AASLD Nov. 12-15, 2021

The Liver Meeting®

DIGITAL **EXPERIENCE**

The Best of The Liver Meeting®

Basic and Translational Research

About the program:

Best of The Liver Meeting 2021 was created by the Scientific Program Committee for the benefit of AASLD members, attendees of the annual conference, and other clinicians involved in the treatment of liver diseases. The program is intended to highlight some of the key oral and poster presentations from the meeting and to provide insights from the authors themselves regarding implications for patient care and ongoing research.

Use of these slides:

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Disruption of pituitary-liver UPR interaction contributes to NAFLD

Objective

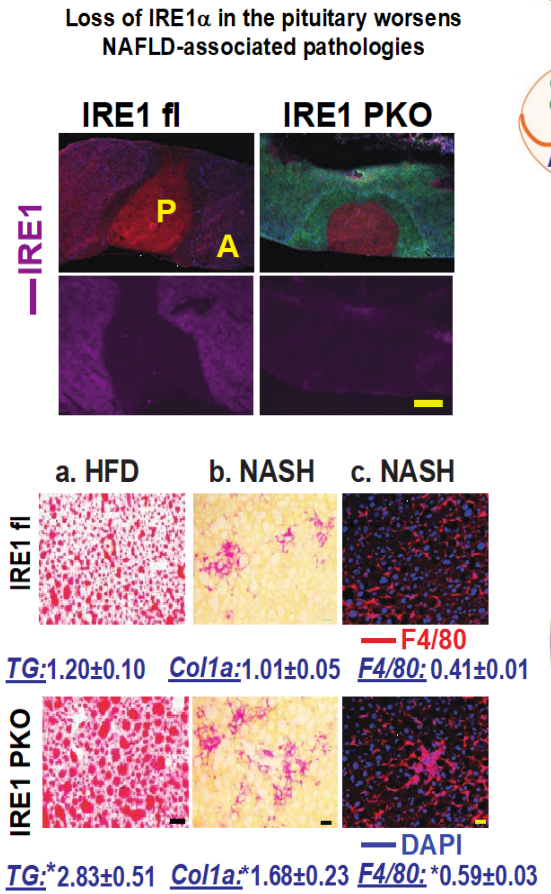
Delineate the molecular mechanisms by which obesity-associated pituitary endocrine dysfunction contributes to NAFLD

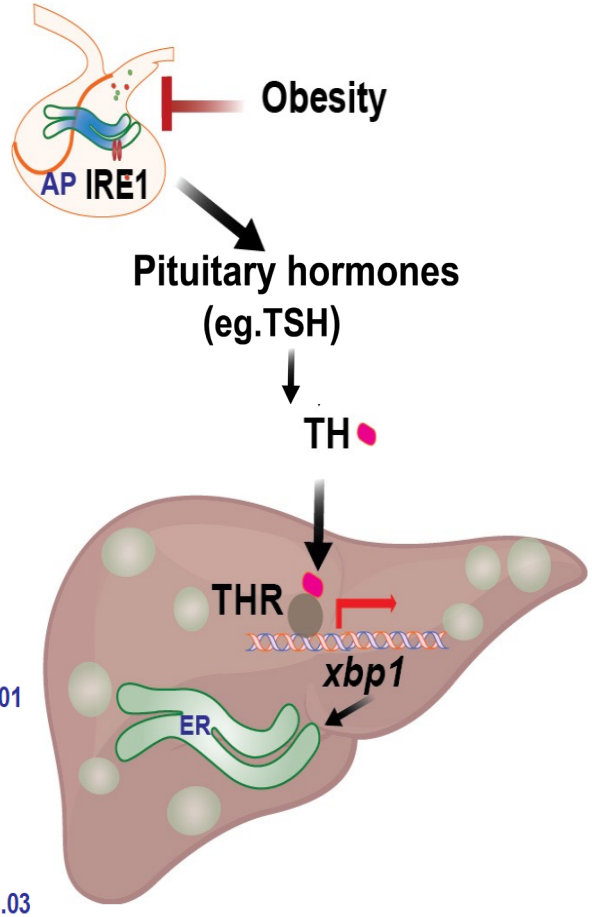
Methods

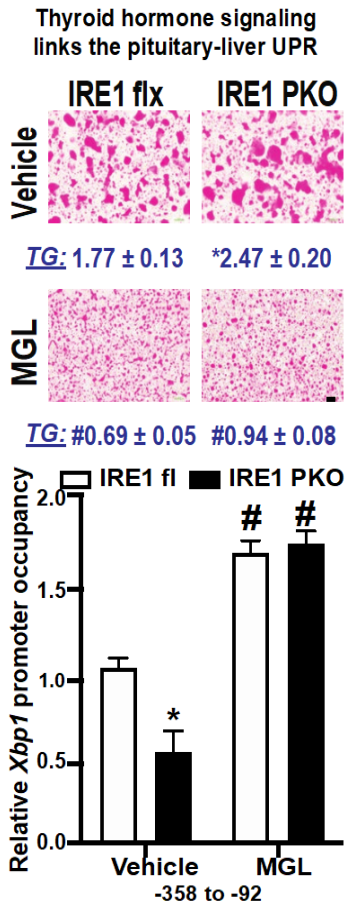
- Bulk and single-cell RNA-Sequencing analyses of the pituitary gland and the liver from mice with diet-induced obesity;
- Mice with genetic gain or loss of IRE1-sXBP1 function in the pituitary or the liver;
- Activation of hepatic thyroid hormone signaling in mice with obesity.

Conclusions

Dysregulation of pituitary hormone-mediated pituitary-liver unfolded protein response communication drives NAFLD.







Qian and Yang, et al., Abstract 1.

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Reduction in alcohol preference and intake is transmitted through colonization of germ-free mice with stools from AUD patients that received fecal microbiota transplant

Objective

- Determine if drinking behavior improvement in humans after FMT could be transmitted to mice and determine microbial taxa associated with these changes

Methods

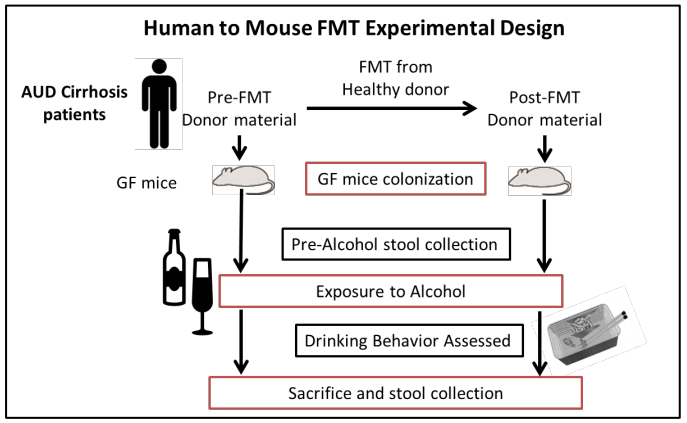
- Stools from humans pre- and post-FMT were used to colonize male germ-free (GF) mice and drinking behavior over 2 days were studied and linked with microbiota composition (experimental design)

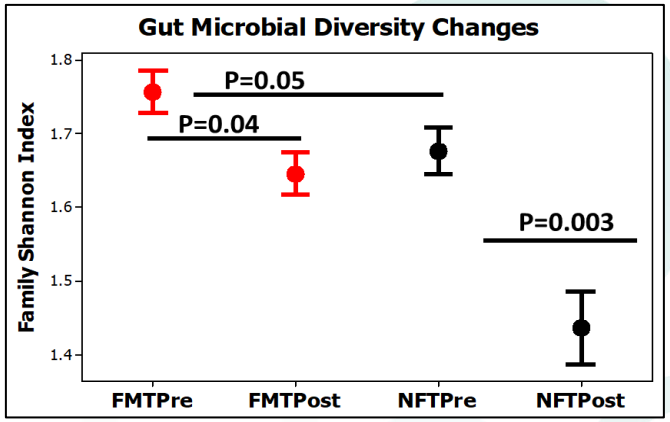
Main Findings

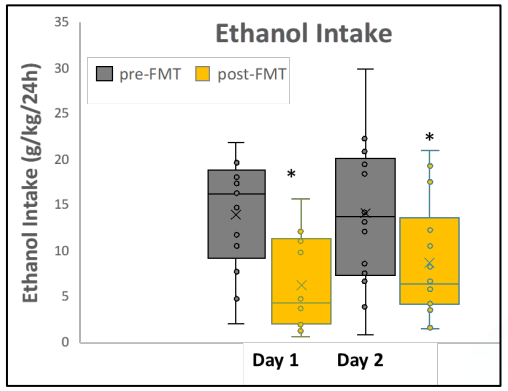
- There was a reduction in total and binge alcohol intake in mice that were colonized with post-FMT stools versus pre-FMT stools, that was linked with Ruminococcaceae and a higher microbial diversity

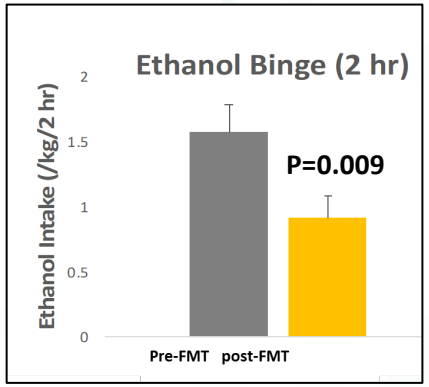
Conclusions

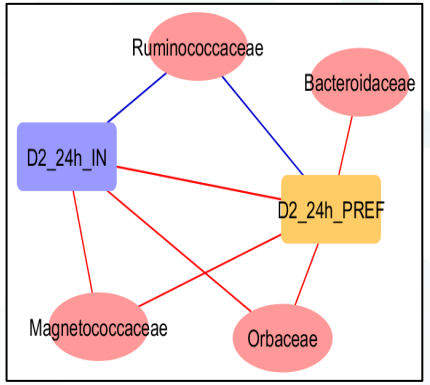
- FMT may be a promising therapy for reducing alcohol intake and craving and transfer of microbiota rich in Ruminococcaceae are associated with lower intake and preference for alcohol in germ-free mice.











Blue=negative linkage
Red=positive linkage

Bajaj J, et al., Abstract 3.

Probiotic *Lactobacillus rhamnosus* GG-derived exosome-like nanoparticles (LDNPS) protect against alcohol-associated liver disease through the intestinal miR194-FXR-FGF15-mediated bile acid synthesis pathway in mice

Aim

- To investigate whether *Lactobacillus rhamnosus* GG-derived exosome-like nanoparticles (LDNPs) attenuate ALD through regulation of intestinal FXR-FGF15 signaling in mice

Methods

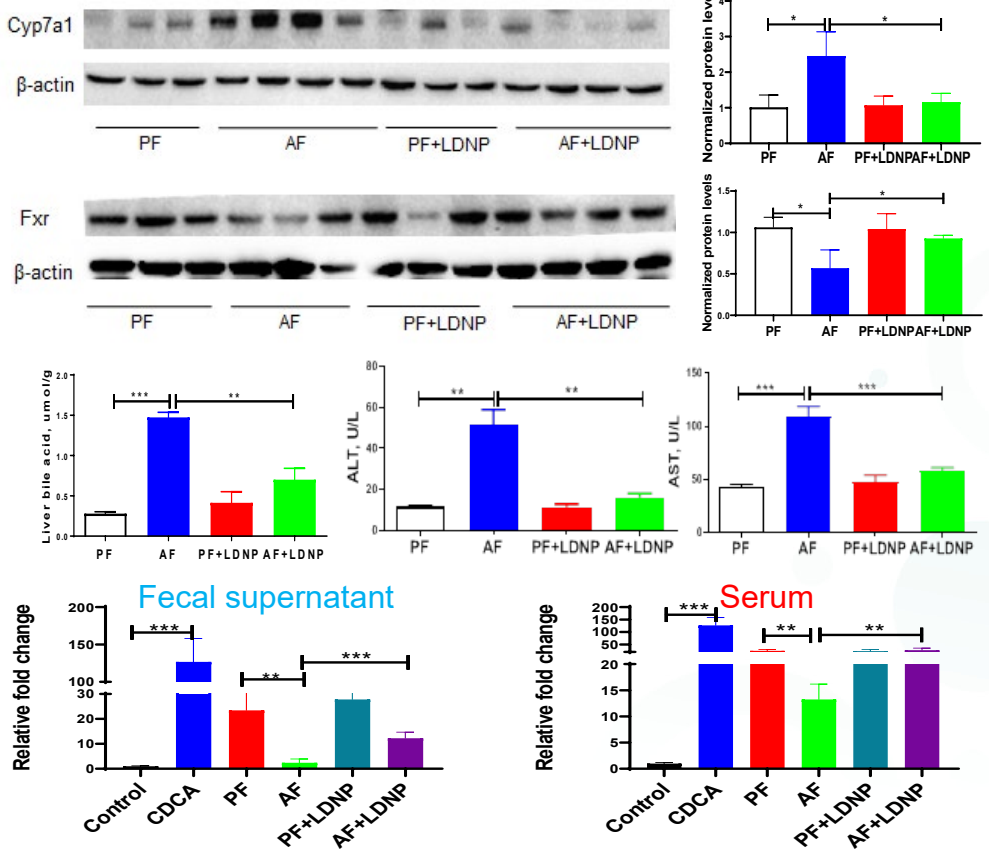
- C57BL/6 and intestinal epithelial cell specific Fxr knockout ($Fxr^{\Delta IEC}$) mice were subjected to NIAAA binge-on-chronic alcohol exposure. Control mice were pair-fed maltose-dextrin in substitution of ethanol.

Conclusions

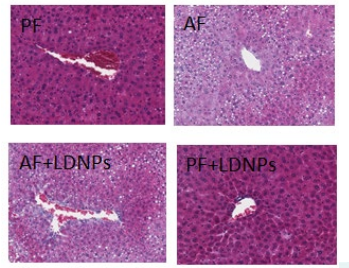
- Our results demonstrate that LDNP treatment inhibits alcohol-induced liver injury by suppressing intestinal *miR194* and improving BA profile that led to an activated Fxr-Fgf15 signaling and suppressed BA *de novo* synthesis in alcohol-associated liver disease.

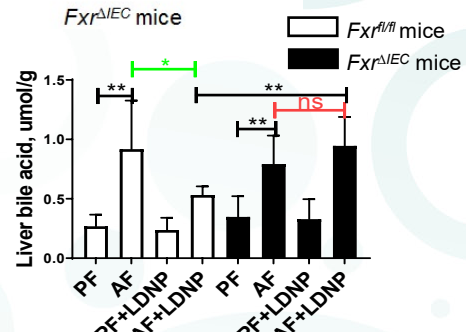
Main Findings

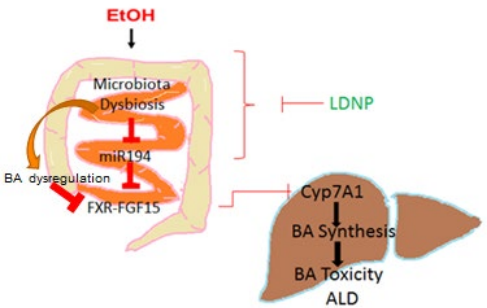
Alcohol disrupted intestinal miR194-FXR-FGF15 signaling and increased liver BA synthesis and injury, which was suppressed by LDNPs



The beneficial effect of LDNPs is abolished in $Fxr^{\Delta IEC}$ mice







Jiang M, et al., Abstract 4.

The portal mesenchymal stem cell niche in liver fibrosis

Aim

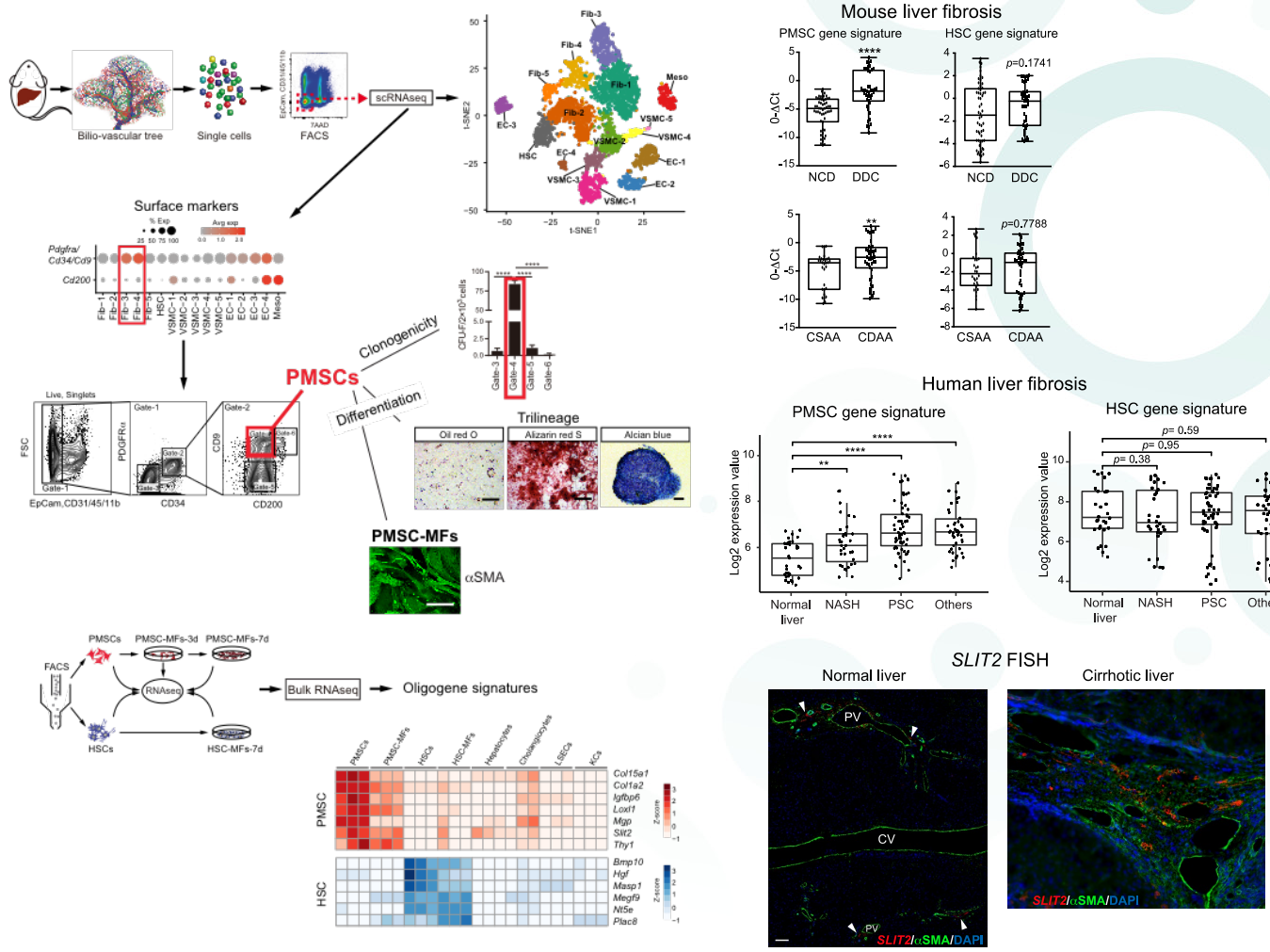
Identify portal mesenchymal progenitors of liver myofibroblasts, distinct from HSCs

Methods

- scRNAseq of portal mesenchymal cells isolated from mouse bilio-vascular tree.
- Selection of surface markers based on scRNAseq to sort portal fibroblasts with mesenchymal stem cell features (PMSCs) and analyze their phenotype and transcriptome *in vitro*.
- Design of oligogene signatures of PMSCs and HSCs with little variation across their myofibroblastic (MF) differentiation to assess their expansion potential in murine and human liver fibrosis.
- FISH of a prototypical gene of PMSC signature (*SLIT2*)

Conclusions

PMSCs, a small population of portal fibroblasts with stem cell features and a perivascular portal distribution, form a reservoir of expansive myofibroblasts, contrarily to HSCs, underlying liver fibrosis in all types of liver disease.



Lei L, et al., Abstract 5.

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Circulating microRNAs improve early diagnosis of bacterial infections in acute decompensation of liver cirrhosis

Objective Sepsis represents a major cause of morbimortality in cirrhotic patients, but its diagnosis is challenging due the non-specific inflammation associated with decompensated cirrhosis. MicroRNAs (miRs) could be relevant biomarkers in sepsis. Therefore, we aimed at identifying circulating miR signatures associated with (i) bacterial infection-triggered acute decompensation (AD) and predictive of (ii) secondary infections and (iii) mortality in these patients.

Methods Prospective observational study including patients with alcohol, dysmetabolic or post-HCV related cirrhosis, in AD (sepsis-triggered or not) or with compensated cirrhosis; profiling of plasma miRs performed with the Nanostring nCounter® technology.

Main Findings The 1-month mortality was 23.5% for the sepsis group and 7.4% for the non-sepsis group. Thirty-four miRs were differentially detected (DD) between the 2 groups (Fig. 1a) ($p<0.05$). A composite score including neutrophils, C reactive protein (CRP) and miR-362-3p could diagnose bacterial infection with an AUC of 0.83 (95% CI: 0.67-0.98; $p < 0.001$) and outperformed each of its components taken separately (Fig. 1b). Furthermore, 127 miRs were DD between AD patients developing nosocomial infections and AD patients without suspected or confirmed sepsis during the hospitalization and who were not treated with antibiotics (Fig. 2). Five miRs could predict 6-months overall survival in AD independently of MELD score (example of let-7g, Fig 3).

Conclusions

Circulating miRs might be useful to improve early bacterial infection diagnosis and outcomes prediction in patients with AD of liver cirrhosis.

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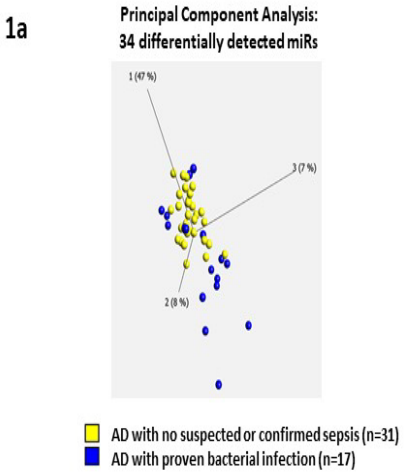

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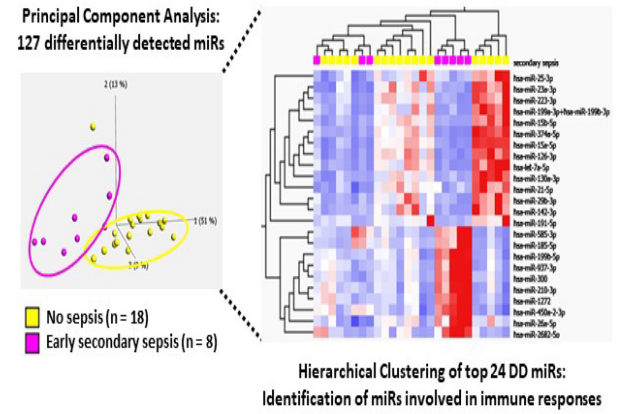

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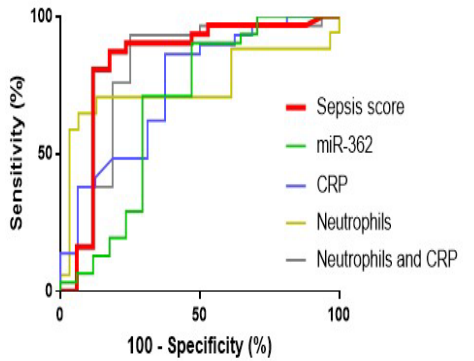

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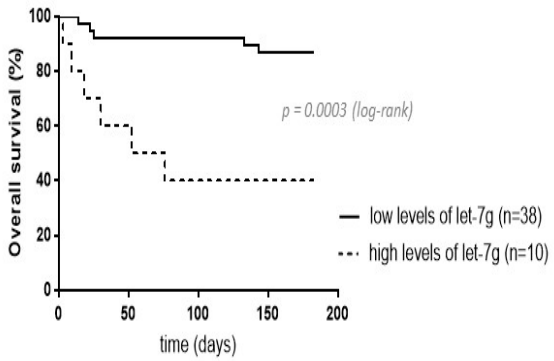

Chouik Y, et al., Abstract 49.

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Y. CHOUIK, F. LEBOSSE, M.L. PLISONNIER, T. ANTONINI, C. BOUCHENY, M. SUBIC, K. HARTIG-LAVIE, D. POINSOT, F. VILLERET, C. GUICHON, A. PAYANCE, P.E. RAUTOU, F. ZOULIM, M. LEVRERO

Hyperammonemia induces cellular senescence causes mitochondrial dysfunctions are reversed by ammonia lowering in skeletal muscle

Hypothesis/Aim/Objective

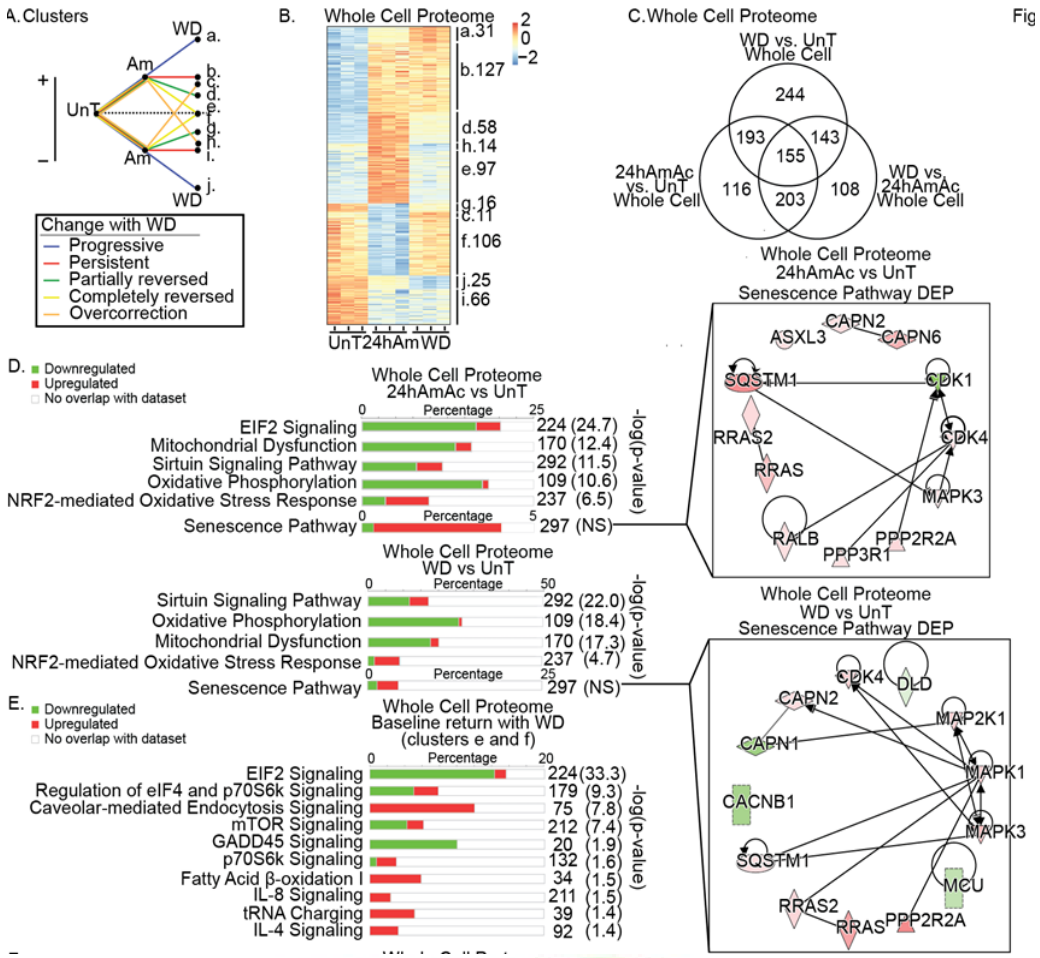
- We determined if ammonia-induced mitochondrial dysfunction causes skeletal muscle senescence and if ammonia lowering can reverse senescence associated molecular phenotype

Methods

- Global molecular responses were determined by analysis of unbiased data including RNAseq; β-galactosidase activity, staining, expression of $P16^{INK}$, P21, and phosphorylated P53 (pP53) were used as senescence-associated molecular phenotype (SAMP) in myotubes and gastrocnemius muscle from rats.

Conclusion

- Ammonia is a mediator of skeletal muscle senescence and ammonia-lowering therapies have the potential to reverse SAMP and sarcopenia in cirrhosis.



Kumar A, et al., Abstract 51.

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Thrombospondin-2 as a biomarker for non-alcoholic steatohepatitis and advanced liver fibrosis

Aims

It is clinically important to non-invasively identify non-alcoholic steatohepatitis (NASH) and advanced fibrosis. We sought for their noninvasive biomarkers.

Methods

We performed whole-transcriptome analysis of liver tissues from 98 NAFLD patients and sought for secreted proteins that identify patients with NASH or advanced fibrosis. We examined the usefulness of serum levels of candidate proteins to identify patients with NASH or advanced fibrosis among 213 NAFLD patients.

Main Findings

Intrahepatic thrombospondin-2 mRNA levels showed the highest AUROC of 0.915 and 0.957 for diagnosing NASH and advanced fibrosis, respectively.

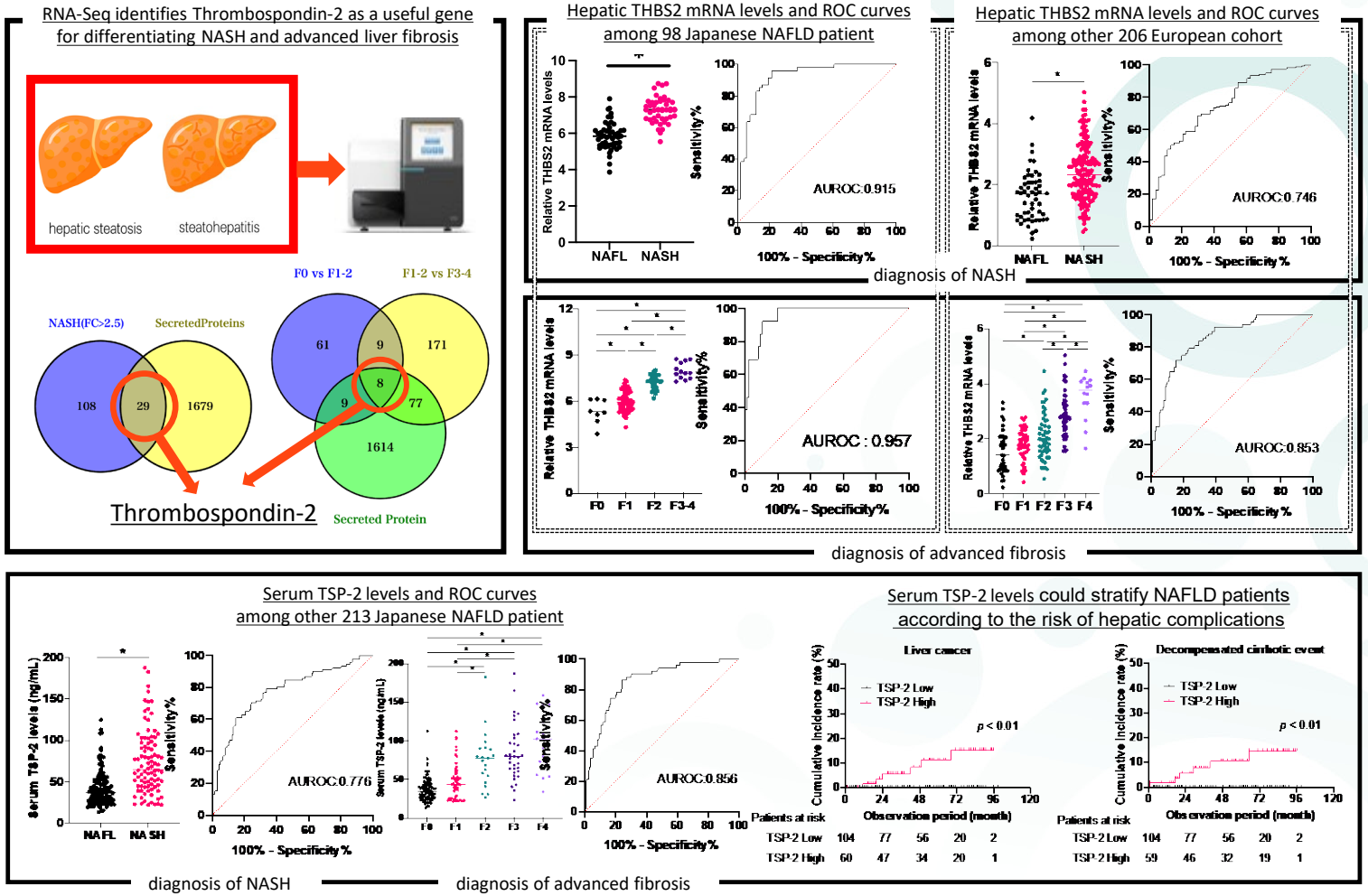
Serum levels of thrombospondin-2 were also significantly elevated in NASH and advanced fibrosis patients of the other cohort and AUROC for diagnosing NASH and advanced fibrosis was 0.776 and 0.856, respectively.

Serum TSP-2 could stratify NAFLD patients according to the risk of adverse hepatic outcomes.

Conclusions

THBS2/TSP-2 is a novel biomarker for NASH and advanced fibrosis in NAFLD patients and could be a potential therapeutic target of liver fibrosis.

Kozumi K, et al., Abstract 73.



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Aging reduces liver resiliency by dysregulating Hedgehog signaling

Hypothesis During aging, signaling that assures hepatocyte resiliency becomes defective, resulting in impaired liver regeneration and thus enhanced vulnerability to liver damage

Methods

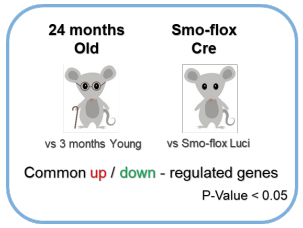
- Compare hepatocyte responses to a regenerative challenge (70% partial hepatectomy, PHx) in old and young mice to identify differences in regenerative responses, gene expression, and signaling pathways.
- Manipulate the candidate signaling pathway in young mice; repeat regenerative challenge; determine if this reproduces the impaired regenerative phenotype that was noted in the old mice.
- Identify plausible targets of the dysregulated signaling pathway that mediate loss of resiliency/impaired regeneration.

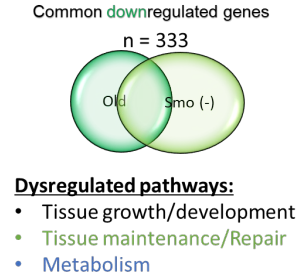
Main Findings

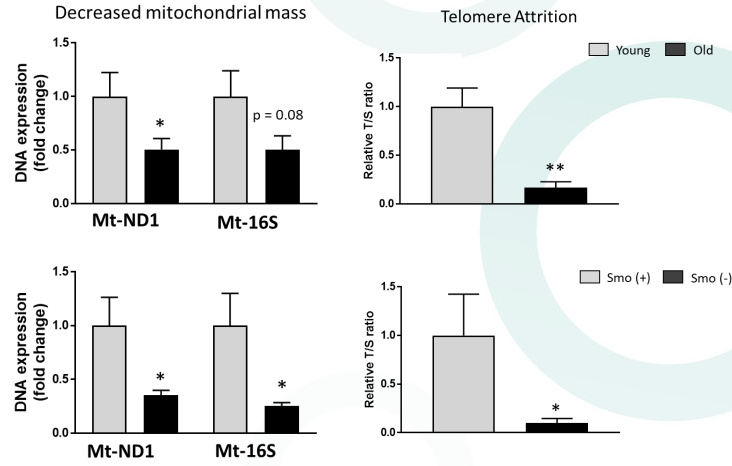
- Liver regeneration is effective and accompanied by significant activation of the Hedgehog signaling pathway in young mice.
- Liver regeneration is inhibited in old mice; old mice also exhibit lower Hedgehog pathway activity than young mice before PHx and fail to increase Hedgehog signaling after PHx.
- In young mice, disrupting hepatocyte Hedgehog signaling (by deleting Smoothened, Smo) phenocopies defective regenerative responses of old mice.
- Deleting Smo in young hepatocytes rapidly evokes mitochondrial dysfunction and telomere shortening (responses that are evident in old hepatocytes and which are known to inhibit cellular resiliency during aging).

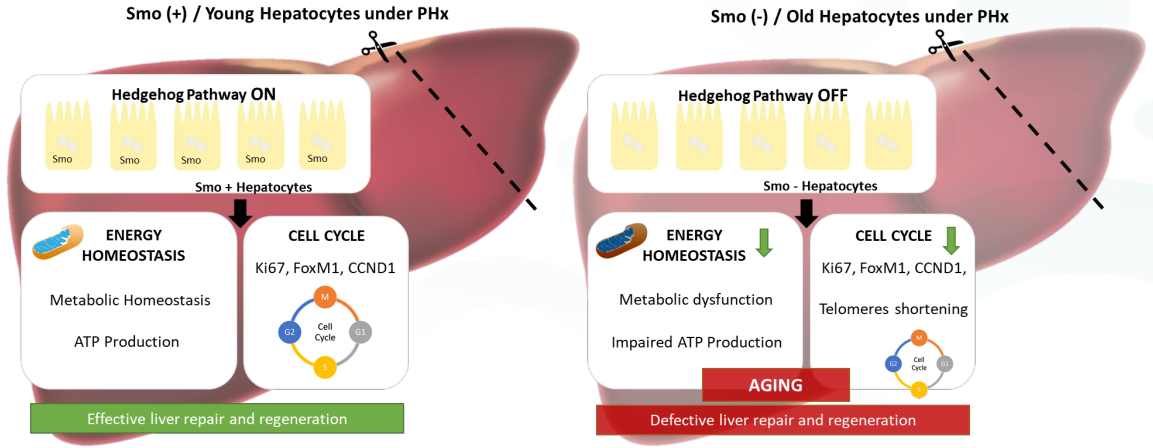
Conclusions

- Disrupting Hedgehog signaling in hepatocytes reduces hepatocyte resiliency and promotes liver degeneration.









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Diaz RM, et al., Abstract 151.

Splicing machinery landscape characterization in hepatocellular carcinoma reveals a central role of EIF4A3 in hepatocarcinogenesis

Aim

- To explore the putative dysregulation, role, and clinical implications of the splicing machinery in HCC

Methods

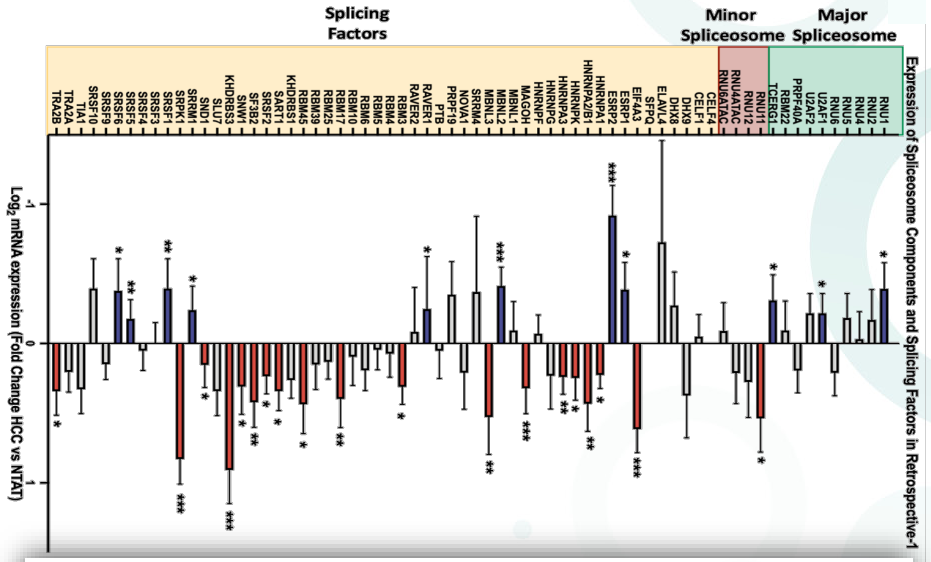
- Expression array of spliceosome components and splicing factors in human HCC samples and functional and molecular characterization of EIF4A3 silencing *in vitro* and *in vivo.*

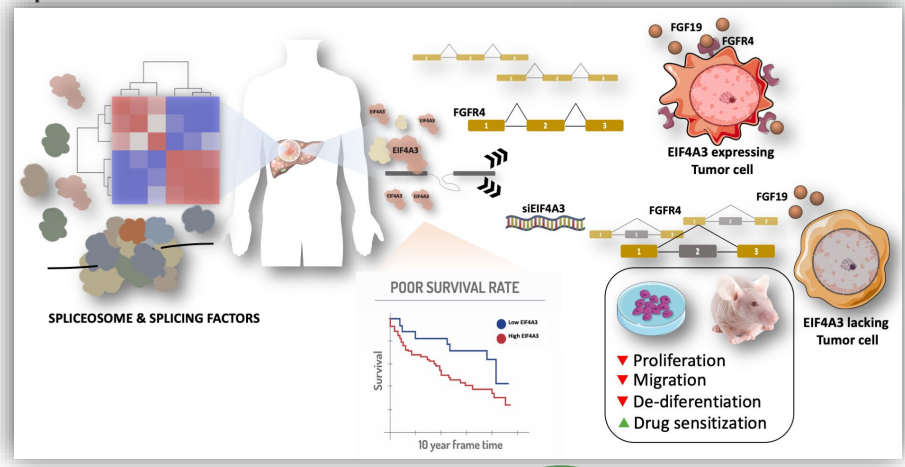
Main Findings

- 42% of analyzed spliceosome components and splicing factors were dysregulated in tumoral tissue, wherein EIF4A3, ESRP2, SRPK1, and RBM3 showed the highest clinical implications.
- *EIF4A3* silencing *in vitro* and *in vivo* reduced HCC aggressiveness through the modulation of the expression and splicing of many genes, including FGFR4, blunting FGFR4/FGF19 signaling.

Conclusions

- The splicing machinery is profoundly dysregulated in HCC, wherein it may represent a promising source of novel diagnostic, prognostic, or therapeutic targets.





Hermán-Sánchez N, et al., Abstract 154.

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Microtubule modifications that alter protein trafficking are an early marker for alcohol-induced liver injury

Aim

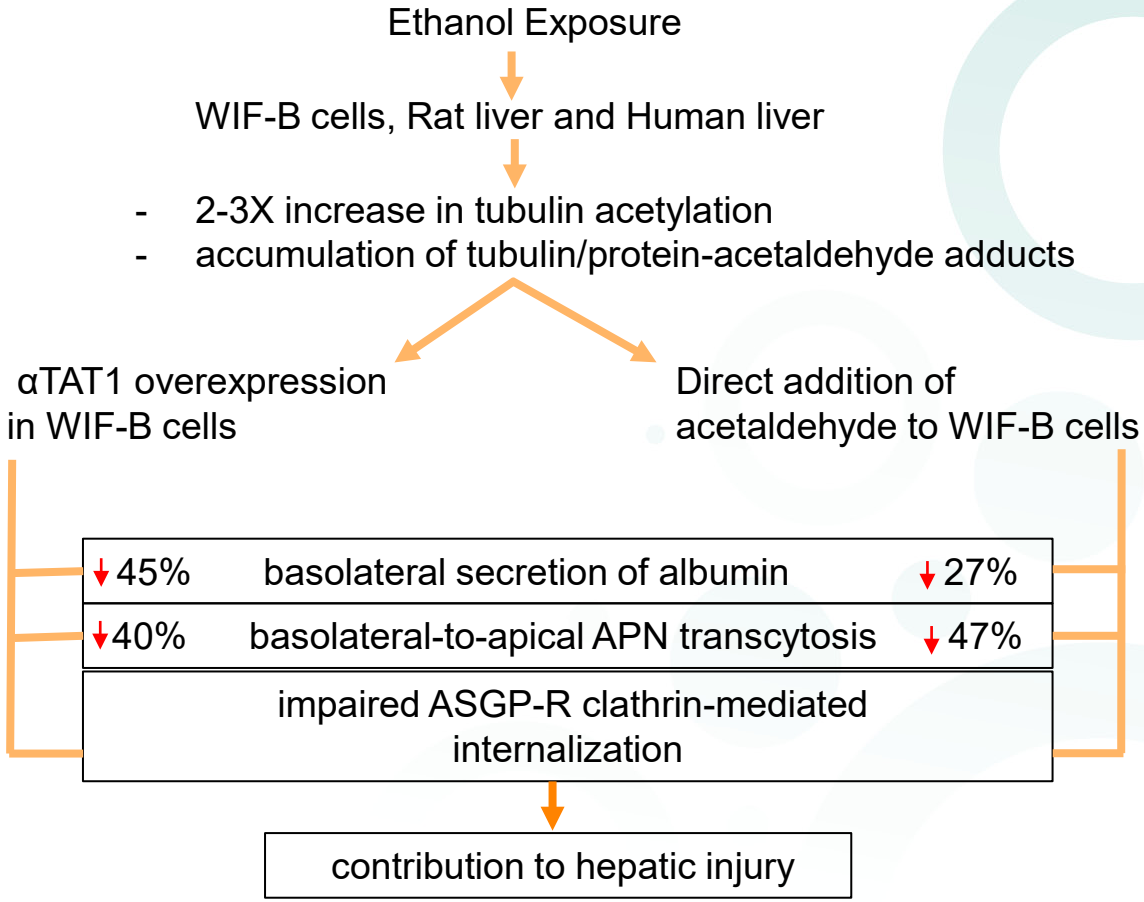
- To directly investigate the relationship between microtubule modification by acetylation or acetaldehyde adduction to defects in hepatic protein trafficking

Methods

- The confirmed ethanol-induced microtubule modifications (acetylation and adduct formation) were produced in WIF-B cells by overexpressing tubulin specific acetylase (αTAT1) or by treating with acetaldehyde directly followed by monitoring selected trafficking steps.

Conclusion

- Ethanol-induced microtubule modification by acetylation or adduct formation can both explain known alcohol-induced defects in protein trafficking possibly through competing for modification of the same lysine residues.



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Adhikari R, et al., Abstract 155.

Emergence of highly fibrogenic *Lrat+Fbln2+* hepatic stellate cell subpopulation in alcoholic hepatitis

Hypothesis/Aim/Objective

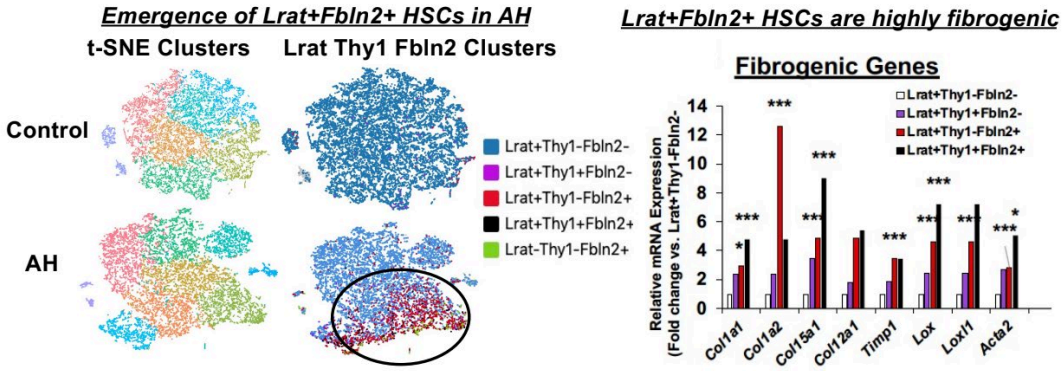
- Unique Hepatic Stellate Cell (HSC) subsets exist in alcoholic hepatitis (AH)

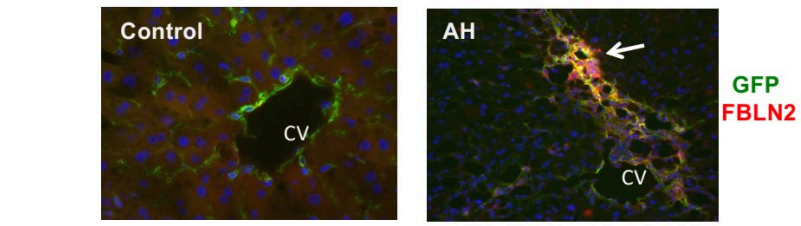
Methods

- Isolated VitA+ and VitA- Col1a1-GFP+ cells via FACS for scRNA sequencing.
- Use of LratCre;mTmG mice subjected to the AH regimen for genetic lineage tracing.

Conclusions

- The Lrat+Fbln2+ HSC subset reflects HSC plasticity, arising from Lrat+HSCs.
- Lrat+Fbln2+ HSCs are highly fibrogenic and may be considered as a therapeutic target.





Fujiwara R, et al., Abstract 171.

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Modulation of a gut neuroimmune circuit can alter NAFLD development in a murine high-fat diet model

Hypothesis/Aim/Objective

- Investigate the modulation of VIP neuron and type 3 Innate Lymphoid Cells neuroimmune circuit for the control of diet-induced NAFLD development in a pre-clinical model

Methods

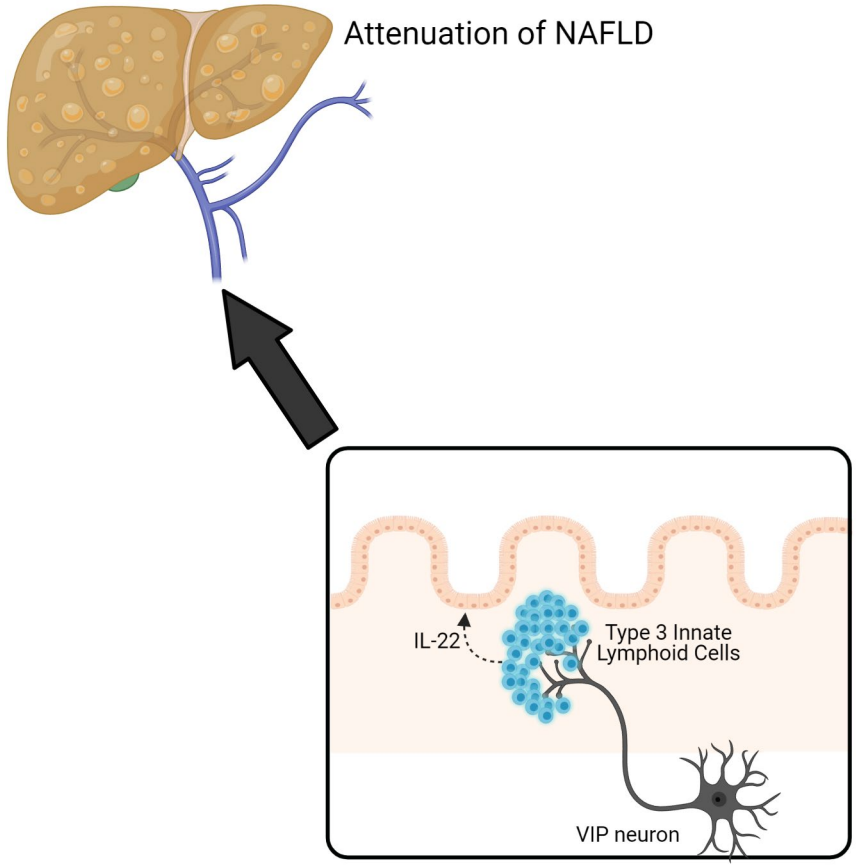
- Murine genetic and chemogenetic models placed on high-fat diet (HFD) to induce NAFLD development.

Main Findings

- IL-22 production by ILC3 was reduced in animals under HFD.
- Mice lacking VIPR2 in ILC3 exhibited higher IL-22 production vs WT littermates under HFD. This genetic blockage of VIPen-ILC3 interaction reduced both the development of liver steatosis and increased body weight associated with this diet.
- Global VIPen inhibition using chemogenetic approach also resulted in significant reduction in hepatic steatosis under HFD.

Conclusions

- Modulation of the VIPen-ILC3 neuroimmune axis can ameliorate the development of hepatic steatosis.



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Nguyen H, et al., Abstract 184.

Copper transporter *ATP7B* modulate susceptibility to anti-tuberculosis drug-induced liver injury (AT-DILI)

Aim

To identify predisposing genetic factors of AT-DILI

Methods

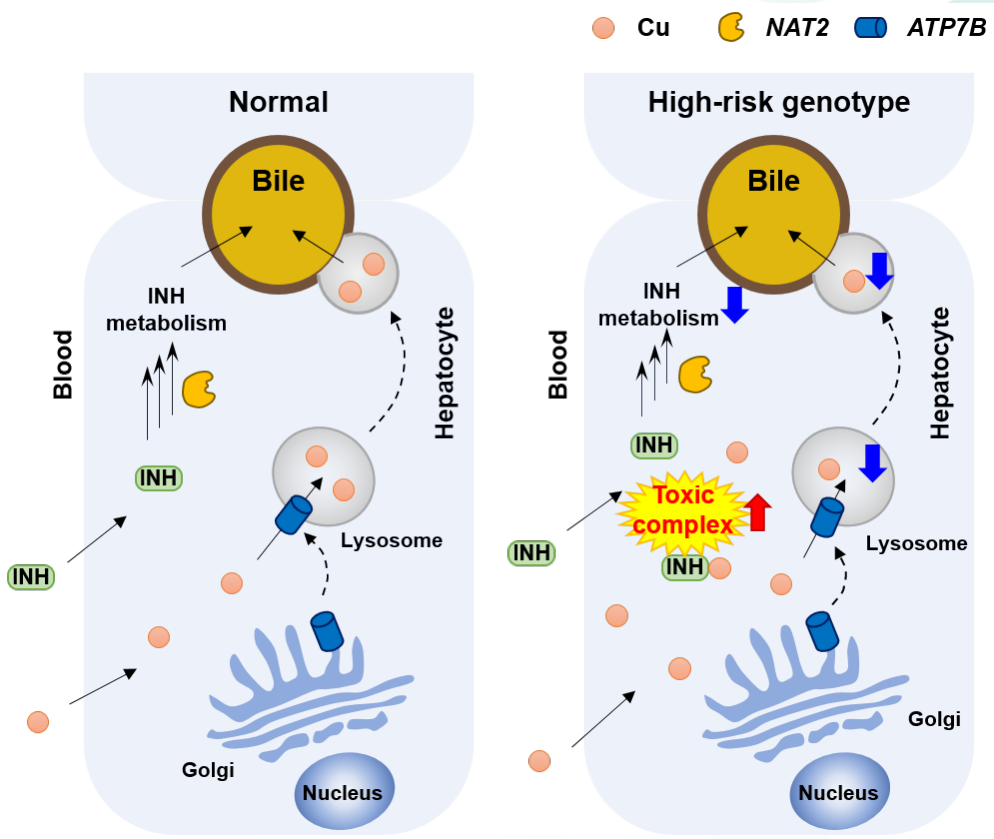
- Exploratory study in 112 patients using next-generation sequencing for 380 pharmacogenes and replication study in 165 patients
- *In vitro* toxicity assay using HepG2 wild-type and ATP7B knock-down cells

Main Findings

- *NAT2* ultra-slow acetylator genotypes (UAs) independently increased the risk of AT-DILI (OR 5.6 [2.5-13.2], $P = 7.2\times10^{-6}$).
- *ATP7B* 832R/R (rs1061472) showed co-occurrence with *NAT2* UAs ($P = 0.017$) and amplified the risk (OR 32.5 [4.5-1423], $P = 7.5\times10^{-6}$).
- Copper amplifies INH toxicity up to ~3,500-folds and *ATP7B* dysfunction increases the toxicity in HepG2 cells.

Conclusions

Copper transporter *ATP7B* 832R/R combined with *NAT2* UA increases susceptibility to AT-DILI via synergistic toxicity between Cu and INH.



***ATP7B* as a risk modifier in AT-DILI**

TLMdX®

Yoon J, et al., Abstract 229.

Basic and Translational Research

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