# CELL THERAPEUTIC APPROACHES FOR THE TREATMENT OF EXPERIMENTALLY INDUCED LIVER FIBROSIS

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**INTRODUCTION.**

Acute and chronic liver diseases are common in Kazakhstan and other countries. These diseases are known to cause significant disability and death. In many cases, liver transplantation is the last resort for patients with end stage liver disease, but it is extremely expensive procedure associated with many risks. Cell transplantation is a potential therapeutic approach for treatment of liver diseases which could become a viable alternative to organ transplantation. However, morphological and functional changes in the liver of patients suffering from chronic liver fibrosis and cirrhosis restrict the effectiveness of direct cell transplantation. Therefore, extra hepatic sites for cell transplantation could be a good therapeutic approach for compensation of the liver functions. Thus, the aim of our study was to evaluate the engraftment of i.p. injected allogeneic hepatocytes into extra hepatic sites in albino rats with chemically induced liver fibrosis (LF).

**MATERIALS AND METHODS.**

Albino rats were randomly divided into 4 groups as following: (1) intact group (n = 18); (2) rats with induced LF (n = 18); (3) rats with induced LF and transplanted with hepatocytes (n=18); to prevent immune response, groups 2 and 3 were subjected to immunosuppression by cyclosporine A (25 mg/kg, per day); (4) as a control, rats were treated with cyclosporine A only (n = 18). LF was induced with N-nitrosodimethylamine (NDMA), i.p., 10 mg/kg, three times a week for 4 weeks and confirmed by histological analysis of the liver samples. Hepatocytes transplantation (HT) has been performed two days after NDMA exposure cessation by i.p. injection of $5\times10^8$ freshly isolated allogeneic hepatocytes. Liver functions were assessed by quantifying blood biochemical parameters (ALT, AST, GGT, total protein, bilirubin and albumin) at 1 week, 1 month and 2 months after hepatocytes transplantation (HT). To confirm a hepatocytes' engraftment, immunohistochemistry of spleen, intestines, stomach and lungs has been conducted.

**RESULTS.**

We observed 30% mortality rate among rats with LF within 1 week after NDMA exposure cessation, while 100% of animals with HT survived. ALT, AST, GGT activities and bilirubin levels were markedly elevated in blood samples of LF rats compared to the control animals. However HT significantly improved ALT, AST, GGT activity as well as bilirubin levels. We also observed decreased levels of total protein and albumin in blood serum of rats with LF, while HT normalized these parameters. At the same time, we have not detected any statistical differences of studied parameters in the control group (4) treated with Cyclosporine A only, compared with the intact animals. HepPar1immunohistochemical staining of the different tissue sections demonstrated the presence of engrafted hepatocytes mainly within enlarged Peyer's patches (aggregated lymphoid nodules in the lowest portion of the small intestine).

**CONCLUSION.**

The results of our study provide evidence that HT improved animal survival and liver functions by generating an ectopic hepatic mass inside the Peyer's patches. These observations point to the conclusion that hepatocyte transplantation into lymph nodes would improve efficacy of cell –based therapy of patients with liver fibrosis and cirrhosis.

**ACKNOWLEDGEMENT.**

This work was supported by Ministry of Education of Kazakhstan Grant N 0111PK00411.