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

PLRC – Weekly Update

December 20, 2018

In this email:

Upcoming Seminars

PLRC Seminar Series

Tuesday, January 15, 2019

12:00-1:00 p.m.

S123 BST

Samira Kiani, MD

Assistant Professor

School of Biological and Health Systems Engineering

Ira A. Fulton Schools of Engineering

Arizona State University

CRISPR Tools for Controllable Gene Therapies *in Vivo*

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.

PLRC Seminar Series

Tuesday, January 22, 2019

12:00-1:00 p.m.

S123 BST

Allison Formal, MBA , Director, Coulter Program

"Implementing the Coulter Translational Research Model for Success"

&

Philip Brooks, MS, MBA, Entrepreneur in Residence, Innovation Institute

“Inspiring Innovators in Translating their Research to the Marketplace”

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

Pizza will be 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"

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

Liver Seminar

Wednesday, January 30, 2019
12:00-1:00 p.m.
1104 Scaife

Chandrashekhar R. Gandhi, Ph.D., FAASLD
Professor of Integrative Medical Sciences

Northeast Ohio Medical University

"NAFLD: Novel Pathogenic Mechanisms and Potential Therapeutics"

PLRC SIG - Tumorigenesis

Tuesday, February 5, 2019
12:00-1:00 p.m.
S123 BST

Dr. Sarangarajan Ranganathan - Histology and Molecular Classification of Hepatoblastoma

Dr. Edward Prochownik - Predicting Hepatoblastoma Phenotypes

Pizza will be provided.

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

Funding Opportunity

Comprehensive Alcohol-HIV/AIDS Research Center (P60 Clinical Trial Optional)
(RFA-AA-19-003)
National Institute on Alcohol Abuse and Alcoholism

Recent Faculty Publications

Wang R, Li Y, **Tsung A**, Huang H, Du Q, Yang M, Deng M, Xiong S, Wang X, Zhang L, **Geller DA**, Cheng B, **Billiar TR**. iNOS promotes CD24(+)CD133(+) liver cancer stem cell phenotype through a TACE/ADAM17-dependent Notch signaling pathway. Proc Natl Acad Sci U S A. 2018 Oct 23;115(43):E10127-E10136. doi: 10.1073/pnas.1722100115. Epub 2018 Oct 8. PubMed PMID: 30297396.

ABSTRACT

The inducible nitric oxide synthase (iNOS) is associated with more aggressive solid tumors, including hepatocellular carcinoma (HCC). Notch signaling in cancer stem cells promotes cancer progression and requires Notch cleavage by ADAM (a disintegrin and metalloprotease) proteases. We hypothesized that iNOS/NO promotes Notch1 activation through TACE/ADAM17 activation in liver cancer stem cells (LCSCs), leading to a more aggressive cancer phenotype. Expression of the stem cell markers CD24 and CD133 in the tumors of patients with HCC was associated with greater iNOS expression and worse outcomes. The expression of iNOS in CD24+CD133+ LCSCs, but not CD24-CD133- LCSCs, promoted Notch1 signaling and stemness characteristics in vitro and in vivo, as well as accelerating HCC initiation and tumor formation in the mouse xenograft tumor model. iNOS/NO led to Notch1 signaling through a pathway involving the soluble guanylyl cyclase/cGMP/PKG-dependent activation of TACE/ADAM17 and up-regulation of iRhom2 in LCSCs. In patients with HCC, higher TACE/ADAM17 expression and Notch1 activation correlated with poor prognosis. These findings link iNOS to Notch1 signaling in CD24+CD133+ LCSCs through the activation of TACE/ADAM17 and identify a mechanism for how iNOS contributes to progression of CD24+CD133+ HCC.

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

Cannella R, **Borhani AA**, Minervini MI, **Tsung A, Furlan A**. Evaluation of texture analysis for the differential diagnosis of focal nodular hyperplasia from hepatocellular adenoma on contrast-enhanced CT images. Abdom Radiol (NY). 2018 Sep 28. doi: 10.1007/s00261-018-1788-5. PubMed PMID: 30267107.

ABSTRACT

PURPOSE: To explore the value of CT texture analysis (CTTA) for differentiation of focal nodular hyperplasia (FNH) from hepatocellular adenoma (HCA) on contrast-enhanced CT (CECT).

METHODS: This is a retrospective, IRB-approved study conducted in a single institution. A search of the medical records between 2008 and 2017 revealed 48 patients with 70 HCA and 50 patients with 62 FNH. All lesions were histologically proven and with available pre-operative CECT imaging. Hepatic arterial phase (HAP) and portal venous phase (PVP) were used for CTTA. Textural features were extracted using a commercially available research software (TexRAD). The differences between textural parameters of FNH and HCA were assessed using the Mann-Whitney U test and the AUROC were calculated. CTTA parameters showing significant difference in rank sum test were used for binary logistic regression analysis. A p value < 0.05 was considered statistically significant.

RESULTS: On HAP images, mean, mpp, and skewness were significantly higher in FNH than in HCA on unfiltered images ($p \leq 0.007$); SD, entropy, and mpp on filtered analysis ($p \leq 0.006$). On PVP, mean, mpp, and skewness in FNH were significantly different from HCA ($p \leq 0.001$) on unfiltered images, while entropy and kurtosis were significantly higher in FNH on filtered images ($p \leq 0.018$). The multivariate logistic regression analysis indicated that the mean, mpp, and entropy of medium-level and coarse-level filtered images on HAP were independent predictors for the diagnosis of HCA and a model based on all these

parameters showed the largest AUROC (0.824).

CONCLUSIONS: Multiple explored CTTA parameters are significantly different between FNH and HCA on CECT.

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

Dr. Monga publishes “Year in Review: Liver regeneration in 2018” in Nature Reviews Gastroenterology and Hepatology. The brief review entitled “Updates on hepatic homeostasis and the many tiers of hepatobiliary repair” summarizes key discoveries in the field of Liver Regenerative Medicine in 2018.

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

Nakao T, Ono Y, Dai H, Nakano R, Perez-Gutierrez A, Camirand G, Huang H, **Geller DA, Thomson AW**. DAP12/TREM2 Expression by Mouse and Human Liver DC: Functional Implications and Regulation of Liver Ischemia-Reperfusion Injury. Hepatology. 2018 Oct 29. doi: 10.1002/hep.30334. [Epub ahead of print] PubMed PMID: 30372546.

ABSTRACT
Liver interstitial dendritic cells (DC) have been implicated in the control of ischemia/reperfusion injury (IRI) and host immune responses following liver transplantation. Mechanisms underlying these regulatory functions of hepatic DC remain unclear. We have shown recently that the transmembrane immunoadaptor DNAX-activating protein of 12 kDa (DAP12) negatively regulates mouse liver DC maturation and their pro-inflammatory and immune stimulatory functions. Here, we used PCR analysis and flow cytometry to characterize expression of DAP12 and its associated triggering receptor, triggering receptor expressed on myeloid cells 2 (TREM2) by mouse and human liver DC and other immune cells compared with DC in other tissues. We also examined the roles of DAP12 and TREM2 and their expression by liver DC in regulation of liver IRI. Injury was induced in DAP12-/- , TREM2-/- or WT mice by 1 hour of 70% clamping and quantified following 6 hours reperfusion. Both DAP12 and TREM2 were co-expressed at comparatively high levels by liver DC. Mouse liver DC lacking DAP12 or TREM2 displayed enhanced levels of nuclear factor κB and co-stimulatory molecule expression. Unlike normal WT liver DC, DAP12-/- liver DC failed to inhibit proliferative responses of activated T cells. In vivo, DAP12-/- and TREM2-/- mice exhibited enhanced IRI accompanied by augmented liver DC activation. Elevated alanine aminotransferase levels and tissue injury were markedly reduced by infusion of WT but not DAP12-/- DC. Conclusions: our data reveal a close association between DAP12 and TREM2 expression by liver DC and suggest that, by negatively regulating liver DC stimulatory function, DAP12 promotes their control of hepatic inflammatory responses. The DAP12/TREM2 signaling complex may represent a novel therapeutic target for control of acute liver injury/liver inflammatory disorders.

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

Klune JR, Bartels C, Luo J, Yokota S, Du Q, **Geller DA**. IL-23 mediates murine liver transplantation ischemia reperfusion injury via IFN-γ /IRF-1 pathway. Am J Physiol Gastrointest Liver Physiol. 2018 Oct 11. doi: 10.1152/ajpgi.00231.2018. [Epub ahead of print] PubMed PMID: 30307739.

ABSTRACT
Interleukin-23 (IL-23) is a pro-inflammatory cytokine initially studied in autoimmune disease which has been more recently linked to innate immunity. We observed that the expression of IL-23 is upregulated during hypoxia in hepatocyte and non-parenchymal cell (NPC) co-culture system, as well as during ischemia-reperfusion (I/R) injury in the liver. Interferon regulatory factor-1 (IRF-1) is a transcription factor that induces expression of multiple inflammatory cytokines and has been shown to play a critical role in liver I/R injury. We observed that IL-23 signaling induces not only the IL-17/CXCL2 pathway, but also the IFN-γ/IRF-1 pathway. Quantification of cytokine genes revealed increased liver expression of IL-17a, CXCL2, and IRF-1 messenger RNA (mRNA) during liver transplantation. Recombinant IL-23 treated hepatocytes and NPC co-culture led to IL-17, CXCL2, IFN-γ, and IRF-1 expression. With anti-IL17 and anti-Ly6G antibody neutralization, neutrophil recruitment and IFN-γ production was decreased during warm I/R injury. Overexpression of IL-23 in vivo through use of an adenovirus vector also led to expression of IL-17, CXCL2, IFN-γ, and IRF-1. The increased expression of IL-23 also led to increased apoptosis in the liver. By neutralization of IL-23 through use of an anti-IL-23p19 antibody, we were able to attenuate liver damage in wildtype mouse but not NKT deficient mouse. This suggests that IL-23 signaling shares a common pathway with NKT cells.

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

Wang H, Dolezal JM, Kulkarni S, Lu J, Mandel J, Jackson LE, Alencastro F, **Duncan AW, Prochownik EV.** Myc and ChREBP transcription factors cooperatively regulate normal and neoplastic hepatocyte proliferation in mice. The Journal of biological chemistry. 2018;293(38):14740-57. PMCID: PMC6153302.

ABSTRACT
Analogous to the c-Myc (Myc)/Max family of bHLH-ZIP transcription factors, there exists a parallel regulatory network of structurally and functionally related proteins with Myc-like functions. Two related Myc-like paralogs, termed MondoA and MondoB/carbohydrate response element-binding protein (ChREBP), up-regulate gene expression in heterodimeric association with the bHLH-ZIP Max-like factor Mlx. Myc is necessary to support liver cancer growth, but not for normal hepatocyte proliferation. Here, we investigated ChREBP's role in these processes and its relationship to Myc. Unlike Myc loss, ChREBP loss conferred a proliferative disadvantage to normal murine hepatocytes, as did the combined loss of

ChREBP and Myc. Moreover, hepatoblastomas (HBs) originating in myc-/-, chrebp-/-, or myc-/-/chrebp-/- backgrounds grew significantly more slowly. Metabolic studies on livers and HBs in all three genetic backgrounds revealed marked differences in oxidative phosphorylation, fatty acid β-oxidation (FAO), and pyruvate dehydrogenase activity. RNA-Seq of livers and HBs suggested seven distinct mechanisms of Myc-ChREBP target gene regulation. Gene ontology analysis indicated that many transcripts deregulated in the chrebp-/- background encode enzymes functioning in glycolysis, the TCA cycle, and β- and ω-FAO, whereas those dysregulated in the myc-/- background encode enzymes functioning in glycolysis, glutaminolysis, and sterol biosynthesis. In the myc-/-/chrebp-/- background, additional deregulated transcripts included those involved in peroxisomal β- and α-FAO. Finally, we observed that Myc and ChREBP cooperatively up-regulated virtually all ribosomal protein genes. Our findings define the individual and cooperative proliferative, metabolic, and transcriptional roles for the "Extended Myc Network" under both normal and neoplastic conditions.

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

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