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Expression of Fibrogenesis Markers after Mesenchymal Stem Cells Therapy for Experimental Liver Cirrhosis

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Abstract : Liver fibrosis is a complex of histological changes resulting from chronic liver disease accompanied by an excessive production and deposition of extracellular matrix components in the hepatic parenchyma. Liver fibrosis is a serious medical and social problem. Hepatic stellate cells (HSCs) make a significant contribution to the extracellular matrix deposition due to liver injury. Mesenchymal stem cells (MSCs) have a pronounced anti-inflammatory, regenerative and immunomodulatory effect; they are able to differentiate into hepatocytes and induce apoptosis of activated HSCs that opens the prospect of their use for preventing the excessive fibro-formation and the development of liver cirrhosis. The aim of the study is to evaluate the effect of MSCs therapy on the expression of fibrogenesis markers genes in liver tissue and HSCs cultures of rats with experimental liver cirrhosis (ELC). Materials and methods: ELC was induced by the common bile duct ligation (CBDL) in female Wistar rats (n = 19) with an average body weight of 250 (220 ÷ 270) g. Animals from the control group (n = 10) were sham-operated. On the 56th day after the CBDL, the rats of the experimental (n = 12) and the control (n = 5) groups received intraportal MSCs in concentration of 1×106 cells/animal (previously obtained from rat's bone marrow) or saline, respectively. The animals were taken out of the experiment on the 21st day. HSCs were isolated by sequential liver perfusion in situ with following disaggregation, enzymatic treatment and centrifugation of cell suspension on a two-stage density gradient. The expression of collagen type I (Col1a1) and type III (Col3a1), matrix metalloproteinase type 2 (MMP2) and type 9 (MMP9), tissue inhibitor of matrix metalloproteinases type 1 (TIMP1), transforming growth factor β type 1 (TGFβ1) and type 3 (TGFβ3) was determined by real-time polymerase chain reaction. Statistical analysis was performed using Statistica 10.0. Results: In ELC rats compared to sham-operated animals, a significant increase of all studied markers expression was observed. The administration of MSCs led to a significant decrease of all detectable markers in the experimental group compared to rats without cell therapy. In ELC rats, an increased MMP9/TIMP1 ratio after cell therapy was also detected. The infusion of MSCs in the sham-operated animals did not lead to any changes. In the HSCs from ELC animals, the expression of Col1a1 and Col3a1 exceeded the similar parameters of the control group ($p < 0.05$) and statistically decreased after the MSCs administration. The correlation between Col3a1 ($Rs = 0.51$, $p < 0.05$), TGFβ1 ($Rs = 0.6$, $p < 0.01$), and TGFβ3 ($Rs = 0.75$, $p < 0.001$) expression in HSCs cultures and liver tissue has been found. Conclusion: Intraportal administration of MSCs to rats with ELC leads to a decreased Col1a1 and Col3a1, MMP2 and MMP9, TIMP1, TGFβ1 and TGFβ3 expression. The correlation between the expression of Col3a1, TGFβ1 and TGFβ3 in liver tissue and in HSCs cultures indicates the involvement of activated HSCs in the fibrogenesis that allows considering HSCs to be the main cell therapy target in ELC.

Keywords : cell therapy, experimental liver cirrhosis, hepatic stellate cells, mesenchymal stem cells
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