Liver Digest

A weekly update of PLRC happenings

September 26, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Wendy Mars

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- Funding Opportunities

Next Week's Seminar

PLRC Seminar Series - Dr. Valerie Gouon-Evans

Tues., October 1, 2019

12:00 to 1:00 p.m.

S120 BST

Valerie Gouon-Evans, Pharm.D., Ph.D.

Associate Professor

Department of Medicine, Section of Gastroenterology

Center for Regenerative Medicine CReM

Boston University School of Medicine and Boston Medical Center

A Multi-modular approach to accelerate liver regeneration

This activity has been approved for AMA PRA Category 1 Credit. #6242 Liver Center Seminars.

Pizza will be provided.

Welcome - New Biospecimen Repository and Processing Core Manager

We are pleased to announce that Kate Smith began her role as the manager of the BRPC on September 23. Kate has worked for a number of years in biobanking, and we are delighted to welcome her to the PLRC! She will be working closely with Drs. Aatur Singhi and Dave Geller, who are the co-directors of the BRPC, and their teams to continue to coordinate and implement the services offered by the BRPC. Welcome, Kate!

For more information on the BRPC, please visit the PLRC website: **http://www.livercenter.pitt.edu/biospecimen-repository-and-processing-core**

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Review Article:

Wang R, **Geller DA**, Wink DA, Cheng B, **Billiar TR**. Nitric oxide and hepatocellular cancer. Br J Pharmacol. 2019 Aug 18. doi: 10.1111/bph.14838. Review. PubMed PMID: 31423564.

ABSTRACT
Nitric oxide (NO) has broad and sometimes dichotomous roles in cancer. The effects of NO in tumors depend on the type and localization of NOS isoforms, concentration and duration of NO exposure, and cellular sensitivity to NO. Hepatocellular cancer (HCC) is a common and lethal disease for which no effective therapy other than surgical resection exists. Over two decades of research has yielded evidence that NO generated by the inducible NO synthase (iNOS or NOS2) contributes to HCC progression in at least a subset of patients

with HCC. The co-expression of iNOS with cyclooxygenase-2 (COX-2) may portend a particularly aggressive cancer phenotype in HCC and at the same time reveal an opportunity for pharmacologic intervention. In this review, we focus what is known about the influence of NO in HCC neoplastic transformation, proliferation and apoptosis, angiogenesis, invasion and metastasis, cancer stem cells, and the host immune response against the tumor. We discuss the implications of recent findings for targeting the NO pathways in HCC.

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

Original Article:

Tirthadipa Pradhan-Sundd*, Karis Kosar*, Harvinder Saggi, Rong Zhang, Ravi Vats, Pamela Cornuet, Sydney Green, Sucha Singh, Gang Zeng, **Prithu Sundd, Kari Nejak-Bowen**. Activation of Wnt/β-catenin signaling and regulation of the FXR/β-catenin complex after murine bile duct ligation. Hepatology. 2019 Sep 6. PMID: 31489648

*co-first authors

ABSTRACT

The Wnt/β-catenin signaling pathway has a well-described role in liver pathobiology. Its suppression was recently shown to decrease bile acid (BA) synthesis, thus preventing the development of cholestatic liver injury and fibrosis after bile duct ligation (BDL). To generalize these observations, we suppressed β-catenin in Mdr2 knockout (KO) mice, which develop sclerosing cholangitis due to regurgitation of BA from leaky ducts. When β-catenin was knocked down (KD) in KO for 2 weeks, hepatic and biliary injury were exacerbated in comparison to KO given placebo, as shown by serum biochemistry, ductular reaction, inflammation, and fibrosis. Simultaneously, KO/KD livers displayed increased oxidative stress and senescence and an impaired regenerative response. Although total liver BA levels were similar between KO/KD and KO, there was significant dysregulation of BA transporters and BA detoxification/synthesis enzymes in KO/KD compared to KO alone. Multiphoton intravital microscopy revealed a mixing of blood and bile in the sinusoids, and validated the presence of increased serum BA in KO/KD mice. Although hepatocyte junctions were intact, KO/KD livers had significant canalicular defects, which resulted from loss of hepatocyte polarity. Thus, in contrast to the protective effect of β-catenin KD in BDL model, β-catenin KD in Mdr2 KO

aggravated rather than alleviated injury by interfering with expression of BA transporters, hepatocyte polarity, canalicular structure, and the regenerative response. The resulting imbalance between ongoing injury and restitution led to worsening of the Mdr2 KO phenotype, suggesting caution in targeting β-catenin globally for all cholestatic conditions.

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

Original Article:

Cannella R, Brancatelli G, Rangaswamy B, Minervini MI, **Borhani AA, Furlan A**. Enhancement pattern of hepatocellular adenoma (HCA) on MR imaging performed with Gd-EOB-DTPA versus other Gd-based contrast agents (GBCAs): An intraindividual comparison. Eur J Radiol. 2019 Aug 6;119:108633. doi: 10.1016/j.ejrad.2019.08.002. PubMed PMID: 31437747.

ABSTRACT

PURPOSE: To conduct an intraindividual comparison of the enhancement pattern of hepatocellular adenoma (HCA) on dynamic MRI study obtained following the injection of Gadoxetic acid (Gd-EOB-DTPA) and other gadolinium-based contrast agents (GBCAs).

METHOD: This is a retrospective, Institutional Review Board-approved study conducted in a single institution. A search of medical records between 2008 and 2017 revealed 17 patients (all females) with at least one pathologically-proven HCA who underwent liver MRI with Gd-EOB-DTPA and another GBCA within 1 year. Enhancement of each lesion on hepatic arterial (HAP), portal venous (PVP), 2 min and 4-5 minutes phases was subjectively evaluated by two abdominal radiologists. Lesions were categorized as hyper-, iso- or hypointense compared to the surrounding liver parenchyma. The presence of a peripheral pseudocapsule was also recorded. The differences in lesion enhancement were assessed using the McNemar Test. A p-value <0.05 was considered statistically significant.

RESULTS: The final population included 35 HCAs (83% inflammatory subtype). There was no significant difference in lesion size ($P = 0.708$) and enhancement on HAP ($P = 0.625$) or PVP ($P = 0.125$). HCAs showed more frequently hypointensity on 2 min (13/35 vs. 1/35, $P < 0.001$) and 4-5 minutes ($P < 0.001$) images obtained after injection of Gd-EOB-DTPA compared to those obtained after other GBCAs. A

pseudocapsule was more frequently noted after administration of Gd-EOB-DTPA (13/35 vs 1/35, P = 0.002).

CONCLUSIONS: Enhancement pattern of HCA differs significantly after the injection of Gd-EOB-DTPA compared to other GBCAs. Lesion hypointensity on 2 min and 4-5 minutes images is more frequent when using Gd-EOB-DTPA.

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

Commentary:

Nejak-Bowen K. If It Looks Like a Duct And Acts Like a Duct: On the Role of Reprogrammed Hepatocytes in Cholangiopathies. Gene Expr. 2019 Aug 22. doi: 10.3727/105221619X15664105014956. PubMed PMID: 31439080.

ABSTRACT

Cholangiopathies are chronic, progressive diseases of the biliary tree, and can be either acquired or genetic. The primary target is the cholangiocyte (CC), the cell type lining the bile duct that is responsible for bile modification and transport. Despite advances in our understanding and diagnosis of these diseases in recent years, there are no proven therapeutic treatments for the majority of the cholangiopathies, and liver transplantation is the only life-extending treatment option for patients with end-stage cholestatic liver disease. One potential therapeutic strategy is to facilitate endogenous repair of the biliary system, which may alleviate intrahepatic cholestasis caused by these diseases. During biliary injury, hepatocytes (HC) are known to alter their phenotype and acquire CC-like features, a process known as cellular reprogramming. This brief review discusses the potential ways in which reprogrammed HC may contribute to biliary repair, thereby restoring bile flow and reducing the severity of cholangiopathies. Some of these include modifying bile to reduce toxicity, serving as a source of de novo CC to repair the biliary epithelium, or creating new channels to facilitate bile flow.

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

Funding Opportunities

Clinical, Translational and Outcomes Research Award

American Association for the Study of Liver Diseases (AASLD)

Bioinformatics Interdisciplinary Predoctoral Fellowship in Diabetes, Endocrinology and Metabolic Diseases (F31)

(PAR-19-378)

National Institute of Diabetes and Digestive and Kidney Diseases

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Bioinformatics Interdisciplinary Postdoctoral Fellowship in Diabetes, Endocrinology and Metabolic Diseases (F32)

(PAR-19-379)

National Institute of Diabetes and Digestive and Kidney Diseases

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