SUMMARY

Myofibroblast expansion is a critical event in the pathogenesis of liver fibrosis. The activation of hepatic stellate cells (HSC) to myofibroblast (MFB) results in the enhanced production of extracellular matrix (ECM). We have studied the effect of fibroblast growth factor 1 (FGF-1) on liver MFB. In the second part we investigated effect of transforming growth factor β1 (TGF-β1) and FGF-1 on cell line HSC-T6. Cells were cultured on plastic dishes and in 3D collagen gel mimicking fibrotic tissue.

MFB were isolated by repeated passaging of nonparenchymal liver cell fraction. The transfer of MFB from plastic dishes to collagen gel resulted in the change in their shape and phenotype. The expression of cytokine TGF-β1 and of MFB markers, α-smooth muscle actin (α-SMA) and cellular fibronectin (EDA-FN) on protein level was significantly decreased in collagen gel. The experiments with SB 431542, the inhibitor of TGF-β receptor type I, showed that EDA-FN and α-SMA are differently regulated. EDA-FN expression is dependent on TGF-β1, while the expression of α-SMA is primarily determined by the environment and modified by TGF-β1. EDA-FN is more sensitive to the U0126, the inhibitor of protein kinases MEK 1 and 2. Collagen gel does not change the expression of metalloproteinase MMP-2 but activates the proenzyme. FGF-1, the cytokine possibly involved in liver fibrosis, decreases the expression of α-SMA and increases the expression of EDA-FN in the cells on plastic when used in combination with heparin. The action of FGF-1 is milder in the gel.

HSC-T6 cell line represents well-established model of activated HSC. These cells strongly expressed α-smooth muscle actin (α-SMA) and fibronectin (FN-EDA) after stimulation with TGF-β1, which is a stimulus for MFB differentiation and ECM production. FGF-1 reduced proteins expression to levels comparable with untreated cells. Mild repression of secreted gelatinases was seen in culture media after FGF-1 treatment. The exposure of cells to collagen gel leads to changes in cell morphology and in expression of MFB markers. Lack of α-SMA in cells embedded to collagen gel was detected. When stimulated with TGF-β1, the cells increased expression of FN-EDA, but not α-SMA. Although the cells on plastic and in collagen gel show different properties, FGF-1 reduced expression of FN-EDA in both conditions.

Disrupting TGF-β1 signalling pathway represents a potential strategy for the treatment of fibrosis. We showed that FGF-1 could antagonize signals initiated by TGF-β1 and had influence on progression of liver fibrosis.