Neohepatocytes from alcoholics and controls express hepatocyte markers and display reduced fibrogenic TGF-beta/Smad3 signaling: advantage for cell transplantation?

BACKGROUND: Liver transplantation is the only definitive treatment for end stage liver disease. Donor organ scarcity raises a growing interest in new therapeutic options. Recently, we have shown that injection of monocyte-derived NeoHepatocytes can increase survival in rats with extended liver resection. In order to apply this technology in humans with chronic liver diseases in an autologous setting, we generated NeoHepatocytes from patients with alcoholic liver disease and healthy controls and compared those to human hepatocytes. METHODS: We generated NeoHepatocytes from alcoholics with Child A and B cirrhosis and healthy controls. Hepatocytes marker expression and transforming growth factor (TGF)-beta signaling was investigated by RT-PCR, Western blot, immunofluorescent staining, and adenoviral reporter assays. Glucose and urea was measured photometrically. Phase I and II enzyme activities were measured using fluorogenic substrates. Neutral lipids were visualized by Oil Red O staining. RESULTS: There was no significant difference in generation and yield of NeoHepatocytes from alcoholics and controls. Hepatocyte markers, e.g., cytokeratin18 and alcohol dehydrogenase 1, increased significantly throughout differentiation. Glucose and urea production did not
differ between alcoholics and controls and was comparable to human hepatocytes. During differentiation, phase I and II enzyme activities increased, however remained significantly lower than in human hepatocytes. Fat accumulation was induced by treatment with insulin, TGF-beta and ethanol only in differentiated cells and hepatocytes. TGF-beta signaling, via Smad transcription factors, critically required for progression of chronic liver disease, was comparable among the investigated cell types, merely expression of Smad1 and -3 was reduced (approximately 30 and approximately 60%) in monocytes, programmable cells of monocytic origin, and NeoHepatocytes. Subsequently, expression of TGF-beta regulated pro-fibrogenic genes, e.g., connective tissue growth factor and fibronectin was reduced. CONCLUSIONS: Generation of NeoHepatocytes from alcoholics, displaying several features of human hepatocytes, offers new perspectives for cell therapeutic approaches, as cells can be obtained repeatedly in a noninvasive manner. Furthermore, the autologous setting reduces the need for immunosuppressants, which may support recovery of patients which are declined for liver transplantation.

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