PLRC – Weekly Update

December 6, 2018

In this email:

Upcoming Seminars

Special Seminar

Thursday, December 6, 2018
12:00-1:00 p.m.
UPMC Hillman Cancer Center Cooper Conference Center

Haitao Guo, PhD

Associate Professor, Department of Microbiology and Immunology
Indiana University School of Medicine

"HBV Nuclear cccDNA: How Is It Made? How to Destroy It?"

Host: Shou-Jiang (SJ) Gao, PhD
Contact person: Olivia Bennett (bennetto@upmc.edu)

Pizza, salad, and beverages provided.

PLRC Seminar Series

Tuesday, January 29, 2019
12:00-1:00 p.m.
S123 BST

Yanqiao Zhang, MD
Professor of Integrative Medical Sciences
Northeast Ohio Medical University

"NAFLD: Novel Pathogenic Mechanisms and Potential Therapeutics"

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

Pizza will be provided.
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Registration URL: https://attendee.gotowebinar.com/register/6607572696840938499

For those viewing thru the webinar, please follow the directions below:

- Please Register for the live Webinar ASAP
- After registering, you will receive the confirmation email
- You will be prompt to download the CitrixOnline application and install on your PC or Laptop
- Please contact your local PC Support if you need help installing the application
- Feel free to email Ishtiaque Ahmed (**ahmedi@upmc.edu**) if you have any questions

NOTE Webinar attendees -- use Telephone/Speakerphone and dial-in instead of using desktop/laptop speakers for better audio quality.

Telephone/Speakerphone Audio option is shown right at the Click to Join Webinar prompt.

For a complete list of upcoming PLRC events, please visit our website: **www.livercenter.pitt.edu/events**

Community Liver Alliance

Dr. Tirthadipa Pradhan-Sundd, Instructor in the Department of Pathology, has been awarded the **Community Liver Alliance's 2018 grant award** for her proposal, "Molecular mechanism of sickle cell hepatic crisis."

2019 You Make a Difference Award Luncheon

The Community Liver Alliance is now accepting award nominations for the 2019 You Make a Difference Award Luncheon. Nominees should be considered for their outstanding accomplishments going above and beyond supporting, advocating and educating our community about the Community Liver Alliance mission.

Who do you know that should be recognized?

THE CRITERIA
Recipients must meet the following criteria (staff members are not eligible for nominations):
• Demonstrate commitment and dedication to the Community Liver Alliance's mission
• Actively advocates to improve the quality of life for those with liver disease throughout the community
• Support the initiatives of the Community Liver Alliance

THE PROCESS
A Selection Committee consisting of a diverse group of Community Liver Alliance supporters from the community will review all nomination forms and select the Award Recipients.

SAVE THE DATE
The You Make a Difference Award will be presented at the luncheon held on
Friday, February 8, 2019 from 11:00 a.m. to 1:00 p.m. at the Grand Hall at the Priory, Pittsburgh, PA.

deadline for submissions is December 7, 2018

Submit a Nomination

Funding Opportunity

Research to Advance HBV Cure: HIV/HBV Co-Infection and HBV Mono-infection (R01 Clinical Trial Not

Allowed)

(PAS-19-097)

National Institute of Allergy and Infectious Diseases

Recent Faculty Publications

Lu P, Cai X, Guo Y, Xu M, Tian J, **Locker J, Xie W**. Constitutive Activation of the Human Aryl Hydrocarbon Receptor in Mice Promotes Hepatocarcinogenesis Independent of Its Coactivator Gadd45b. Toxicol Sci. 2018 Oct 22. doi: 10.1093/toxsci/kfy263. PMID: 30346592

ABSTRACT

2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), or dioxin, is a potent liver cancer promoter through its sustained activation of the aryl hydrocarbon receptor (Ahr) in rodents. However, the carcinogenic effect of TCDD and AHR in humans has been controversial. It has been suggested that the inter-species difference in the carcinogenic activity of AhR is largely due to different ligand affinity in that TCDD has a 10-fold lower affinity for the human AHR compared to the mouse Ahr. It remains unclear whether the activation of human AHR is sufficient to promote hepatocellular carcinogenesis. The goal of this study is to clarify whether activation of human AHR can promote hepatocarcinogenesis. Here we reported the oncogenic activity of human AHR in promoting hepatocellular carcinogenesis. Constitutive activation of the human AHR in transgenic mice was as efficient as its mouse counterpart in promoting diethylnitrosamine (DEN)-initiated hepatocellular carcinogenesis. The growth arrest and DNA damage-inducible gene 45 β (Gadd45b), a signaling molecule inducible by external stress and UV irradiation, is highly induced upon AHR activation. Further analysis revealed that Gadd45b is a novel AHR target gene and a transcriptional coactivator of AHR. Interestingly, ablation of Gadd45b in mice did not abolish the tumor promoting effects of the human AHR. Collectively, our findings suggested that constitutive activation of human AHR was sufficient to promote hepatocarcinogenesis.

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

James E. Squires, Patrick McKiernan. Molecular Mechanisms in Pediatric Cholestasis. Gastroenterology Clinics of North America, 2018-12-01, Volume 47, Issue 4, Pages 921-937. PMID: 30337041.

ABSTRACT

Pediatric cholestasis often results from mechanical obstruction of the biliary tract or dysfunction in the processes of forming and excreting bile. Various genetic defects with resulting molecular inaccuracies are increasingly being recognized, often with specific clinical characteristics. Identifying of the molecular abnormality can enable implementation of timely, appropriate treatment in some affected individuals and

provide prognostic indicators for both families and care teams.

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

Tsagianni A, **Mars WM**, Bhushan B, Bowen WC, Orr A, Stoops J, Paranjpe S, Tseng GC, Liu S, **Michalopoulos GK**. Combined Systemic Disruption of MET and Epidermal Growth Factor Receptor Signaling Causes Liver Failure in Normal Mice. Am J Pathol. 2018 Oct;188(10):2223-2235. doi: 10.1016/j.ajpath.2018.06.009. Epub 2018 Jul 20.

ABSTRACT

MET and epidermal growth factor receptor (EGFR) tyrosine kinases are crucial for liver regeneration and normal hepatocyte function. Recently, we demonstrated that in mice, combined inhibition of these two signaling pathways abolished liver regeneration after hepatectomy, with subsequent hepatic failure and death at 15 to 18 days after resection. Morbidity was associated with distinct and specific alterations in important downstream signaling pathways that led to decreased hepatocyte volume, reduced proliferation, and shutdown of many essential hepatocyte functions, such as fatty acid synthesis, urea cycle, and mitochondrial functions. Herein, we explore the role of MET and EGFR signaling in resting mouse livers that are not subjected to hepatectomy. Mice with combined disruption of MET and EGFR signaling were noticeably sick by 10 days and died at 12 to 14 days. Mice with combined disruption of MET and EGFR signaling mice showed decreased liver/body weight ratios, increased apoptosis in nonparenchymal cells, impaired liver metabolic functions, and activation of distinct downstream signaling pathways related to inflammation, cell death, and survival. The present study demonstrates that, in addition to controlling the regenerative response, MET and EGFR synergistically control baseline liver homeostasis in normal mice in such a way that their combined disruption leads to liver failure and death.

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

Wilkinson PD, Delgado ER, Alencastro F, Leek MP, Roy N, Weirich MP, Stahl EC, Otero PA, Chen MI, Brown WK, **Duncan AW.** The polyploid state restricts hepatocyte proliferation and liver regeneration. Hepatology. 2018 Sep 23. doi: 10.1002/hep.30286. [Epub ahead of print]

ABSTRACT

The liver contains a mixture of hepatocytes with diploid or polyploid (tetraploid, octaploid, etc.) nuclear content. Polyploid hepatocytes are commonly found in adult mammals, representing ~90% of the entire hepatic pool in rodents. The cellular and molecular mechanisms that regulate polyploidization have been well-characterized; however, it is unclear if diploid and polyploid hepatocytes function similarly in multiple contexts. Answering this question has been challenging because proliferating hepatocytes can increase or decrease ploidy, and animal models with healthy diploid-only livers have not been available. Mice lacking E2f7 and E2f8 in the liver (LKO) were recently reported to have a polyploidization defect but were otherwise healthy. Herein, livers from LKO mice were rigorously characterized, demonstrating a 20-fold increase in diploid hepatocytes and maintenance

of the diploid state even after extensive proliferation. Livers from LKO mice maintained normal function but became highly tumorigenic when challenged with tumor-promoting stimuli, suggesting that tumors in LKO mice were driven, at least in part, by diploid hepatocytes capable of rapid proliferation. Indeed, hepatocytes from LKO mice proliferate faster and out-compete control hepatocytes, especially in competitive repopulation studies. In addition, diploid or polyploid hepatocytes from wild-type mice were examined to eliminate potentially confounding effects associated with E2f7/E2f8 deficiency. The wild-type diploid cells also showed a proliferative advantage, entering and progressing through the cell cycle faster than polyploid cells, both in vitro and during liver regeneration. Diploid and polyploid hepatocytes responded similarly to hepatic mitogens, indicating that proliferation kinetics are unrelated to differential response to growth stimuli.

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

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