AASLD November 13-16, 2020
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THE BEST OF THE LIVER MEETING® 2020

Alcohol-associated Liver Disease

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About the program:

Best of The Liver Meeting 2020 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.

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Use of these slides:

Fecal microbiota transplant improves long-term outcomes in patients with alcohol use disorder (AUD)

Objective

To define the long-term safety and impact of FMT compared to placebo in patients with AUD and cirrhosis in a randomized, clinical trial

Methods

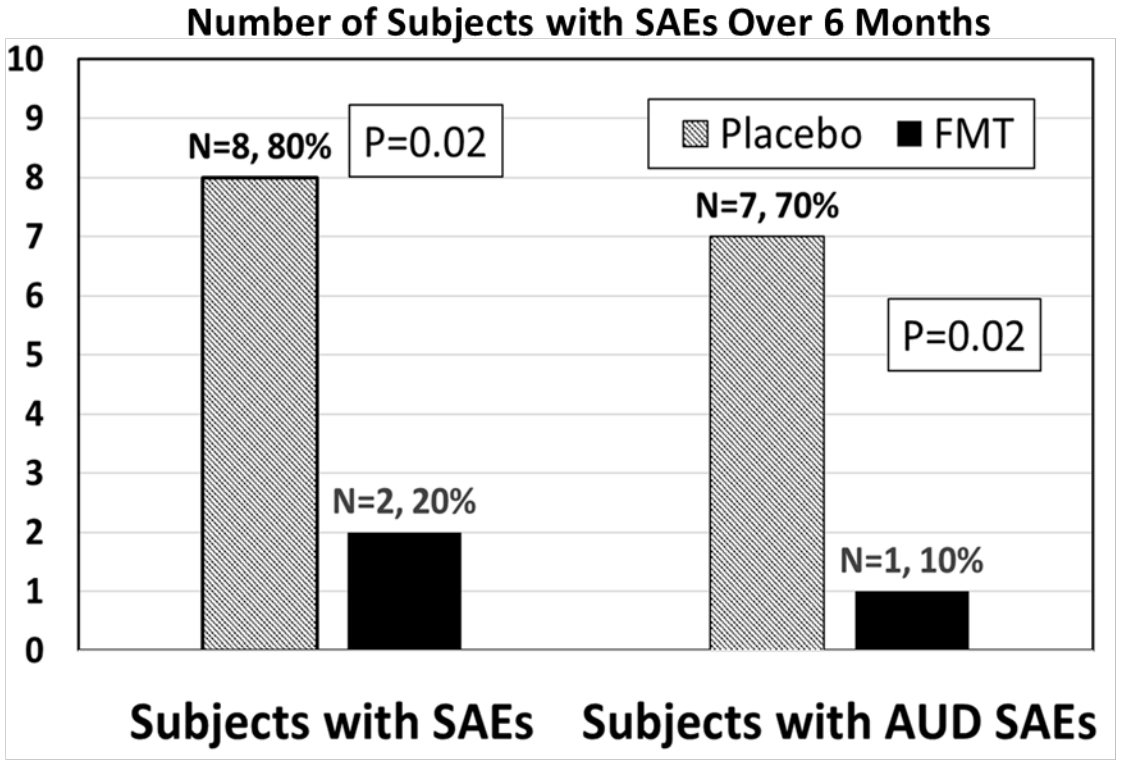
Phase 1 double-blind, randomized, placebo-controlled trial of FMT in men with cirrhosis with 6-month follow-up for serious adverse events (SAE) related/unrelated to AUD

Main Findings

SAEs, including AUD-related, per patient [median (IQR), 1.5 (1.25) vs 0 (0.25) in FMT, *p*=0.02] and total were higher in placebo compared to FMT-assigned patients at 6 months (see Figure).

Conclusions

FMT is safe and well-tolerated, and associated with reduction in short-term craving, with lower total and AUD-related serious adverse events over long-term follow-up over 6 months.



Bajaj JS, et al., Abstract 7

The effect of malnutrition on the infectious outcomes of hospitalized patients with alcoholic hepatitis

Objective

To identify the relationship between malnutrition and infectious risks in patients admitted with alcoholic hepatitis

Methods

US national registry of inpatient data was used to analyze the relationship between malnutrition and local and systemic infection rates in patient admitted with alcoholic hepatitis.

Conclusions

This study showed malnutrition is associated with increased mortality and increased rates of sepsis and localized infections in patients admitted with alcoholic hepatitis.

Univariate Variable	Malnutrition-Present	Malnutrition-Absent	p-value	OR	95%CI
	n = 10,132 (11.3%)	n = 79,183 (88.7%)			
Age (median years)	50.8	47.2y	< 0.01		
Female (%)	39.50	30.00	< 0.01		
Mortality (%)	5.03	1.88	< 0.01	2.77	(2.50-3.07)
Sepsis (%)	14.10	4.82	< 0.01	3.24	(3.03-3.45)
Pneumonia (%)	10.50	4.15	< 0.01	2.70	(2.51-2.90)
UTI (%)	14.70	7.49	< 0.01	2.13	(2.00-2.26)
Cellulitis (%)	3.09	2.05	< 0.01	1.52	(1.35-1.72)
Cholangitis (%)	0.34	0.14	< 0.01	2.34	(1.59-3.43)
Clostridium Difficile (%)	1.67	0.70	< 0.01	2.40	(2.02-2.85)

Dependent Variable	Independent Variable	aOR	95%CI	p-value
Hospital Mortality	Malnutrition	1.35	(1.20-1.52)	< 0.01
Sepsis	Malnutrition	2.24	(2.09-2.41)	< 0.01
Pneumonia	Malnutrition	1.41	(1.24-1.60)	< 0.01
Uti	Malnutrition	1.57	(1.47-1.68)	< 0.01
Cellulitis	Malnutrition	1.41	(1.24-1.60)	< 0.01
Cholangitis	Malnutrition	1.71	(1.13-2.53)	< 0.01
C Diff Infection	Malnutrition	2.05	(1.71-2.45)	< 0.01

Lee DU, et al., Abstract 37

Increasing alcohol use and alcohol-associated hepatitis among individuals ≤35 years: analysis of 3 US databases

Aim

To examine host factors associated with increasing burden of alcohol-associated liver disease (ALD) among young adults 35 years or below.

Methods

We analyzed NHANES, national inpatient sample (NIS), and UNOS (2006-2016).

Main Findings

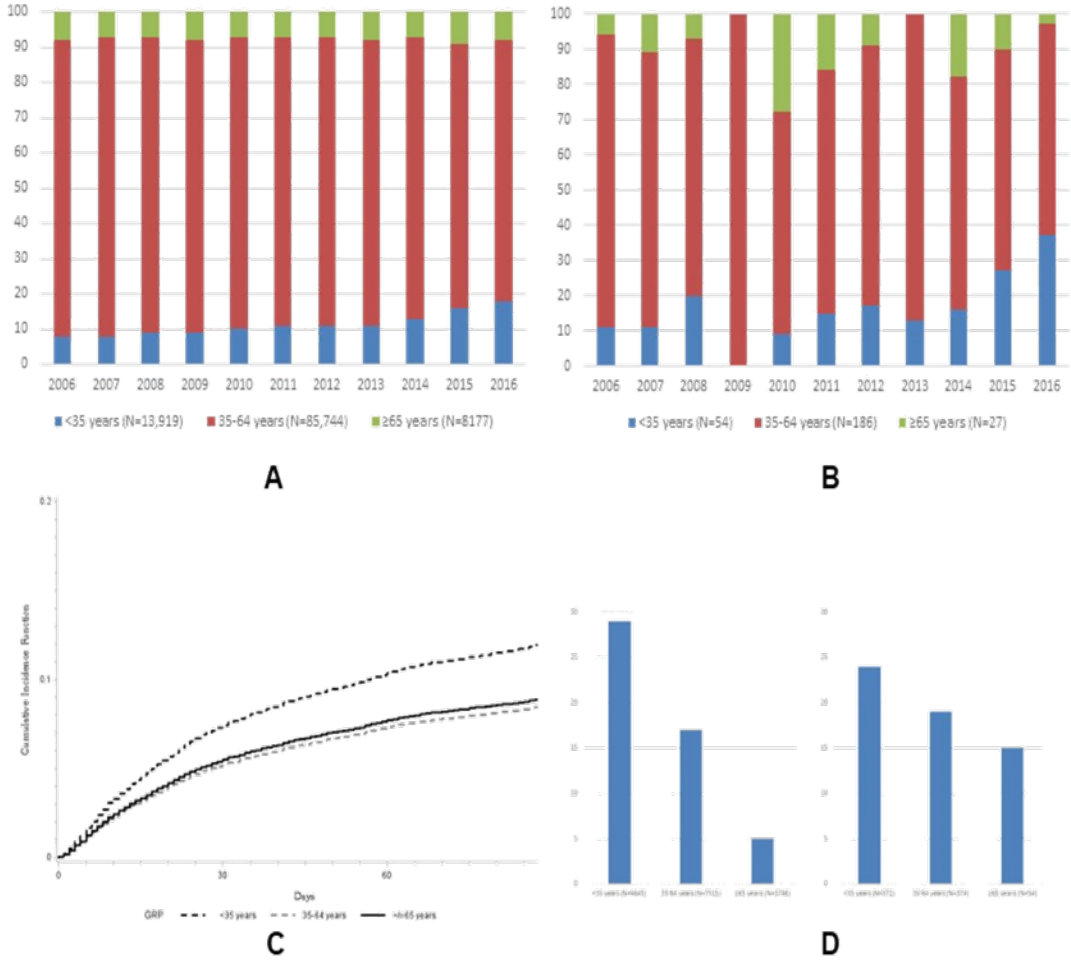
Of 593,600 ALD admissions, 5%, 77%, and 18% among <35 (G1), 35-64 (G2), and ≥65 (G3) years. G1 vs G2-G3 were females (34 vs 28-25%), Hispanics (25 vs 17-15%), and have AH (48 vs 19-8%).

- % AH increased from 8% in 2006 to 18% in 2016 (see Figure A).
- AH and ACLF were associated with 1.2 and 7.2 folds increased mortality.
- Of 20,242 ALD LT listings (4%, 84%, and 12% in G1-G3, respectively), G1 vs G2-3 candidates were females (25 vs 26-18%), Hispanics (23 vs 21-18%), have AH (8 vs 1%), and ACLF (51 vs 28-23%).
- % AH among ALD listings increased 11% in 2006 to 37% in 2016 (see Figure B).
- Cumulative 90-d waitlist (WL) mortality higher in G1 vs G2-3, *P*<0.03 (see Figure C).
- In a fine and gray model, females, Black and other race, AH, ACLF, MELD at listing were associated with WL mortality.
- Of 15,906 subjects in NHANES database, harmful alcohol use (>2 drinks/d in females and >3 in males in past 12 months) and binging was highest in G1 (see Figure D).
- In a logistic model, alcohol use was over 8 folds and 2 folds higher in G1 vs G3 and G2, respectively. Male gender and Hispanic race were other predictors.

Conclusions

AH is contributing to increasing ALD burden in the US among individuals aged ≤35 years and is associated with significant gender and ethnic disparities. Studies are needed to develop strategies on screening for harmful alcohol use and interventions to reduce alcohol use in young individuals, as basis to reduce burden from ALD.

Singal A, et al., Abstract 38



Chronic plus acute binge alcohol induces steatohepatitis and fibrosis in mice with hepatic deficiency of tuberous sclerosis 1

Aim

To investigate chronic plus acute binge alcohol-induced liver injury and fibrosis in mice with persistent hepatic mTORC1 activation

Methods

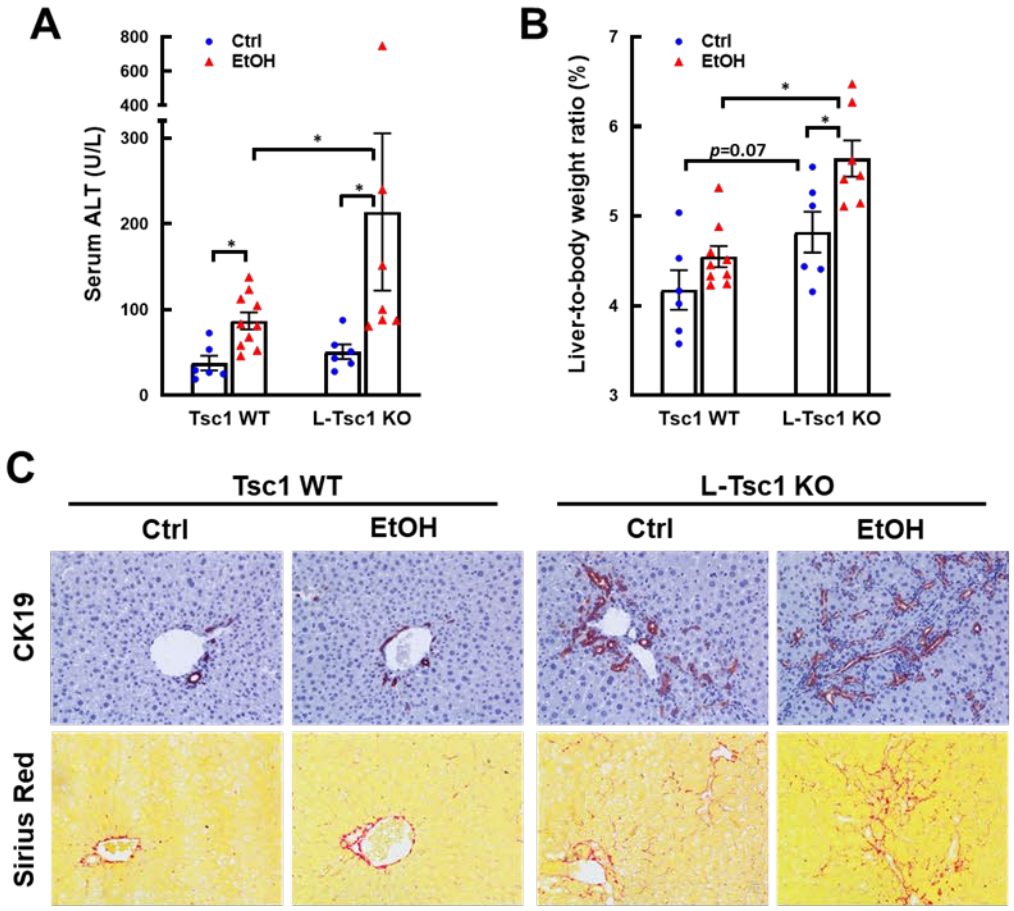
Liver-specific Tsc1 KO ($Tsc1^{flox/flox}$, Albumin-Cre+, L-Tsc1 KO) mice and their matched wild type ($Tsc1^{flox/flox}$, Albumin-Cre-, WT) littermates are subjected to chronic plus acute binge alcohol model (Gao-binge alcohol model).

Main Findings

Hepatic Tsc1 deletion increases liver injury, hepatomegaly, ductular reaction, and fibrosis in alcohol-fed mouse livers.

Conclusions

Combination of genetic loss of Tsc1 and alcohol exposure leads to persistent mTORC1 activation and decreased autophagy resulting in increased cholangiocyte features, inflammation, and liver fibrosis, which phenocopy human alcoholic hepatitis.



Chao X, et al., Abstract 40

Stress responsive gene *FKBP5* mediates alcohol-induced liver injury through hippo pathway and CXCL1 signaling

Aim

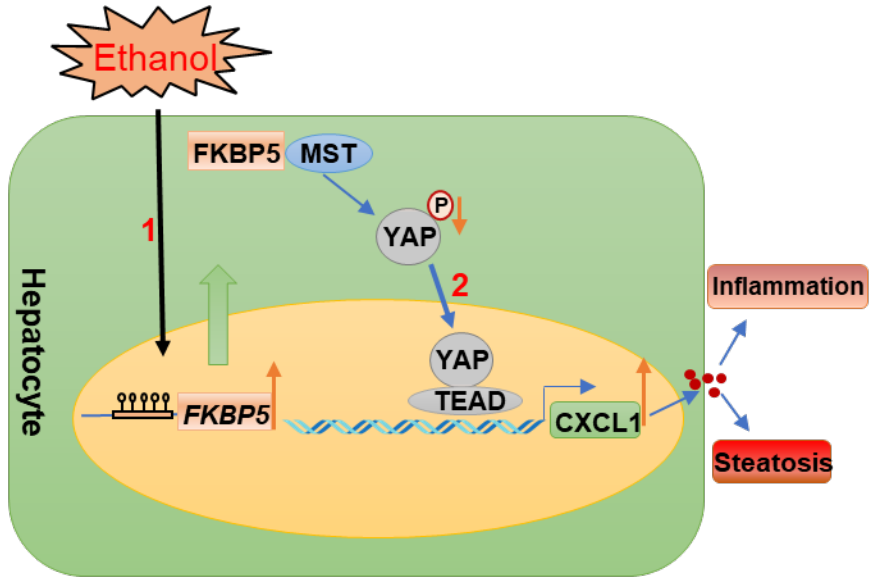
To examine the molecular mechanism of *FKBP5* in alcohol-induced liver injury

Methods

Wild type (C57BL/6J) and *FKBP5*$^{-/-}$ mice were fed with either control or ethanol containing diet for 10 days followed by a single binge of maltose or ethanol. The hepatic expression of *FKBP5* was also examined in patients with alcohol-associated liver disease.

Main Findings

- Hepatic *FKBP5* transcripts and protein expression are increased in patients with ALD and in ethanol-fed wild type mice.
- *FKBP5*$^{-/-}$ mice are protected against alcohol-induced hepatic steatosis and inflammation.
- Ethanol-induced *FKBP5* expression is secondary to hypomethylation at its 5' UTR promoter region.
- *FKBP5* interacts with Yap upstream kinase, Mst1, leading to Yap nuclear translocation and activate transcription factor Tead1.
- Activation of Tead1 led to increased expression of its novel target, CXCL1, mediates neutrophil recruitment, causing hepatic inflammation and neutrophil infiltration.



Conclusions

We identified a novel role of FKBP5-YAP-TEAD1-CXCL1 axis in the pathogenesis of ALD. Loss of *FKBP5* ameliorates alcohol-induced liver injury, suggesting its potential role as the therapeutic target for ALD.

Kusumanchi P, et al., Abstract 41

RvD1-FPR2 signaling attenuates alcohol-associated liver injury via suppression of hepatic STAT1 activity and pyroptosis

Objective

Elucidate whether RvD1-FPR2 signaling is protective in alcohol-associated liver disease (ALD) and identify potential mechanisms

Methods

Animal models of experimental ALD, cell culture, and human samples were used.

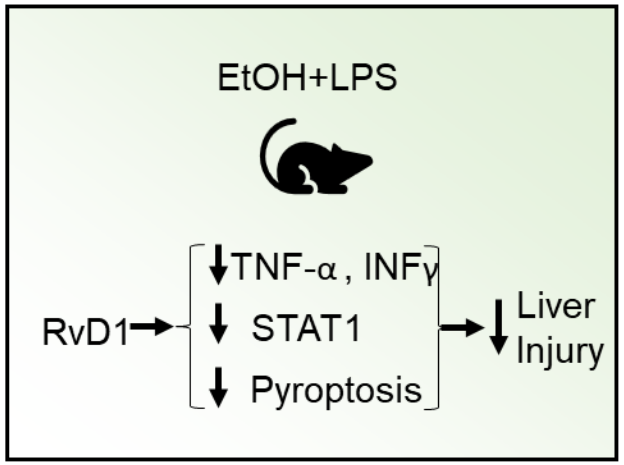
- A RvD1 treatment paradigm was tested in an ALD model and *Fpr2*$^{-/-}$ mice were used in a proof of principle ALD study.
- WT and *Fpr2*$^{-/-}$ Kupffer cells and macrophages were used for flow cytometry, gene expression, and cytokine release assays.
- Alcoholic hepatitis patient liver samples were used to measure RvD1, FPR2, GPR32, STAT1, and pyroptosis mediators.

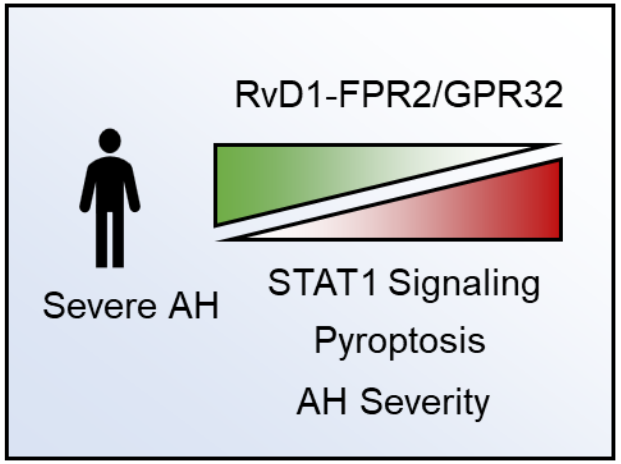
Main Findings

RvD1-FPR2 signaling is compromised in AH and protective in ALD models.

Conclusions

RvD1-FPR2 signaling is protective in ALD through attenuation of STAT1 and pyroptosis.





Hardesty JE, et al., Abstract 42

Deletion of myeloid-specific ER resident chaperone GP96 decreases alcohol-induced inflammation by facilitating restorative macrophages conferring protection from liver injury

Hypothesis

Myeloid-specific GP96 plays a crucial role in liver macrophage activation and contributes to alcohol-induced liver injury.

Methods

M-GP96KO mice subjected to different models of alcohol feeding

Main Findings

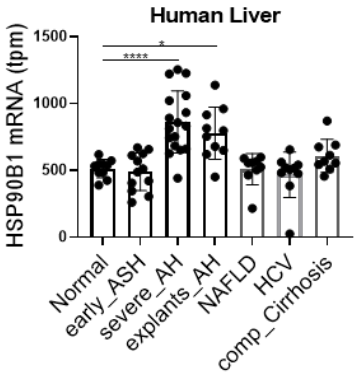
- HSP90B1/GP96 is elevated in human AH livers and in mouse alcoholic liver, prominently in liver macrophages.
- M-GP96 deletion protects against alcohol-induced liver injury, reduces inflammatory markers, and facilitates restorative macrophage markers.
- Targeted inhibition of M-GP96 reduces inflammation.

Conclusions

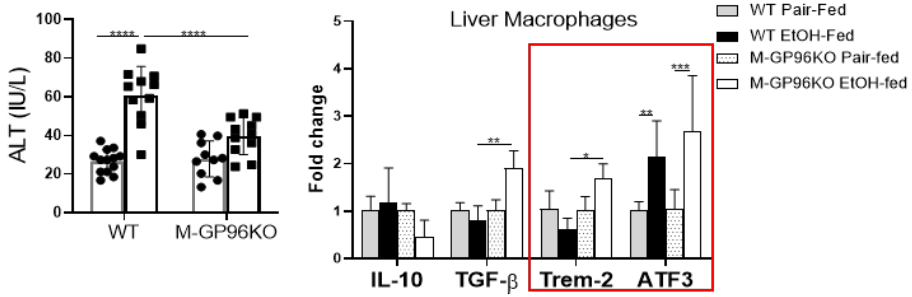
M-GP96 deletion favors restorative phenotype in liver macrophages, prevents ALD pathogenesis, and its targeted inhibition represents a promising approach to curb inflammation in AH patients.

Ratna A, et al., Abstract 163

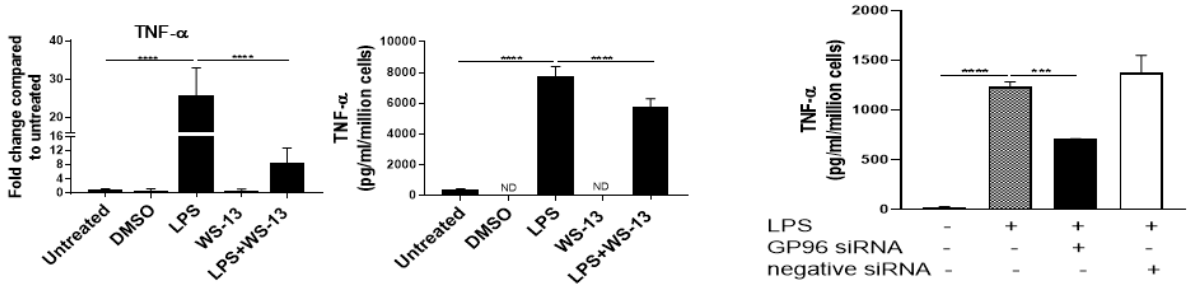
HSP90B1/GP96 Is Induced in Human AH Patients



M-GP96 Deficiency Alleviates Chronic Alcohol-Induced Liver Injury and Facilitates Restorative Macrophages



GP96 Inhibition Using WS-13 Inhibitor and siRNA Reduces LPS-induced Pro-inflammatory Cytokine Production



Application of supervised machine learning techniques for classification of alcohol-associated hepatitis and acute cholangitis in patients with elevated liver enzymes and systemic inflammatory response

Aim

To use supervised machine learning techniques and feature selection to separate out patients with alcohol-associated hepatitis (AH) and cholangitis based on routine laboratory variables

Methods

- Retrospective study of 460 patients admitted to Mayo Clinic, Rochester with either AH (N=265) or cholangitis (N=195)
- Seven supervised machine learning techniques trained to correctly classify AH vs cholangitis using routine lab variables.

Conclusions

Supervised machine learning techniques and feature selection algorithms can serve valuable roles in cases of diagnostic uncertainty where accurate histories are not available.

Table 1: Predictive Performance Metrics Using 10 Laboratory Variables

Algorithm	Accuracy	AUC	PPV	Sensitivity	Specificity
k-Nearest Neighbor	0.914	0.938	0.944	0.906	0.931
Logistic Regression	0.925	0.977	0.931	0.939	0.910
SVM	0.927	**0.983**	0.924	**0.956**	0.895
Decision Tree	0.865	0.861	0.877	0.887	0.834
Naïve Bayes	0.874	0.947	0.861	0.932	0.804
ANN	**0.936**	0.960	**0.956**	0.931	**0.945**
Random Forest	0.927	0.977	0.928	0.948	0.902

SVM, Support Vector Machine; **ANN,** Artificial Neural Network.

Ahn JC, et al., Abstract 219

Deletion of ceramide synthase 6 attenuates alcoholic liver disease by downregulating lipid droplet associated proteins

Objectives

- Metabolic pathways involving ceramide synthase 6 (CerS6) are perturbed in alcoholic liver disease (ALD).
- We investigated the role of ceramide synthase 6 (CerS6) in the regulation of ethanol (EtOH)-induced hepatic lipid accumulation.

Methods

- CerS6 was deleted in human hepatocytes (VL-17A) using CRISPR/Cas9, and incubated with either 0mM or 100mM EtOH for 48 hr.
- WT and CerS6 KO mice received either Lieber-Decarli control or 15% EtOH diet for 6 weeks.

Main Findings

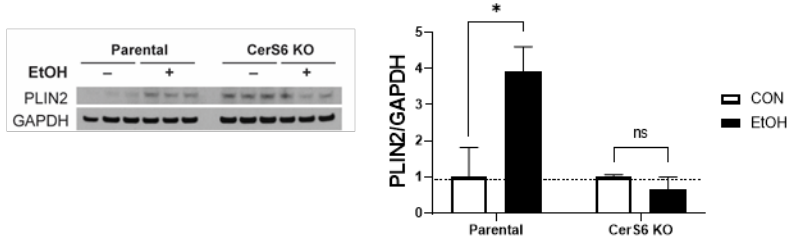
CerS6 deletion downregulates lipid droplet (LD)-associated proteins and reduces steatosis in the liver.

Conclusions

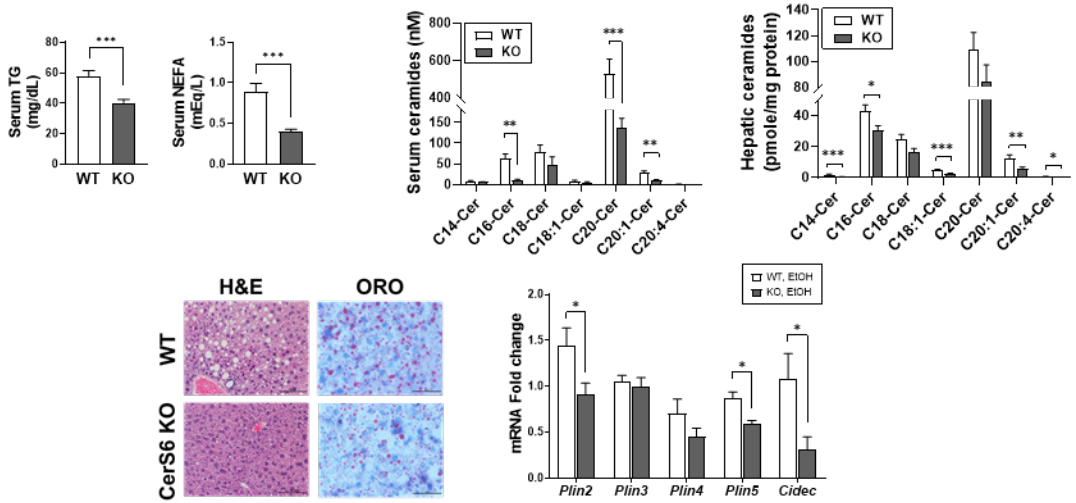
CerS6 may serve as a potential therapeutic target for early-stage ALD.

Jeon S, et al., Abstract 227

CerS6 Deletion Using CRISPR/Cas9 Reduces Ethanol-mediated PLIN2 Upregulation in VL17A Cells



CerS6 Ablation Reduces Serum and Hepatic Lipids and Downregulates the Expression of LD-associated Proteins in EtOH-fed Mice



Stanford Integrated Psychosocial Assessment for Transplant (SIPAT) outperforms SALT in predicting alcohol relapse in patients with alcoholic liver disease undergoing evaluation for liver transplant

Aim

To compare clinical characteristics and SIPAT domains/subdomains between patients with ALD who did and did not have alcohol relapse after LT evaluation including post-transplantation

Methods

- N=348 patients with ALD were identified from a database of 1447 patients undergoing LT evaluation between 2012-2019 at Loyola University Medical Center. Of those evaluated, 30.5% (n=106) received a liver transplant.
- SIPAT scores were compared by alcohol relapse using chi-square or Fisher's exact tests for nominal variables and t-tests or Wilcoxon rank sum tests for continuous variables.

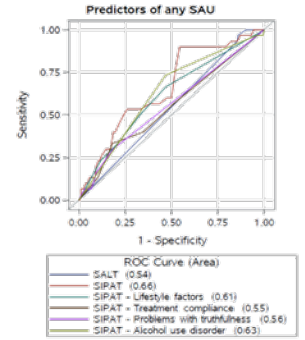
Main Findings

Alcohol relapse was associated with higher SIPAT scores, readiness/illness mgmt. and substance abuse subscale. Our model showed younger age, severe alcohol hepatitis, and treatment compliance and adherence subscales. SIPAT outperformed SALT in predicting SAU, but both performed poorly.

Conclusions

Overall SIPAT and subscales (namely treatment compliance and adherence) is associated with alcohol relapse. SIPAT and SALT both perform poorly overall to predict alcohol relapse in ALD.

	Overall n=348	Alcohol relapse n=56 (16.1%)	No alcohol relapse n=292 (83.9%)	p-value
Total SIPAT, median (IQR)	28 (21-37)	32 (26-40)	27 (20-36)	0.01
Subscales, median (IQR)				
Readiness and illness management	4 (2-9)	8 (3-12)	4 (1-9)	0.02
Social support level	4 (0-6)	2 (0-7)	4 (0-6)	0.54
Psychological stability	5 (2-8)	5 (2-8)	5 (2-8)	0.85
Lifestyle and substance use	13 (10-17)	15 (12-20)	13 (10-16)	0.02



	Model 1		Model 2		Model 3		Model 4	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age (5 year increase)	0.83 (0.70-0.98)	0.03	0.79 (0.67-0.92)	0.003	0.83 (0.70-0.98)	0.02	0.83 (0.70-0.98)	0.03
Alcoholic hepatitis								0.04
Yes	2.05 (0.99-4.21)	0.052			2.07 (1.01-4.24)	0.048		
No	1 (reference)				1 (reference)		1 (reference)	
Treatment Compliance/Adherence		0.09		0.11		0.03	2.15 (1.05-4.40)	
Excellent	1 (reference)		1 (reference)		1 (reference)			
Good or moderate	1.12 (0.53-2.34)		1.02 (0.49-2.13)		1.20 (0.58-2.47)			
Limited or poor	2.26 (1.04-4.89)		2.09 (0.97-4.53)		2.57 (1.25-5.27)			
Lifestyle factors								0.01
Self-initiated/responsive							1 (reference)	
Reluctant/late/resistant							2.14 (1.18-3.88)	
Influence of Personality Traits		0.46		0.40				
None	1 (reference)		1 (reference)					
At least minimal	1.37 (0.60-3.14)		1.42 (0.63-3.22)					
Problems with Truthfulness		0.77		0.70				
None	1 (reference)		1 (reference)					
At least minor	1.12 (0.52-2.40)		1.16 (0.55-2.46)					
Alcohol use disorder				0.20				
Not dependent			1 (reference)					
Dependent			1.49 (0.81-2.77)					
Model AUC (95% CI)	0.72 (0.65-0.79)		0.71 (0.64-0.78)		0.71 (0.64-0.79)		0.71 (0.63-0.78)	

Singh J, et al., Abstract 286

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