Biosketch

Gyongyi Szabo, MD, PhD is the Worcester Foundation for Biomedical Research Endowed Chair, Professor and Vice Chair of Medicine and Associate Provost at the University of Massachusetts Medical School. Dr. Szabo is an internationally recognized leader in the field of liver immunology and inflammation. Her clinical investigations focus on alcoholic hepatitis, non-alcoholic fatty liver disease and viral hepatitis. She is the lead investigator on an NIH-supported multicenter clinical trial in alcoholic hepatitis. Her laboratory studies the molecular mechanisms of inflammation and innate immunity in liver injury to identify therapeutic targets in liver diseases. She is an expert in Toll-like receptor and Nod-like receptor signaling pathways in alcoholic and non-alcoholic liver diseases. Her investigations recently revealed the importance of micro-RNAs and extracellular vesicles in liver diseases. She is member of the Hungarian Academy of Sciences, serves on the Editorial Board of Hepatology and on the Advisory Boards for NIH and several leading academic institutions. She is a Past President (2015) of the American Association for the Study of Liver Diseases (AASLD).

Abstract: 2017 I-1: Alcoholic hepatitis is a drug-induced disorder

G. Szabo, A. Iracheta-Vellve, A. Satichandran, S. Bala, K. Kodys. University of Massachusetts Medical School, Worcester, MA 01655

The metabolism of alcohol involves many pathways that are common to the metabolism of other drugs. Specifically, the synergistic effects of alcohol and acetaminophen (APAP) are due to the common pathways of Cyp2E1 and glutathione that lead to reactive oxygen and nitrogen species formation. The result is activation of hepatocyte death pathways due to mitochondrial dysfunction and ATP depletion. Our recent studies gained insight into miR-122 and Stimulator of Interferon Genes (STING) signaling, distinct yet simultaneous pathways common to both alcohol and drug-induced liver injury.

Both chronic alcohol and APAP administration increase the levels of circulating miR-122, an early indicator of liver/hepatocyte damage. We found that chronic alcohol reduces miR-122 levels in livers, specifically in hepatocytes, of alcohol-fed mice. This can be mimicked by administration of a self-complementary adeno-associated viral vector (scAAV) that provides sustained knockdown of miR-122 via an RNA polymerase II U6
promoter driven Tough Decoys (TuDs) in hepatocytes. miR-122 downregulation recapitulated features of alcoholic liver disease including steatosis, inflammation and liver damage. Furthermore, we found that alcohol and miR-122 TuD treatment, independently and together, resulted in a reduction of GSH/GSSH ratio with a concurrent increase in Cyp2E1 expression indicating an increase oxidative stress. These results suggested that miR-122 decrease in hepatocytes have functional consequences by increasing oxidative stress. In support of this hypothesis, we showed that over-expression of miR-122 with an scAAV8 vector can ameliorate alcohol-induced liver injury, steatosis and inflammation in mice.

Another determinant of alcohol-induced liver injury, hepatocyte death, mitochondrial apoptosis and inflammation is the transcription factor Interferon Regulatory Factor 3 (IRF3) that is activated by STING. We showed that STING deficient mice show attenuated liver damage after alcohol binge. We found, that acute APAP administration in WT mice resulted in early phosphorylation of IRF3 and Type I IFN production, followed by hepatocyte death, indicated by increased serum ALT and Caspase-3 cleavage in the liver. APAP administration also led to liver inflammasome activation via cleavage of Caspase-1 and induction of IL-1β, followed by liver necrosis and death. In contrast to WT mice, APAP administration to mice deficient in STING, an upstream ER adaptor of IRF3, resulted in attenuated serum ALT, IL-1β, and TNFα, and decreased cleavage of Caspase-3 compared to WT mice. STING deficiency also protected from increased levels of APAP-induced liver inflammasome activation, as measured by cleaved Caspase-1. Remarkably, STING-deficiency protected from APAP-induced liver necrosis and mortality. Our findings demonstrate that STING deficiency is protective from hepatocyte apoptosis, liver injury and inflammation not only after alcohol binge but also after APAP overdose. These results show what IRF3 and STING collectively link hepatocyte death and liver inflammation in acute drug-induced liver injury.