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P0693 EATING BEHAVIOR CORRECTION IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE DEPENDING ON POLYMORPHISMS OF THE PPARG2 AND ADRB2 GENES

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Introduction: According to the World Health Organization, the health of the population is 68-74% dependent on lifestyle and 18-20% on genetics. At the present stage in the treatment of patients with non-alcoholic fatty liver disease (NAFLD) not enough attention is paid to the study of the individual characteristics of eating behavior (EB) and nutrigenetiki. At the same time, EB violations are a modifiable risk factor, the correction of which can positively modulate nutrigenic features - a possible metabolic response to the use of certain nutrients. Personalized approach is a priority in improving the effectiveness of treatment of patients with NAFLD. The study of nutrigenetics and its application in practice in the correction of nutrition is an important step towards personalized medicine.
Aims & Methods: Fifty patients (26 men and 24 women) with NAFLD were examined. The control group consisted of 30 practically healthy patients reciprocating by sex and age. All patients studied the characteristics of EB (DEBQ questionnaire), anthropometric indicators, lipid and carbohydrate metabolism, the degree of liver steatosis, the area of visceral adipose tissue (CT scan), nutrigenetic features (definition of 5 polymorphisms: Pro12Ala of the PPARG2 gene (rs1801282), Gln27Glu of the ADRB2 gene (rs1042714), Arg16Gly of the ADRB2 gene (rs1042713), Trp64Arg of the ADRB3 gene (rs4994) and Thr54Ala of the FABP2 gene (rs1799883), associated with the risk of metabolic disorders. Patients were prescribed individual nutritional correction for 12 months, taking into account the identified polymorphisms associated with EB violation, namely: carriers of the Pro12Ala genotype of the polymorphism of the PPARG2 gene were prescribed a therapeutic diet with moderate fat intake of 1.1-1.2 g / kg / day and carbohydrate restriction of 2.5-3 g / kg / day, Pro12Pro genotype carriers - diet with restriction of fats up to 1.0 g / kg / day and moderate consumption of carbohydrates up to 3.5-4 g / kg / day.
Results: After 12 months after individual correction, significant positive dynamics of the main anthropometric and laboratory-instrumental indicators were observed: a decrease in body mass index and waist circumference by a factor of 1.2 ($p < 0.05$), a decrease in the level of total cholesterol and low-density lipoproteins of 1.5 and 1.3 times, respectively ($p < 0.001$), the level of triglycerides, 2.1 times ($p < 0.001$) and the increase in high-density lipoproteins by 1.4 times ($p < 0.001$)), a decrease in HOMA-IR in 2.2 times ($p < 0.001$)), liver samples (reduction of alanine aminotr nsferase 2.4 times and aspartate aminotransferase 2.5 times ($p < 0.05$)), CT scan - signs of steatosis (35% increase in liver x-ray density ($p < 0.001$)) and indicators of visceral obesity (a decrease of 2.1 times the area of visceral adipose tissue (($p < 0.001$). In addition, during the control questionnaire, normalization of EB was observed in 86% of patients and a decrease in the degree of eating disorders in 14% of patients compared with baseline indicators ($p < 0.001$).
Conclusion: Thus, the appointment of individual correction of EB taking into account nutritional features for at least 12 months contributes to a significant improvement in metabolic parameters associated with the risk of development and progression of NAFLD, the formation and stabilization of proper eating habits, which improves the effectiveness of treatment of patients with NAFLD.
Disclosure: All authors have declared no conflicts of interest.

P0694 A NEW METHOD OF TREATMENT FOR DECOMPENSATED LIVER CIRRHOSIS: ENDOSCOPIC ULTRASOUND-GUIDED TRANSGASTRIC, TRANSHEPATIC INTRAPORTAL AUTOLOGOUS BONE MARROW TRANSPLANTATION

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Introduction: Stem cell therapy recently has been explored extensively as a promising treatment for decompensated liver cirrhosis. However, the genomic instability of cultured stem cells and the low efficiency in obtaining them hindered the progress of stem cell transplantation. Moreover, it is pivotal to optimizing transplantation routes by which the stem cells can be delivered effectively. Here we report the novel Endoscopic ultrasound (EUS)-guided transgastric and transhepatic intraportal autologous bone marrow transplantation to achieve therapeutic goals in patients with decompensated liver cirrhosis.
Aims & Methods: To investigate the effects of EUS-guided intraportal autologous bone marrow transplantation in decompensated liver cirrhosis, five patients with decompensated liver cirrhosis were recruited. All patients were successfully performed autologous bone marrow transplantation through EUS-guided portal vein (PV) access using the transgastric and transhepatic approach. Regular revisiting was conducted every 1 month and now in 6 months follow-up.
Results: Clinical symptoms of patients underwent portal vein transfusion of autologous bone marrow were improved obviously, while no side effects and complications were observed within 6 months follow-up. Specifically, albumin levels, ascites degree, and Child-Pugh score were significantly ameliorated in 1 month, and all follow-up data indicated the continuing improvement irrespective of postoperative time.

Characteristic	Baseline	1st month	P value (1st month vs Baseline)	6th month	P value (6th month vs Baseline)
Albumin, g/L	27.58±4.91	35.76±5.87	0.044	38.68±8.98	0.041
Tbil, umol/L	22.08±10.99	24.48±11.92	0.749	22.58±13.40	0.951
PT, sec	16.02±1.73	14.48±1.11	0.132	14.36±1.60	0.153
No ascites	0% (0/5)	20% (1/5)	-	60% (3/5)	-
Mild ascites	40% (2/5)	40% (2/5)	-	20% (1/5)	-
Moderate and large ascites	60% (3/5)	40% (2/5)	-	20% (1/5)	-
Child-pugh class A	20% (1/5)	40% (2/5)	-	80% (4/5)	-
Child-Pugh class B	60% (3/5)	60% (3/5)	-	20% (1/5)	-
Child-Pugh class C	20% (1/5)	0% (0/5)	-	0% (0/5)	-

[Characteristics of patients]

Conclusion: EUS-guided intraportal transplantation of autologous bone marrow improves both clinical symptoms and liver function for patients with decompensated liver cirrhosis. It may thus provide a safe, effective, non-radioactive, and minimally invasive treatment.
Disclosure: Nothing to disclose

P0695 GENETICALLY MODIFIED HSCS STIMULATES LIVER REGENERATION AND COULD BE A NEW PERSPECTIVE APPROACH FOR DEVELOPMENT LIVER DISEASE TREATMENT

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Introduction: Mortality from chronic liver disease is rising exponentially. Nowadays a lot of effort is made to find new approaches to stimulate liver regeneration and to develop new methods for liver diseases treatment. Cell and gene therapy methods, which are based on using regional stem

cells seems to be perspective. Currently a particular interest is paid to hepatic stellate cells (HSCs). Besides, it's known that HSC is the only source of hepatocyte growth factor (HGF) and fibroblast growth factor 4 (FGF4) in the liver - growth factors, which play a key role in hepatocytes differentiation during embryogenesis and liver regeneration. It is assumed that using genetically modified HSCs (gmHSCs) that express these growth factors could enhance their therapeutic potential.
Aims & Methods: The aim of our work was to study gmHSCs properties *in vitro* and their influence on liver regeneration after transplantation into the rats after partial hepatectomy (PH). HSCs were isolated from Wistar rat's liver, genetic modification was carried out by adenovirus Ad5-optHGF-optFGF4-RFP, which contained HGF, FGF4 and reporter gene of Red Fluorescent Protein (RFP). At first, we have studied gmHSCs phenotype *in vitro*, then we have injected gmHSCs into the rats' portal vein during PH operation (experimental group-EG). Control group (CG) of animals received HSCs, transdused by Ad5-RFP vector, which contains only RFP. The animals were sacrificed on 1, 2, 3, 5, 7, 10, 14 and 21 days after HSC transplantation. Paraffin slices were stained immunohistochemically with antibodies to RFP (reporter), α-FP (hepatoblasts) and α-SMA (myofibroblasts).
Results: The results demonstrated that *in vitro* gmHSCs expressed hepatoblast marker α -FP earlier than native HSCs and the gene expression level (by RT-PCR) was also significantly higher in gmHSCs group than in native one. This means positive influence of HGF and FGF4 on gmHSCs differentiation in hepatocyte direction *in vitro*. *In vivo* transplanted HSCs saved their viability and migrated to liver parenchyma. A large number of RFP+hepatocyte-like cells were detected even on the 1st day after transplantation (4,94±2,37 %) in the EG, then their number increased to 8,57±5,15 % by the 2nd day. After that, RFP+ cells quantity gradually decreased to 4,82±3,64 % by the 14th day. In the CG dynamics was the same, but the average number of cells was less. α-FP+ hepatocytes were also detected in both groups, but in the EG α-FP+ cells amount was significantly higher than in the CG. In all the groups α-SMA+ myofibroblasts, responsible for liver fibrosis, were not detected.
Conclusion: gmHSCs transplantation had more intensive repopulating effect on hepatocytes during the transplantation. It proves the positive effect of the inserted HGF and FGF4 genes on the liver regeneration process. Thus, gmHSCs transplantation stimulates liver regeneration and contributes to hepatocytes repopulation without risk of liver fibrosis.
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Disclosure: All authors have declared no conflicts of interest.

P0696 THE EFFECT OF MESENCHYMAL STEM CELLS DERIVED MICROVESICLES TRANSPLANTATION ON 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.
Aims & Methods: To study the effect of transplantation of mesenchymal stem cells microvesicles derived from adipose fat tissue on liver regeneration after partial hepatectomy in rats.
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 the 4th day, but in experimental - by the 7th 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.
References: Work supported by Program of Competitive Growth of KFU.
Disclosure: All authors have declared no conflicts of interest.

P0697 HUMAN DUODENAL SUBMUCOSAL GLANDS CONTAIN STEM CELLS WITH POTENTIAL FOR LIVER AND PANCREATIC REGENERATIVE MEDICINE

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Introduction: Regenerative medicine of liver and pancreas has a paramount importance. Common precursors for liver, biliary tree and pancreas exist at early stage of development in the definitive ventral endoderm forming the foregut (1).
Aims & Methods: Therefore, the aims of the present study were:
i) to evaluate whether adult human duodenal submucosal glands (SGs) contain cells expressing stem cell traits,
ii) to establish a protocol for isolating these cells based on their anatomical and phenotypic traits,
iii) to characterize self-renewal properties of duodenal SG cells and their potency to generate functional liver and β-pancreatic cells.
Human duodenum (N=15) were obtained from deceased adult organs and analyzed by immunohistochemistry and immunofluorescence (2). The entire duodenum was processed through a chemical dissolution of the mucosa layer that preserved the sub-mucosa, which was successively digested mechanically and enzymatically (2). Isolated cells were immune-selected for the markers of pluripotent stem cells Tra-1-60+ SG cells and successively cultured in self-renewal or differentiation media (2). Parallel experiments were conducted in vivo through injection of Tra-1-60 + cells in the spleen of immunocompromised mice, or in streptozotocin-induced diabetic mice, or in Krt19CreTdTomatoLSL C57BL6/J mice (1, 2).
Results: In human duodenum, SGs contain cells expressing stem cell markers and with a phenotype which differs from intestinal crypts. Uniquely, duodenal SGs contained Ck7+ and Tra-1-60+ cells which are not present in intestinal crypts. Lineage tracing study in mice demonstrates homeostatic