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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 Immediate Past President of the American Association for the Study of Liver Diseases (AASLD).

Abstract: Role of exosomes in DILI and alcoholic hepatitis

Exosomes are small membrane coated vesicles produced by different cell types and found in the circulation. Exosomes contain nucleic acids, proteins and the cargo of exosomes may change under disease condition. Increasing evidence suggests that exosomes play a role in cell-to-cell and inter-organ communication and may be potential biomarkers. We have previously demonstrated that circulating exosomes in APA-induced DILI contain microRNA-122 and this is an early marker of liver injury in mice. Alcohol and its metabolites also induce hepatocyte damage and recruitment of inflammatory monocytes/macrophages and neutrophils leading to alcoholic hepatitis. Currently there is no reliable biomarker of alcoholic hepatitis. miR-122 is abundantly expressed in hepatocytes, not in immune cells and increased levels of circulating miR-122 were found in liver injury. We hypothesized that EV-associated miRs can serve as biomarkers and modulate intercellular signaling between hepatocytes and immune cells in alcoholic hepatitis. In this study, EVs were isolated from chronic alcohol-fed (5 weeks of Lieber DeCarli diet) or pair-fed mice sera and from serum of patients with alcoholic hepatitis. EVs were characterized by transmission electron microscopy, western blot, nanoparticle tracking analysis system and miRNA analysis. We found that the total number of circulating EVs was significantly increased in alcohol-fed mice as compared to control mice. Exosomes (40-150nm) represented most of the EVs (~80%). MicroRNA array of circulating EVs revealed a significant increase of 7 inflammatory miRs including: miR-192, 122, 30a, 744, 1246, 30b and miR-130a in alcohol-fed mice compared to controls. The ROC analyses indicated excellent diagnostic value of miR-192, 122, and 30a to identify alcohol-induced liver injury. In patients with acute alcoholic hepatitis, we found a significant increase in the number of circulating EVs compared to normal controls and miR-192 and miR-30a were significantly increased in the EVs from alcoholic hepatitis patients. Serum miR-122 was increased after alcohol binge drinking. In the liver, miR-122 is abundantly expressed in hepatocytes and monocytes/macrophages have low levels. In vitro experiments revealed that exosomes derived from ethanol-treated human hepatocytes were taken up by monocytes and transferred mature miR-122 into monocytes. This horizontally transferred miR-122 inhibited the hemeoxygenase-1 expression, a target of miR-122 and sensitized monocytes to LPS stimulation to increase production of pro-inflammatory cytokines, TNF-α and IL-1β; all of these effects were inhibited by exosome-mediated delivery of a miR-122 inhibitor in monocytes. Our results suggest that elevated levels of EVs and their miR signature could serve as biomarkers of alcoholic hepatitis. This study reveals a novel EV-mediated mechanism of alcohol-induced communication

between hepatocytes and monocytes by transferring hepatocyte-derived miR-122 that reprograms monocytes promoting inflammation in alcoholic hepatitis.