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Abstract 144

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Liver cell proliferation determines MELD score improvement in decompensated alcoholic liver disease

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Destination : Liver / transplantation (BASL/BLIC)

Oral presentation only

Introduction
The prognostic significance of liver progenitor cell (LPC) and macrophage expansion in the regeneration of decompensated alcoholic liver disease (ALD) remains ill defined.

Aim
In a well-characterized population of patients with acutely decompensated ALD (Spahr L. et al. *Hepatology* 2011, A62), we analysed macrophage infiltration, proliferative LPC and differential expression of hepatic genes at baseline in relation to outcome at 3 months follow up.

Methods
Fifty-eight patients (MELD 20) were included. Liver biopsy at inclusion was used for (1) immunohistological analysis of proliferative LPC (MIB1+/CK7+), proliferative hepatocytes (MIB1+/CK7- parenchymal cells), morphometric analysis of macrophage infiltration (CD68) and LPC expansion (CK7), and (2) transcriptome profiling using Affymetrix GeneChip Human arrays. Serum markers of regeneration (cytokines and growth factors) were measured by immunoassays. A = 3 points decrease in MELD at 3 months as compared to baseline defined the improvers. Fifteen abstinent cirrhotics served as controls. CD68 and SPINK3 mRNA expressions were determined in various mice models of liver injury.

Results
At baseline, patients with decompensated ALD presented a significant expansion of CD68+ macrophages and CK7+ cells compared to abstinent cirrhotics. Patients who will improve (n=34) were characterized at baseline by a higher number of CK7+/MIB1+ cells (1.9 ± 1.5 versus 0.9 ± 0.9 cells/field, $p<0.01$), MIB1+ hepatocytes (4.1 ± 3.6 versus 1.8 ± 1.4 cells/field, $p<0.01$), an increased expansion of liver macrophages (4.4% versus 3.3% of surface area, $p<0.05$) and a higher level of serum HGF ($p<0.05$), compared to those who will not (n=24). Transcriptome analysis revealed that the first pathways upregulated in improvers were related to cell cycle and a 7-fold increase of liver serine peptidase inhibitor Kazal type I (SPINK1) compared with non-improvers ($p=0.005$). SPINK1 liver expression positively correlated with CD68 ($r=0.46$) and cyclinE1 ($r=0.6$). In mice, a 20-fold increase in liver SPINK3 expression, the homolog of human SPINK1, was evidenced following partial hepatectomy, concurrent with hepatocyte proliferation.

Conclusions
Baseline markers of liver macrophages and liver cell proliferation predict the clinical

Abstract 144

outcome in decompensated ALD. This study reveals an unexpected implication of SPINK1, an acute phase reactant, in liver regeneration and human ALD.

Abstract 144