STIMULATION OF HEPATIC OVAL CELL PROLIFERATION BY HEPATOCYTE GROWTH FACTOR GENE TRANSFER

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[Background and aims] Liver regeneration is usually accomplished by proliferation of differentiated hepatocytes. However, when hepatocyte proliferation is impaired, hepatic oval cells proliferate and differentiate into hepatocytes to perform liver regeneration. In addition, since oval cells express several receptors for hepatocyte growth factor (HGF), transforming growth factor (TGFα), transforming growth factor β (TGFβ) and stem cell factor (SCF), oval cells may be under the control of these ligands. To clarify the effect of HGF on proliferation of hepatic oval cells, HGF gene was transferred into liver of the Solt-Farber rat model.

[Materials and methods] pAxCAHGF was constructed by insertion of rat HGF cDNA in CAG promoter driving adenovirus lacking E1A, E1B and E3. In case of pAxCALacZ, LacZ was inserted instead of HGF cDNA. The pellets of 2-AAF, a mito-inhibitor for mature hepatocytes, were subcutaneusly inserted 7 days before 70% partial hepatectomy (PH). In group I, pAxCAHGF ($1x10^9$ pfu) was administered into tail vein just after PH. In group II,pAxCALacZ was infused instead of pAxCAHGF. The rats were sacrificed at 4,7,9 and 13 days after PH. Immunohistochemistry was performed by using antibodies against CK-19,OV-6,c-kit,SCF,PCNA and albumin. RT-PCR of the genes of HGF,c-met,SCF and c-kit was done.

[Results] A preliminary study by using pAxCALacZ showed that pAxCALacZ was expressed mainly in hepatocytes but not in oval cells,suggesting that the HGF gene transduced in this vector acts in a paracrine fashion for oval cells. In group I, expression of HGF gene showed its peak at 4 days and decreased at 7 days. No expression was found thereafter. c-met expression was similar between group I and II. Oval cells appeared at 4 days. They were stained with CK-19 and OV-6 antibodies. The numbers of oval cells at 4,7,9 and 13 days were 18.0 ± 6.3, 147.0 ± 17.0, 200.0 ± 25.4 and 150.0 ± 38.0 in group II. Those in group I were 19.7 ± 2.9, 192.0 ± 23.0, 410.0 ± 44.7 and 374.0 ± 93.1, being higher at 7,9 and 13 days in group I. The numbers of PCNA-positive oval cells in group II at 4,7,9 and 13 days were 16.4 ± 5.7, 78.0 ± 10.2, 65.0 ± 8.3 and 21.5 ± 5.4, on the other hand, they were increased to 17.2 ± 2.5, 126.7 ± 15.2, 142.0 ± 15.6 and 64.0 ± 15.9 in group I. Under these circumstances, SCF mRNA was up-regulated at 7 days in group I. Expression of c-kit mRNA was also higher at any time points in group I than in group II.

[Conclusion] In vivo transfer of HGF gene can accelerate proliferation of hepatic oval cells in rats.