Therapeutic effect of hepatocyte growth factor-secreting mesenchymal stem cell in established rat liver fibrosis model

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Hepatocyte growth factor (HGF) is known to be a promising therapeutic cytokine to fibrotic diseases such as liver fibrosis. As a 'proof of concept', we addressed first, whether mesenchymal stem cell (MSC) might be useful as a vehicle to carry HGF into fibrotic liver, thus results in a better therapeutic effect than MSC alone and second, what is the mechanism continuous with that. Liver fibrosis was induced by the intraperitoneal injection of dimethylnitrosamine. Adenovirus with HGF cDNA was infected to MSC to provide HGF-secreting MSC (MSC/HGF). Normal or fibrotic rats were intra-splenically injected with the cells, and sacrificed at 12 d after. Evidently, tissue fibrosis measured histochemically was reduced by MSC, and even more by MSC/HGF, corroborating with the HGF level. Surprisingly, collagen level from liver extract measured by Sirius red dye revealed actual decrease comparing to that prior to the injection of the cells, suggesting the lysis of the fibrosis. As expected, transplanted cells in both groups were identified mainly in liver and spleen. HGF mRNA in liver and protein in portal vein were higher in HGF/MSC group than in MSC group. Furthermore, mRNA level of the fibrogenic cytokines, PDGF-bb and TGF- β 1, was significantly decreased by MSC/HGF comparing to MSC. In relation to the decrease of collagen, expression of MMP-9, MMP-13, MT1-MMP and uPA was increased by HGF/MSC, whereas that of Timp-1 and Timp-2 was decreased. Conclusion: MSC is useful as a vehicle to carry HGF into fibrotic liver, thus results in a better therapeutic effect than MSC alone.

Keywords: liver fibrosis, mesenchymal stem cell, hepatocyte growth factor

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