content were greater in steatotic livers from donors who consumed alcohol when compared to those who did not. In conclusion, these data suggest that ethanol exposure enhances HSC activation through HA production. Inhibiting HA production by HSC may therefore attenuate liver disease progression in ALD patients. *Supported by P20GM103549 & P30GM118247.*

2159 A Non-mitogenic FGF1$^{\Delta HBS}$ Variant Protects from Nonalcoholic Fatty Liver Disease via Activating AMPK-Mediated Pathways

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Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disorder. Fibroblast growth factor 1 (FGF1) demonstrated protection against NAFLD in type 2 diabetic and obese mice by an uncertain mechanism, and its strong mitogenic activity limits its potential clinical application. Our recently engineered FGF1 variant (FGF1$^{\Delta HBS}$) exhibits greatly reduced proliferative potential, while preserving the full metabolic activity of wild-type FGF1. We investigated the therapeutic activity and mechanism of FGF1$^{\Delta HBS}$ against NAFLD in the present study. FGF1$^{\Delta HBS}$ administration was effective in 9-month old *db/db* mice with NAFLD; liver weight, lipid deposition and inflammation declined, and liver injury decreased. FGF1$^{\Delta HBS}$ reduced oxidative stress by stimulating nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) and elevation of antioxidant protein expression. FGF1$^{\Delta HBS}$ also inhibited activity and/or expression of lipogenic genes, coincident with phosphorylation of AMP-activated protein kinase (AMPK) and its substrates. Mechanistic studies on palmitate exposed hepatic cells demonstrated that NAFLD-like oxidative damage and lipid accumulation could be reversed by FGF1$^{\Delta HBS}$. In palmitate-treated hepatic cells, siRNA knockdown of Nrf2 abolished only FGF1$^{\Delta HBS}$ anti-oxidative actions but not improvement of lipid metabolism. In contrast, AMPK inhibition by pharmacological inhibitor or siRNA abolished FGF1$^{\Delta HBS}$ benefits on both oxidative stress and lipid metabolism that were FGF receptor 4 (FGFR4) dependent. Further support of these findings is that liver-specific AMPK knockout abolished therapeutic effects of FGF1$^{\Delta HBS}$ against high-fat/high-sucrose diet-induced hepatic steatosis. Moreover, FGF1$^{\Delta HBS}$ improved high-fat/high-cholesterol diet-induced steatohepatitis and fibrosis in apolipoprotein E knockout mice. FGF1$^{\Delta HBS}$ decreased the liver weight, lipid deposition, fibrosis, inflammation and ameliorated the liver injury, coincident with the upregulation of the phosphorylation of AMPK and its substrate. These findings indicate that FGF1$^{\Delta HBS}$ is effective for preventing and reversing liver steatosis and steatohepatitis and acts by activation of AMPK via hepatocyte FGFR4. FGF1$^{\Delta HBS}$ might be a therapeutic approach for the treatment of NAFLD without promoting undesired tissue hyperproliferation.

2160 Interaction of Environmental Vinyl Chloride Exposure and Diet: Potential Role of the Epitranscriptome

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Obesity as the primary factor of nonalcoholic fatty liver disease (NAFLD) doesn't completely drive the overall interindividual risk for the development of severe NAFLD. In addition to genetic variation, risk may also be driven by environmental exposures, e.g. vinyl chloride (VC). At high exposure levels VC directly causes liver disease and cancer. However, we and others have shown that lower exposure levels (i.e., <OSHA limit) that are currently considered 'safe' exacerbate underlying liver disease and have been linked with human liver diseases. C57Bl/6J mice were fed Western diet (WD), or low-fat control diet (CD) for up to 1 year. During the first 12 weeks of feeding, mice were also exposed to VC on at concentrations below the current OSHA limit (<1 ppm) or room air for 6 hrs/d, 5 d/wk. Plasma and liver samples were collected (during and after VC) for determination of injury and of chemical modifications on RNAs via LC-MS. Early changes due to VC exposure include dysregulated energy homeostasis and mitochondrial dysfunction - even in the absence of WD. In toto, VC limits the bioenergetic reserve capacity of the liver and exacerbates metabolic stress caused by obesity. Late changes include an increased number of tumors, ranging from moderately to poorly differentiated HCC. Interestingly, although VC significantly altered expression/activity of several key metabolic regulatory proteins in the liver, these changes were not reflected at the level of steady-state mRNA expression. In contrast, the expression of several key epitranscriptomic modulators (e.g., *Rbm15*, *Wtap*, *Kiaa1429* and *Ythdf1*) were altered by VC. Given that VC is well known to attack nucleic acids (e.g., DNA), that VC may be mediating this disconnect between mRNA and protein expression by also adducting mRNA is distinctly possible. Indeed, a total of 29 modified nucleosides were significantly altered in mouse liver by VC and/or diet. We hypothesize that epitranscriptomic regulation of these target RNAs may contribute, at least in part, the observed disconnect between protein/activity and mRNA expression under our conditions. Taken together, our data indicate that VC sensitizes the liver to other stressors (e.g., WD) resulting in enhanced tumorigenesis. These data emphasize that current OSHA safety restriction may be insufficient to account for other factors that can influence hepatotoxicity in humans.

2161 Welding Fume Inhalation Exposure and High-Fat Diet Change Lipid Homeostasis in Rat Liver

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It is estimated that greater than one million workers are exposed to welding fume (WF) by inhalation daily. The potentially toxic metals found in WF are known to cause multiple adverse pulmonary and systemic effects, including cardiovascular disease, and these metals have also been shown to translocate to the liver. This occupational exposure combined with a high fat (HF) Western diet, which has been shown to cause hyperlipidemia and non-alcoholic fatty liver disease (NAFLD), has the potential to cause significant mixed exposure metabolic changes in the liver. Matrix assisted laser desorption ionization (MALDI) mass spectrometry allows for direct analysis of tissues for the identification and relative quantification of multiple biomolecules, including lipids. The goal of this study was to use matrix assisted laser desorption ionization imaging mass spectrometry (MALDI-IMS) to analyze the spatial distribution and abundance changes of lipid species in Sprague Dawley rat liver maintained on a HF diet combined with WF inhalation. Male Sprague Dawley rats from each diet were exposed by inhalation to stainless steel WF at a target concentration of 20 mg/m^3 for 3 hours per day for 5 weeks or filtered air as the control. The results of the MALDI-IMS analysis revealed unique hepatic lipid profiles for each treatment group at 12 weeks post-exposure. Pulmonary exposure to WF alone increased the levels of ceramide-1-phosphate and lyso-phosphatidylinositol (18:0) which are both markers of inflammation. The HF diet group had significantly increased abundance of triglycerides and phosphatidylinositol lipids, as well as decreased lysophosphatidic lipids and cardiolipin. The increased hepatic triglycerides were found in conjunction with significantly increased serum triglycerides and oil-red-O staining showed increased lipid deposition in the HF diet animals. Ceramide-1-phosphate was found at higher abundance in the regular (REG) diet WF-exposed group which has been shown to regulate the eicosanoid pathway involved in pro-inflammatory response. The results of this study showed that the combined effects of WF inhalation and a HF diet significantly altered the hepatic lipidome.

2162 Biliary Iron Excretion in Slc30a10- and Slc39a14-Deficient Mouse Models

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In diseases of iron (Fe) overload, the liver accumulates Fe resulting in fibrosis, cirrhosis, and carcinomas. Fe is believed to be eliminated by the body by sloughing of intestinal epithelium and other passive means. However, Fe can also be excreted into bile, although the mechanisms and relevance to Fe homeostasis are not known. In the current study, we investigated biliary Fe excretion using Slc30a10 and Slc39a14 knock-out mouse models via a dietary approach. Wild-type and mutant mice were raised on Fe-sufficient and -rich diets for one month and subject to surgical collection of bile followed by organ harvest. Liver and biliary Fe levels were decreased in Slc39a14-deficient (10-fold in liver, 13-fold in bile) mice raised on the Fe-rich diet but not in Slc30a10-deficient mice raised on the Fe-rich diet. Histopathological examination using Prussian Blue Fe stain identified Fe accumulation primarily in hepatocytes of Slc30a10-deficient mice and in extrahepatic cells in Slc39a14-deficient mice. Mass spectrometric analysis of bile from wild-type mice raised on a Fe-rich diet showed a significant changes in relative abundance of ferritin and other proteins. We are currently investigating the biochemical form of Fe excreted in the bile. Results from these experiments provide insights into novel molecular targets that can be further explored to increase biliary Fe excretion and reduce total Fe burden in the diseases of Fe excess and toxicity.

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