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FGF4 and HGF promote differentiation of mouse bone marrow mesenchymal stem cells into hepatocytes via the MAPK pathway

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ABSTRACT. Our research demonstrated the potential for mouse bone marrow mesenchymal stem cells (mBMMSCs) to differentiate into hepatocytes *in vitro* and *in vivo*. However, the exact mechanism of this process remains unknown. In this study, we investigated the role of the mitogen-activated protein kinase (MAPK) cell-signaling pathway in the differentiation of mBMMSCs into hepatocytes. mBMMSCs were isolated from femurs and tibias, and hepatic differentiation was induced in Isove's modified Eagle's medium supplemented with 10% fetal bovine serum, containing human growth factor and fibroblast growth factor 4. After seven days of induction, morphological characteristics were examined. For inhibition of signaling molecular activities, the inhibitors p38 (SB203580), ERK1/2 (U0126), and MSK1 (H89) were added to the differentiation medium. Real-time polymerase chain reaction and Western blot analysis were used to evaluate the gene expression profiles

and protein expression of several markers, including the early specific markers of hepatocytes (*AFP* and *FOXa2*), phosphorylated-p38 (p-p38), phosphorylated-ERK1/2 (p-ERK1/2), and phosphorylated-MSK1 (p-MSK1). Expressions of p-p38, p-ERK1/2, and p-MSK1 were effectively inhibited by their respective inhibitors. Expressions of early specific markers, *AFP* and *FOXa2*, in the p38, ERK1/2, and MSK1 inhibitor-treated groups were significantly decreased compared to those of the cytokine-induced control. Notably, the expressions of *AFP* and *FOXa2* in the p38 inhibitor group were more obviously reduced than those in the ERK1/2 inhibitor group. The MAPK signaling pathway, especially p38, is sufficient to drive differentiation of mBMMSCs into hepatocytes. This could increase the efficiency of hepatocyte differentiation, which would benefit clinical applications.

Key words: BMMSCs; MAPK; Hepatocyte; Hepatic differentiation; Cytokines

