

Speaker Center

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25999:
SUPPRESSION OF
OXIDATIVE
STRESS INHIBITED
OSTEOPONTIN
EXPRESSION AND
PREVENTED
EXPERIMENTALLY
INDUCED LIVER
INJURY IN RATS

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SUPPRESSION OF OXIDATIVE STRESS INHIBITED OSTEOPONTIN EXPRESSION AND PREVENTED EXPERIMENTALLY INDUCED LIVER INJURY IN RATS

as part of Abstracts

Session title: Liver Fibrogenesis and Non-Parenchymal Cell Biology; Basic Fibrosis Research and Stellate Cell Biology; Kupffer Cell Biology; Imaging and Noninvasive Markers of Liver Diseases; Clinical and Translational Fibrosis Research scheduled for Friday, November 12, 2021: 6:00 AM - 11:55 AM

ePoster Information

ePoster Update

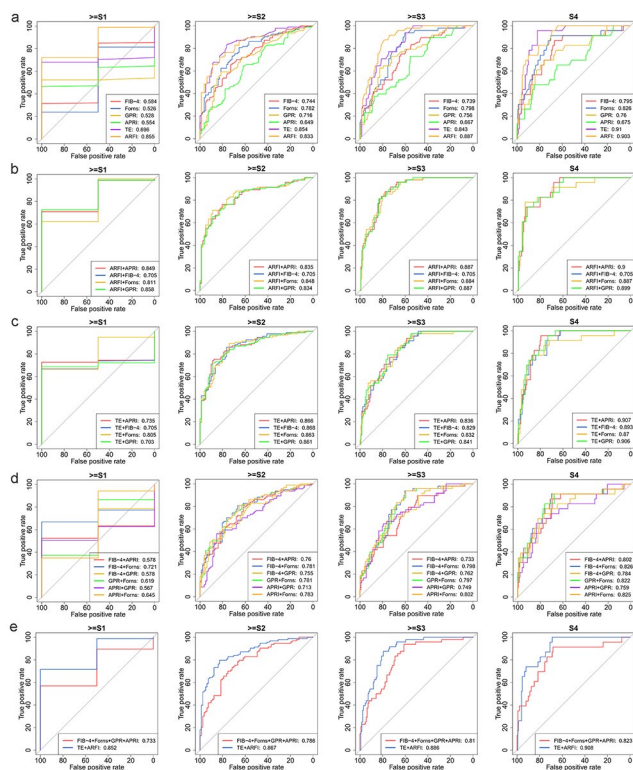
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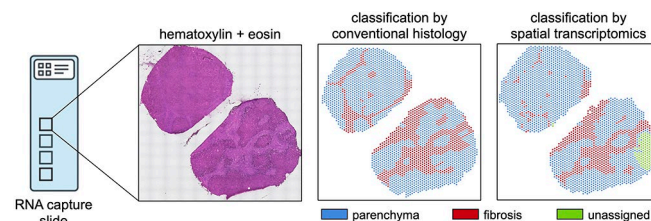
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Disclosures:

The following people have nothing to disclose: Liang Xu

location (parenchyma: 80.5% mean overlap, range: 35.7-99.3%; fibrosis: 72.3% mean overlap, range: 16.7-97.7%) of parenchymal and fibrotic areas as classified by conventional histology. To disentangle the cellular composition of liver fibrosis, gene expression detected by spatial transcriptomics was deconvoluted by CIBERSORTx analysis and stratified into cellular subsets defined by scRNAseq. *RGS5+* and *COL3A1+* mesenchymal cells, *CCL21+* and *SPARCL1+* endothelial cells, *IL17RA+* monocytes and *VCAM1+* Kupffer cells were detected at 2.5-fold higher proportions in the fibrotic compartments of PSC, PBC and ALD liver whereas *IGHM+* and *IGHG+* plasma cells were localized to fibrotic areas primarily in PBC livers. **Conclusion:** Our findings support that gene content associated with specific cell lineages is enriched in liver fibrosis and demonstrate the power of combining RNA-based sequencing methodologies for dissecting complex microenvironments in search of novel anti-fibrotic targets.



Disclosures:

The following people have nothing to disclose: Brian K Chung, Tom H. Karlsen

Disclosure information not available at the time of publication: Jonas Øgaard, Henrik Mikael Reims, Espen Melum

1398

SPATIAL TRANSCRIPTOMICS IDENTIFIES LOCALIZATION OF ENRICHED CELL TYPES IN HUMAN LIVER FIBROSIS

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Background: Liver fibrosis has limited therapeutic options and represents a serious unmet patient need that can lead to cirrhosis. Recent application of single-cell RNA sequencing (scRNAseq) has identified enriched cell types in cirrhotic livers however the microanatomical localization of these lineages and their gene expression has not been determined.

Methods: To assess if fibrotic liver regions harbour unique cell types, we analyzed cirrhotic explants from patients with primary sclerosing cholangitis (n=4), primary biliary cholangitis (n=2) and alcoholic liver disease (n=2) by combining whole tissue spatial transcriptomics (Figure 1), scRNAseq data and gene deconvolution analysis by CIBERSORTx. **Results:** Spatial transcriptomics clearly identified areas of distinct gene expression in cirrhotic liver regions which strongly corresponded to the total number (parenchyma: Spearman $r=0.86$, $P=0.01$, fibrosis: $r=0.90$, $P=0.005$) and precise

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SUPPRESSION OF OXIDATIVE STRESS INHIBITED OSTEOPONTIN EXPRESSION AND PREVENTED EXPERIMENTALLY INDUCED LIVER INJURY IN RATS

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Background: Osteopontin (OPN) is a matricellular cytokine and a stress-induced pro-fibrogenic molecule that promotes activation of stellate cells during pathogenesis of hepatic fibrosis. The current investigation was aimed to study the effect of epigallocatechin gallate (EGCG) to decrease osteopontin expression and subsequent arrest of experimentally induced hepatic fibrosis. **Methods:** Hepatic fibrosis was induced with intraperitoneal injections of *N*-nitrosodimethylamine (NDMA) in a dose of 1 mg/100 g body weight on 3 consecutive days of a week for 4 weeks. A group of animals received 0.2 mg EGCG/100 g body weight orally 2 h prior to NDMA administration and the remaining days during the study. The animals were sacrificed on the 28th day from the beginning of exposure. Serum levels of AST, ALT, OPN, malondialdehyde, type IV collagen, and hyaluronic acid were measured. Immunohistochemistry and Western blotting were performed for collagen type I, α -SMA, 4-HNE, and OPN. **Results:** Serial administration of NDMA produced well developed fibrosis and early cirrhosis in rat liver. Treatment with EGCG significantly reduced serum levels of AST, ALT, OPN, malondialdehyde, type IV collagen, and hyaluronic acid and prevented deposition of collagen fibers in the hepatic tissue. Immunohistochemical staining and Western blotting demonstrated marked decrease in the expression of α -SMA, OPN, and production of 4-HNE. **Conclusion:** Treatment with EGCG prevented excessive

generation of reactive oxygen species, suppressed oxidative stress, significantly reduced serum and hepatic OPN levels, and markedly attenuated hepatic fibrosis. The results indicated that EGCG could be used as a potent therapeutic agent to prevent hepatic fibrogenesis and related adverse events. *Presenting author: georgej@kanazawa-med.ac.jp

Disclosures:

The following people have nothing to disclose: Joseph George, Mikihiro Tsutsumi, Mutsumi Tsuchishima

1400

THE MEASUREMENT OF LIVER STIFFNESS USING LOGIQ S8 SHEAR WAVE ELASTOGRAPHY, ITS RELIABILITY AND DIAGNOSTIC ACCURACY

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Background: The aim of this study was to evaluate the usefulness of two different type of 2D Shear-wave elastography (2D-SWE) for predicting of liver fibrosis stage and to compare with transient elastography (TE), by using the histologic METAVIR scoring system as the reference method.

Methods: A total of 203 patients with chronic liver disease were prospectively enrolled. Two different 2D-SWEs (LOGIQ S8 and E9 system, GE healthcare, Chalfont St Giles, United Kingdom) were assessed for the liver stiffness measurement in patients with chronic liver diseases. Patients were performed 2D-SWE measurement using S8 and E9 system as well as TE (Fibroscan®, EchoSens, France), liver biopsy.

Results: Most common etiology of chronic liver disease was non-alcoholic fatty liver disease (28.7%) and followed by chronic hepatitis B (25.1%). Liver fibrosis stage consisted of F0 (22.6%), F1 (29.7%), F2 (16.9%), F3 (12.8%) and F4 (17.9%). Overall success rate of S8 was 96.1% (195/203). Overall, S8 and E9 were well correlated with histologic fibrosis stage, respectively. The optimal cut-off value of S8 and E9 to differentiate significant fibrosis ($\geq F2$) were 6.69 kPa and 6.42, respectively. And the cut off values of S8 and E9 for distinguishing liver cirrhosis were 9.15 and 8.87 kPa, respectively. Of 195 patients who underwent both S8 and E9, measured liver stiffness showed good inter-equipment correlation (ICC: 0.819, $p < 0.001$). When compared diagnostic ability with transient elastography (Fibroscan®), no significant differences were shown in detecting every stage. **Conclusion:** 2D-SWE using LOGIQ S8 and E9 (GE healthcare) are useful non-invasive tools for predicting significant fibrosis and liver cirrhosis in comparison with TE.

Disclosures:

The following people have nothing to disclose: Jeong-Ju Yoo, Sang Gyune Kim, Young Seok Kim

1401

THE USE OF NON-INVASIVE MARKERS IN DETECTING LIVER DISEASE IN PATIENTS WITH LIPODYSTROPHY

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Background: Inherited and acquired lipodystrophies are disorders characterized by variable loss of adipose tissue resulting in leptin deficiency, metabolic complications, and progressive nonalcoholic steatohepatitis (NASH). Although liver biopsy is the gold standard in diagnosing and staging liver disease, it is invasive, which has led to the use of serologic noninvasive tests (NITs). This study assessed the performance of serologic NITs in detecting advanced fibrosis in patients with lipodystrophy, determined if their performance could be improved, and created a new predictive model specific to patients with lipodystrophy. **Methods:** Existing NITs (Table 1) were calculated at the time of liver biopsy in patients with lipodystrophy and assessed using area under the receiver operator characteristic curves (AUROC) with optimization via Youden index. Logistic regression on a randomized training subset was utilized to build a new predictive model for detecting advanced fibrosis (NASH CRN score $\geq F3$). The performance of the new model was then assessed on a randomized validation subset and a separate external cohort. **Results:** 105 lipodystrophy patients (NIH cohort=82, External cohort=23) with liver biopsy were included in the study. The NIH cohort was randomized into training and validation cohorts without statistical differences between groups. The NIH cohort had median age 19 (IQR:15-35) years; 79% female, 87% diabetic, and 32% with advanced fibrosis. The external cohort had median age: 42(IQR:34-51) years, 78% female, 91% diabetic, and 4% with advanced fibrosis. Across established non-invasive predictive models for detecting advanced fibrosis and cirrhosis, APRI performed the best in patients with lipodystrophy with AUROC 0.74 (Table 1). Three novel predictive models (Models A, B, & C in Table 1) incorporated BMI, total bilirubin, triglycerides, platelet count and leptin. These new scores outperformed APRI in detecting advanced fibrosis or cirrhosis in patients with lipodystrophy with AUROC > 0.8 across 2 unique cohorts with better sensitivity, specificity, positive predictive value, and negative predictive value. **Conclusion:** Existing serologic NITs utilized to detect NASH-related fibrosis perform poorly in patients with lipodystrophy. Utilizing clinical tests, a newly developed non-invasive model can identify advanced fibrosis in these patients.



AASLD CERTIFICATE OF PARTICIPATION

Presented to:

Joseph George

for the contributing to the educational programming during The
Liver Meeting[®].

Date: Friday, November 12, 2021

Presentation Title: SUPPRESSION OF OXIDATIVE STRESS
INHIBITED OSTEOPONTIN EXPRESSION AND PREVENTED
EXPERIMENTALLY INDUCED LIVER INJURY IN RATS

Role: Author

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