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Background: Liver progenitor cells (LPC) are usually considered to be activated in case of impaired hepatocyte replication and hence markers of disease severity. However, their exact role as well as their interaction with hepatocytes and macrophages also implicated in liver regeneration remain poorly characterized in humans. The aim of this study is to characterize hepatocyte, LPC and macrophage populations in severe alcoholic steatohepatitis (sASH) and to link them with liver injury and patients' outcomes. **Methods:** Immunohistochemical and morphometric studies for total LPC (keratin 7^+ cells), macrophages ($CD68^+$ cells), proliferative hepatocytes ($Ki67^+$ hepatocytes) and proliferative LPC (double keratin 7^+ and $Ki67^+$ cells) were performed on the admission biopsies of patients with sASH recruited prospectively in 16 different centers. The material used for this study is derived from a recent trial on enteral nutrition in sASH. Patients were divided into improvers or non-improvers, according to MELD score change at 3 months and in responders or non-responders to corticosteroids, according to the Lille score at day 7. **Results:** Liver biopsies were available for 68 patients with sASH. Eleven biopsies were excluded due to poor quality. 57 cases were included for histological and morphometric assessment (mean age 50 years, mean Maddrey discriminant function 54 (range 43.2-71.5)). A greater degree of steatosis was the only histological parameter associated with a better prognosis based on MELD score evolution at 3 months ($p=0.002$). The total amount of LPC was positively correlated to the severity of the disease evaluated by the MELD score ($r=0.3416$, $p<0.01$). A higher number of macrophages was associated with a higher proliferation of both hepatocytes and LPC ($r=0.3012$, $p=0.02$). Increased hepatocyte replication was also correlated to a higher proliferative LPC count ($r=0.8112$, $p<0.0001$). No difference of total LPC, proliferative LPC, proliferative hepatocytes or macrophages was observed between improvers and non-improvers nor between the favorable and unfavorable Lille score groups. **Conclusion:** In human biopsy proven sASH, the proliferation of hepatocytes and LPC occurres in parallel, showing that LPC start to replicate even in the absence of massive hepatocyte senescence in humans, which contrasts with data coming from animal experiments. Liver macrophage expansion is correlated to the proliferation of both hepatocytes and LPC suggesting a potential role for driving the regenerative response.

Disclosures:

Peter Stärkel – Gilead: Grant/Research Support; Abbvie: Grant/Research Support; Abbvie: Advisory Committee or Review Panel; Gilead: Advisory Committee or Review Panel

Hans Orlent – Gilead: Grant/Research Support

Nicolas Lanthier – Promethera biosciences: Advisory Committee or Review Panel: Fresenius Kabi: Speaking and Teaching

The following people have nothing to disclose: Adrienne Lejeune, Alexandre Louvet, Axel Hittelet, Luc I. Lasser, Jean Delwaide, Anja Geerts, Chantal De Galocsy, Virginie Putzeys, Phillippe Langlet, Sven M. Francque, Mina Komuta

Disclosure information not available at the time of publication: Céline Bazille, Boris Bastens, Xavier Dekoninck, Sergio Negrin Dastis, Hendrik Reynaert

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Hepatic xCT Promotes Endocannabinoid Production in Alcoholic Fatty Liver through Glutamate-Mediated mGluR5 Activation in Stellate Cells

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Background: Paracrine activation of hepatic cannabinoid receptor 1 by hepatic stellate cell (HSC)-derived 2-arachidnoylglycerol (2-AG) is one of the critical mechanisms mediating alcoholic steatosis by stimulating *de novo* lipogenesis in hepatocytes. However, the precise mechanism of 2-AG production in HSCs is unknown. **Methods:** Levels of plasma glutamate were measured in the samples from 33 patients with biopsy-proven alcoholic liver disease and 4 healthy individuals (controls). To examine alcohol-induced glutamate excretion, endocannabinoid production and consequent steatosis, C57BL/6 wild type, global metabotropic glutamate receptor 5 (mGluR5) knockout and hepatocyte-specific xCT knockout mice were fed liquid ethanol diet for 8 weeks. In addition, mGluR5 specific antagonist or xCT inhibitor was treated to ethanol-fed mice to test their therapeutic potentials. For in vitro experiments, freshly isolated primary HSCs and hepatocytes were used. RNA sequencing, histology, immunoblots, quantitative polymerase chain reaction, and metabolite measurements were performed. **Results:** We found that chronic ethanol consumption significantly increased glutamate levels in blood and liver of ethanol-fed mice and blood of patients with alcoholic liver disease compared to controls. To figure out the mechanism, RNA sequencing analysis exhibited the upregulation of xCT (a cystine-glutamate antiporter) through the antioxidant transcription factor Nrf2 in the liver of ethanol-fed mice. Mechanistically, cysteine deficiency and subsequent glutathione depletion was induced by impaired transsulfuration pathway in ethanol-fed mice, which leads to the glutamate excretion for cystine uptake (immediately reduced to cysteine) via upregulation of xCT in hepatocytes. Intriguingly, comparing with other hepatic cells, the mGluR5 was highly expressed in HSCs and 2-AG production in HSCs was remarkably increased by mGluR5 activation. Consistently, genetic or pharmacologic inhibition of mGluR5 or xCT significantly attenuated alcoholic steatosis in ethanol-fed mice, followed by suppression of 2-AG production and *de novo* lipogenesis. **Conclusion:** Taken together, our findings demonstrate that increased excretion of hepatic glutamate by xCT as a lipogenic mediator promotes alcoholic

all control cohorts (HC, AC, NAFLD) identified a set of 101 proteins which specifically differentiated AH. A clear signature of significantly higher abundance proteins in AH (CRP, C163A, CADM1, CD166, LAMA2, JAM1, GOLM1) centered on acute phase, cell adhesion, and extracellular matrix component disruption. Proteins downregulated in AH plasma (FETUA, FETUB, HGFA, CO6, CO8) included hepatokines, complement cascade components, and hepatocyte growth activators among others. Longitudinal comparison of patients undergoing corticosteroid treated patients identified 163 plasma proteins which were altered upon treatment at either day 29 or week 12. Patients were stratified by Lille score, revealing differing longitudinal protein signatures between responsiveness to treatment (i.e. SODM, CSPG2, CDHR2, among others). **Conclusion:** Identification of AH specific protein abundances in the blood plasma provide a signature to identify and stratify patients in the context of often overlapping liver disease conditions, particularly alcoholic cirrhosis. Longitudinal analysis of corticosteroid treatment provided insights into the molecular mechanisms of treatment correlated with outcome.

Disclosures:

Timothy R Morgan – Genfit: Grant/Research Support; Merck: Grant/Research Support; AbbVie: Grant/Research Support; Gilead: Grant/Research Support

The following people have nothing to disclose: Jon Jacobs, Zhang-Xu Liu, Trina Norden-Krichmar, Ramon Bataller

Disclosure information not available at the time of publication: Marina Gritsenko, Komal Kedia

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Increasing Trends in Hospital-Resource and Post-Hospital Care Utilization in Patients Hospitalized with Acute Alcoholic Hepatitis: A United States Perspective 2005-2014

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Background: Acute Alcoholic hepatitis (AAH) is associated with significant morbidity and mortality amongst patients with alcohol abuse. There is limited data on recent trends in health care utilization during and post hospitalization for patients with AAH. The aim of this study was to investigate trends and predictors of hospitalization costs (HC), length of stay (LOS) and Post-Hospital Care (PHC) utilization. **Methods:** A retrospective study extrapolating data on AAH for adult patients from the National Inpatient Survey (NIS), admitted 2005-2014, were evaluated. Cases with missing data on age/gender/inpatient mortality were excluded. ICD-9-CM codes were used to extract AAH patients, as well as other comorbidities (Table). PHC utilization was defined as discharge to another acute-care hospital, skilled nursing/ rehabilitation facilities or home with home-healthcare. HC were inflation-adjusted. Bivariate analyses used the T-test/ Mann-Whitney and chi-square tests. Trends were assessed by mixed-models logistic regression. Predictors of PHC, HC and LOS were assessed by multivariable mixed-models logistic, linear regression and accelerated-failure time models, respectively. NIS weights yielded national estimates in all analyses. **Results:** A total of 816,327 AAH patients were identified. Median age was 49 years, with 70% men. Overall inpatient mortality was 3.6%, but for patients with acute-on-chronic liver failure it was noted to be 13.9%, and among those with alcoholic cirrhosis 7.5%. Median LOS was overall 4 days, with 6 days in the PHC group vs. 4 days in the non-PHC group (p<0.001). Overall PHC rate 21.1% and mean HC $11,928±87 (medians: $7,293 overall; $6,618 in non-PHC group vs. $11,460 in PHC group; p<0.001). PHC utilization significantly increased from 20.0% in 2005 to 24.5% in 2014 (p-trend<0.001). Overall mean HC have been increasing, from $10,744 to $13,145 (p-trend<0.001), with patients in the PHC group exhibiting a faster rising trend (Δ-slope p<0.001), from $14,463 to $20,812, in contrast to the non-PHC group (from $9,442 to $9,788). Similarly, overall LOS had an increasing trend (p-trend<0.001), with the PHC group having a faster rising trend (mean 7.8 to 9.6 days; p-trend<0.001), compared to the non-PHC group (Δ-slope p<0.001), which exhibited a stable LOS trend (p-trend=0.469). Predictors of PHC, LOS and HC are shown in the Table. **Conclusion:** AAH patients have been increasingly requiring more PHC, and patients with acute liver failure had a higher mortality rate. Furthermore, patients who required PHC, exhibited increasingly higher mean HC and longer LOS. Predictors for AAH patients requiring PHC can potentially enable earlier discharge to PHC facilities, while decreasing utilization of hospital resources and healthcare costs.

Hospitalization Costs Predictors	Length of Stay Predictors	Post-Hospital Care Predictors
[illegible]	[illegible]	[illegible]

Disclosures:

Chakradhar M. Reddy – Allergan Pharma: Speaking and Teaching; Echosens: Speaking and Teaching; Salix Pharma: Speaking and Teaching; Gilead Sciences: Speaking and Teaching; Dova Pharma: Speaking and Teaching

Nikolaos T. Pyrsopoulos – VITAL THERAPIES: Grant/Research Support; CONATUS: Grant/Research Support; MERCK: Advisory Committee or Review Panel; BAYER: Grant/Research Support; HOLOGIC: Grant/Research Support; GILEAD: Grant/Research Support; PROMETHEUS: Grant/Research Support; GENFIT: Grant/Research Support; ABBVIE: Grant/Research Support; SHIRE: Grant/Research Suppor

The following people have nothing to disclose: Paris Charilaou

Disclosure information not available at the time of publication: Kalpit Devani

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New Concepts in Liver Regeneration Mechanisms in Human Severe Alcoholic Steatohepatitis

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