Role of microvesicles derived from adipose mesenchymal stem cells in liver regeneration after partial hepatectomy in rats

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Introduction. There are numerous studies of stimulation of liver regeneration by transplantation of mesenchymal stem cells. Their effect is explained by direct intercellular interactions and paracrine communications. One of the alternative ways to influence on liver regeneration is injection of microvesicles. Microvesicles are extracellular vesicles that contain growth factors and cytokines and play a major role in intercellular paracrine communications. It is said, that in compare to cells microvesicles transplantation is not accompanied by risk of metaplasia and mutations, because they do not contain any genetic information.

Aim. To study the effect of transplantation of mesenchymal stem cells microvesicles derived from adipose fat tissue on liver regeneration after partial hepatectomy in rats.

Methods. Mesenchymal stem cells, isolated from visceral rat fatty tissue (adMSC), were treated by Cytochalasin B to derive microvesicles. These microvesicles were transplanted into portal vein of rats after partial hepatectomy. Control group of rats after partial hepatectomy received injection of PBS. On 2, 5, 7 and 14 days after operation rats were sacrificed. Functional parameters of liver were analyzed by biochemical tests, morphological changes were studied by immunohistochemical staining of liver slices with antibodies to desmin (HSC marker), Ki-67 (proliferation marker), α-SMA (myofibroblasts marker), CK-19 (cholangiocytes marker).

Results. According to immunohistochemistry results injection of microvesicles: 1) inhibits activation of HSC – there were 20% less desmin+ cells; 2) there were no transformation of HSC into α-SMA+ myofibroblasts and no risk of liver fibrosis; 3) inhibition of cellular proliferation. So, Ki-67+ hepatocytes number (area of portal tract and central vein) decreased in compare to control group. Number of Ki-67+ nonparenchymal cells in portal tract area was 2 times less, than in control. 4) there were no differences in CK-19 expression in experimental and control groups. As far as the cellular proliferation and thus liver regeneration was inhibited, we`ve seen higher numbers of ALT levels in experimental group. Decreased regeneration could be also visualized by lower triglycerides and

cholesterol levels, there were less, than normal values. Blood urea nitrogen normalized in control group on 14^{th} day, but in experimental – on 7^{th} day already.

Conclusion. Injection of adMSC microvesicles inhibits general cellular response to partial hepatectomy. Inhibition of hepatocytes activation and proliferation slows down liver regeneration, that is proved by biochemical tests. Inhibition of HSC activation means also lesser risk of their transformation into myofibroblasts and fibrosis development. Thus microvesicles transplantation is not for stimulation of liver regeneration. Probably these inhibitory effects could be applied for treatment of liver fibrosis, that needs to be studied.

All authors have declared no conflicts of interest. Work supported by Program of Competitive Growth of KFU.