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A Safe And Effective Way Of Overcoming Liver Fibrosis: Utilization The Secretome Obtained From MFG-E8-transfected Adipose Derived Stem Cells.

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Background : The beneficial effects of ASCs on hepatic fibrosis have been previously suggested, although the therapeutic outcome is still controversial. Herein we utilized Milk Fat Globule-EGF Factor 8 (MFGE8) to reinforce the antifibrogenic effects of ASCs. MFGE8 is a soluble glycoprotein consisting of N-terminal notch-like EGF domains with a highly conserved arginine-glycine-aspartic acid (RGD) motif and C-terminal discoidin-like Factor 5/Factor 8 domains. It has been demonstrated that the activation of hepatic stellate cells (HSCs) was significantly decreased by MFGE8 protein, revealing potent anti-fibrogenic potential of MFGE8. In this study, we were intended to determine the antifibrogenic effects of MFGE8-tranfected adipose-derived stem cells (ASCs) in the mouse model of liver fibrosis.

Methods : For in vitro experiments, we co-cultured MFGE8-transfected ASCs – which had been grown in the 3D cell culture scaffolds – with activated HSCs, thereafter determining the expression of Co1A1, alpha-SMA, MMP2, and TIMP1 using real-time PCR and Western blotting. In vivo model of liver fibrosis was generated by intraperitoneal administration of 200 mg/kg thioacetamide into the BALB/C mice. Subsequently, we infused MFGE8-transfected ASCs into the mouse of liver fibrosis and determined the change of the degree of liver fibrosis using real-time PCR and Western blotting, immunohistochemistry .

Results : In the in vitro model of liver fibrosis, the secretome released from MFGE8-transfected ASCs induced the lowered expression of Co1A1, alpha-SMA, and MMP2 and higher expression of TIMP1 than control ASCs. In the in vivo model of liver fibrosis, the secretome released from MFGE8-transfected ASCs significantly increased the expression of the markers related to anti-fibrosis compared to the effects of the control secretome. In addition, immunohistochemical and Masson-trichrome stains also validated the enhanced anti-fibrotic effects of the secretome released from MFGE8-transfected ASCs. Moreover, the groups injected with the secretome released from MFGE8-transfected ASCs exhibited the significantly reduced serum levels of pro-inflammatory cytokines (interleukin-6 and tumor necrosis factor-gamma) and liver enzymes (AST and ALT) compared to those with control secretome.

Conclusions : The superior therapeutic potential of the MFGE8-secretome over the naïve secretome was demonstrated in terms of higher antifibrogenic, anti-inflammatory, and regenerative potentials. Therefore, the use of secretome released from MFGE8-overexpressing ASCs could be an effective strategy to enhance the therapeutic potentials of ASCs.

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