fas-induced apoptosis of hepatocytes [5], its effect on liver fibrosis has never been studied so far. In the present study, we investigated the effect of TJ135 and its component on the activation of rat hepatic stellate cells in primary culture [6]. *In vivo* effect of TJ135 on an experimental liver fibrosis caused by thioacetamide (TAA) administration was also studied.

Methods

Isolated rat HSCs were cultured on plastic dishes in DMEM in the presence or absence of 10% FBS for 2 days and were successively exposed to TJ135 or its component for the following 2 days. DNA synthesis was evaluated by BrdU uptake. Effect of TJ135 and its component on the expression of smooth muscle alpha-actin and PDGFR beta was evaluated by western blot. Effect of these agents on the phosphorylations of MAPK, Akt, c-raf-1 and PDGFR beta was estimated using phospho-specific antibodies.

In vivo experimental liver fibrosis was induced in rats by injecting TAA. TJ135 was administered every day orally. After 3 weeks, rats were sacrificed. Formalin-fixed liver sections were stained with sirius red.

Results

HSCs exposed to TJ135 dose-dependently maintained quiescent phenotype in culture. TJ135 dose-dependently inhibited serum-stimulated DNA synthesis of HSCs without affecting the expressions of smooth muscle alpha-actin and PDGFR beta. In addition, TJ135 dose-dependently inhibited DNA synthesis of HSCs under PDGF stimulation (20 ng/ml). Analysis of the signal transduction under PDGF stimulation indicated that TJ135 inhibited expressions of phospho-tyrosine at 170 kDa, phospho-Raf, phospho-MAPK and phospho-Akt without affecting their total protein level.

HSCs exposed to *Rhubarb Rhizome*, a TJ135 component, dose-dependently maintained quiescent morphology with dendritic processes. *Rhubarb Rhizome* dose-dependently inhibited DNA synthesis of HSCs, but had negligible effect on the expressions of smooth muscle alpha-actin and PDGFR beta. Further analysis revealed that emodin, a component of *Rhubarb Rhizome*, dose-dependently inhibited DNA synthesis of HSCs.

In vivo, TJ135 administration suppressed the development of liver fibrosis.

Discussion

In the present study, TJ 135 was found to suppress the proliferation of HSC [7] by hampering the action of PDGF-BB. Emodin contained in *Rhubarb Rhizome* may be a major player inhibiting HSC proliferation and morphological transformation into myofibroblasts. *In vivo*, TJ135 was found to suppress the development of liver fibrosis. Thus, TJ135 might have a clinical potential suppressing liver fibrogenesis.

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