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Effect of bone marrow mesenchymal stem cells on the TGF-β1/*Smad* signaling pathway of hepatic stellate

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ABSTRACT. This study investigated the effect of bone marrow mesenchymal stem cells (BMCs) on the transforming growth factor-β1 (TGF-β1)-induced activation of the *Smad* signaling pathway in rat hepatic stellate cells (HSCs). There were four experimental groups: 1) a blank control group, 2) a TGF-β1 treatment group, 3) an MSC-combined group, and 4) an induced MSC-combined group. Isolation and culture of rat liver HSCs *in vitro* and the proliferation of HSCs in each group were detected by MTT method. The expression of α-SMA and the TGF receptors (TβRI and II) were determined by immunohistochemical staining of HSCs in all groups, while *Smad2/3*, *Smad4*, and *Smad7* mRNA expressions were detected by RT-PCR for HSCs in each group. TGF-β1 treatment significantly promoted the

proliferation of HSCs ($P < 0.01$); it has different inhibition effects on the proliferation of HSCs in the MSC-combined group and in the induced MSC-combined group ($P < 0.05$). TGF-β1 treatment also enhanced the expression of α-SMA as compared to the control group ($P < 0.01$). Alternatively, when compared with the pure TGF-β1 group, the MSC-combined group and the induced MSC-combined group showed lower α-SMA expression ($P < 0.05$). Activation of HSCs induced by TGF-β1, TβRI and TβRII fluorescence was (+ + +); the fluorescences of TβRI and TβRII in MSC-combined group and in induced MSC-combined group were (+ +) and (± ~ +), respectively. The expressions of TβRI and TβRII in activated HSCs induced by TGF-β1 were significantly decreased in the MSC-combined group ($P < 0.05$) and in the induced MSC-combined group ($P < 0.01$). The expression of HSC *Smad2*/3 and *Smad4* was reduced in the MSC-combined group ($P < 0.05$) and in the induced MSC-combined group ($P < 0.01$), as compared to the TGF-β1 group. However, the expression of *Smad7* in HSCs was upregulated in the MSC-combined group ($P < 0.05$) and in the induced MSC-combined group ($P < 0.01$). These results indicate that BMCs can inhibit the activation and proliferation of HSCs by downregulating the expression of TβRI and TβRII in the cell membrane of HSCs. Moreover, BMCs can upregulate the expression of *Smad7* and downregulate the expression of *Smad2/3* and *Smad4* in the HSCs induced by TGF-β1, which resulted in an inhibition of HSC activation.

Key words: Hepatic stellate cells; TGF-β1/Smad pathway; Bone marrow mesenchymal stem cells