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Liver Digest

A weekly update of PLRC happenings

March 5, 2020

PITTSBURGH LIVER RESEARCH CENTER
A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Alessandro Furlan

REMINDER: Please acknowledge support from the PLRC (NIH/NIDDK P30DK120531) in your publications and presentations.

In this issue

Cleveland IDEAS Symposium

The 2020 Cleveland International Digestive Education and Science (IDEAS) Symposium

The 3rd Cleveland IDEAS Symposium will be held September 13 - 15th, 2020 *(Young Investigator & Basic Science Symposium)* & September 19th, 2020 *(Clinical Course)* at Case Western Reserve University School of Medicine.

Important dates:
Young Investigator Abstract Submission due **April 1, 2020.**
Registration Deadline is **July 1, 2020.**

For details, please visit: **https://case.edu/medicine/dhri/2020clevelandideas**

Upcoming Seminars

Liver Seminar - Dr. Nicolas LaRusso

Wed, 03/11/2020 -

12:00 to 13:00

Nicolas F. LaRusso, MD

Professor of Biochemistry and Molecular Biology

Professor of Medicine

Mayo Clinic

Rochester, Minnesota

Polycystic Liver Disease: Pathogenic Perspectives and Therapeutic Targets

Department of Pathology seminar, co-sponsored by PLRC

Pediatric Gastroenterology, Hepatology, and Nutrition Lecture Series

Tuesday, April 28, 2020

4:00-5:00 p.m.

UPMC Children's Hospital, Rangos Conference Center B&C

Dr. Simon Horslen

Professor of Pediatrics

University of Washington School of Medicine

Medical Director Solid Organ Transplantation, Seattle Children's Hospital

Developing Concepts in the Understanding of Indeterminate Acute Liver Failure in Children

CME credit is available.

The full schedule of Enrichment activities is posted

on **https://www.livercenter.pitt.edu/events**

BRPC Survey

We are asking all PLRC members to please complete the one-minute survey on the Biospecimen Repository and Processing Core, which is available **here**. One of the activities that the PLRC needs to do (now that we are a funded DDRCC) is regularly monitor the Core services that our members use and would like to see available. If you have already completed the survey, thank you!

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:

Dong K, Du Q, Cui X, Wan P, Kaltenmeier C, **Luo J**, Yan B, Yan Y, **Geller DA**. MicroRNA-301a (miR-301a) is induced in hepatocellular carcinoma (HCC) and down-regulates the expression of interferon regulatory factor-1. Biochem Biophys Res Commun. 2020 Jan 24;S0006-291X(20)30088-7. doi: 10.1016/j.bbrc.2020.01.034. PMID: 31987500.

ABSTRACT

Hepatocellular carcinoma (HCC) tumors evade death in part by downregulating expression of the tumor suppressor gene Interferon regulatory factor-1 (IRF-1). However, the molecular mechanisms accounting for IRF-1 suppression in HCC have not been well described. In this study, we identified a novel microRNA-301a (miR-301a) binding site in the 3'-untranslated region (3'- UTR) of the human IRF-1 gene and hypothesized a functional role for miR-301a in

regulating HCC growth. We show that miR-301a is markedly upregulated in primary HCC tumors and HCC cell lines, while IRF-1 is down-regulated in a post-transcriptional manner. MiR-301a regulates basal and inducible IRF-1 expression in HCC cells with an inverse relationship between miR-301a and IRF-1 expression in HCC cells. Chronic hypoxia induces miR-301a in HCC in vitro and decreases IRF-1 expression. Finally, miR-301a inhibition increases apoptosis and decreases HCC cell proliferation. These findings suggest that targeting of IRF-1 by miR-301a contributes to the molecular basis for IRF-1 downregulation in HCC and provides new insight into the regulation of HCC by miRNAs.

For full text, please **click here**.

Original Article:

Moon AM, Jiang Y, **Rogal SS**, Tapper EB, Lieber SR, Barritt AS 4th. Opioid prescriptions are associated with hepatic encephalopathy in a national cohort of patients with compensated cirrhosis. Aliment Pharmacol Ther. 2020 Jan 21;10.1111/apt.15639. doi: 10.1111/apt.15639. PMID: 31960985.

ABSTRACT

Background: Opioids are often prescribed for pain in cirrhosis and may increase the risk of hepatic encephalopathy (HE).

Aim: To assess the association between opioids and HE in patients with well-compensated cirrhosis.

Methods: We used the IQVIA PharMetrics (Durham, NC) database to identify patients aged 18-64 years with cirrhosis. We excluded patients with any decompensation event from 1 year before cirrhosis diagnosis to 6 months after cirrhosis diagnosis. Over the 6 months after cirrhosis diagnosis, we determined the duration of continuous

opioid use and classified use into short term (1-89 days) and chronic (90-180 days). We assessed whether patients developed HE over the subsequent year (ie 6-18 months after cirrhosis diagnosis). We used a landmark analysis and performed multivariable Cox proportional hazards regression to assess associations between opioid use and HE, adjusting for relevant confounders.

Results: The cohort included 6451 patients with compensated cirrhosis, of whom 23.3% and 4.7% had short-term and chronic opioid prescriptions respectively. Over the subsequent year, HE occurred in 6.3% patients with chronic opioid prescriptions, 5.0% with short-term opioid prescriptions and 3.3% with no opioid prescriptions. In the multivariable model, an increased risk of HE was observed with short-term (adjusted hazard ratio, HR 1.44, 95% CI 1.07-1.94) and chronic opioid prescriptions (adjusted HR 1.83, 95% CI 1.07-3.12) compared to no opioid prescriptions.

Conclusion: In this national cohort of privately insured patients with cirrhosis, opioid prescriptions were associated with the risk of incident HE. Opioid use should be minimised in those with cirrhosis and, when required, limited to short duration.

For full text, please **click here**.

Original Article:
Shen Y, Malik SA, Amir, M., Kumar, P., Cingolani, F., Wen, J., Liu, Y., Zhao, E., Farris, A. B., **Raeman**, **R.**, & Czaja, M. J. Decreased Hepatocyte Autophagy Leads to Synergistic IL-1β and TNF Mouse Liver Injury and Inflammation [published online ahead of print, 2020 Feb 28]. Hepatology. 2020;10.1002/hep.31209. doi:10.1002/hep.31209.

ABSTRACT
Background & Aims

The proinflammatory cytokine IL-1β has been implicated in the pathophysiology of nonalcoholic and alcoholic steatohepatitis. How IL-1β promotes liver injury in these diseases is unclear as no IL-1β receptor-linked death pathway has been identified. Autophagy functions in hepatocyte resistance to injury and death and findings of decreased hepatic autophagy in many liver diseases suggest a role for impaired autophagy in disease pathogenesis. Recent findings that autophagy blocks mouse liver injury from lipopolysaccharide led to an examination of autophagy's function in hepatotoxicity from proinflammatory cytokines.

Approach & Results

AML12 cells with decreased autophagy from a lentiviral Atg5 knockdown were resistant to toxicity from TNF, but sensitized to death from IL-1β which was markedly amplified by TNF co-treatment. IL-1β/TNF death was necrosis by trypan blue and propidium iodide positivity, absence of mitochondrial death pathway and caspase activation, and failure of a caspase inhibitor or necrostatin-1s to prevent death. IL-1β/TNF depleted autophagy-deficient cells of ATP, and ATP depletion and cell death were prevented by supplementation with the energy substrate pyruvate or oleate. Pharmacological inhibitors and genetic knockdown studies demonstrated that IL-1β/TNF-induced necrosis resulted from lysosomal permeabilization and release of cathepsins B and L in autophagy-deficient cells. Mice with a tamoxifen-inducible, hepatocyte-specific Atg5 knockout were similarly sensitized to cathepsin dependent hepatocellular injury and death from IL-1β/TNF in combination, but neither IL-1β nor TNF alone. Knockout mice had increased hepatic inflammation, and IL-1β/TNF-treated, autophagy-deficient AML12 cells secreted exosomes with proinflammatory damage-associated molecular patterns (DAMPs).

Conclusions

The findings delineate novel mechanisms by which decreased hepatocyte autophagy promotes IL-1β/TNF-induced necrosis from impaired energy homeostasis and lysosomal permeabilization and inflammation through the secretion of exosomal DAMPs.

For full text, please **click here**.

Original Article:

Rachakonda V, Bataller R, Duarte-Rojo A. Recent advances in alcoholic hepatitis. F1000Res. 2020 Feb 10;9:F1000 Faculty Rev-97. doi: 10.12688/f1000research.20394.1. PMID: 32089834; PMCID: PMC7014576.

ABSTRACT

Alcoholic hepatitis is the severest clinical presentation of alcoholic liver disease. Lacking an effective pharmacologic treatment, alcoholic hepatitis is associated with a poor prognosis and its recovery relies mostly on abstinence. With alcohol use disorder being universally on the rise, the impact of alcoholic hepatitis on society and health-care costs is expected to increase significantly. Prognostic factors and liver biopsy can help with timely diagnosis, to determine eligibility and response to corticosteroids, and for prognostication and transplant referral. Although recent discoveries in the pathophysiology of alcoholic hepatitis are encouraging and could pave the way for novel treatment modalities, a multidisciplinary approach considering timely identification and treatment of liver-related complications, infectious and metabolic disease, malnutrition, and addiction counseling should be emphasized. Apart from proper selection of candidates, transplant programs should provide adequate post-transplant addiction support in order to make of early liver transplantation for alcoholic hepatitis the ultimate sobering experience in the next decade.

For full text, please **click here**.

Funding Opportunity

Rational Design of Vaccines Against Hepatitis C Virus (U19 Clinical Trial Not Allowed)

(RFA-AI-20-019)

National Institute of Allergy and Infectious Diseases

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