Liver Digest

A weekly update of PLRC happenings

May 2, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Donna Stolz

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Upcoming Seminars

Starzl Transplant Institute Conference Series Internal Grand Rounds

Friday, May 3, 2019

8:00 – 9:00 a.m.

LHAS Auditorium, 7th Floor, Montefiore Hospital

Shari Rogal, MD

John J. Fung Assistant Professor of Transplant Surgery
Assistant Professor of Gastroenterology, Hepatology and Nutrition
University of Pittsburgh Staff Physician
VA Pittsburgh Healthcare System Core Investigator, Center for Healthcare Research and Promotion
VA Pittsburgh Healthcare System

"Using Implementation Science to Improve Care for Liver Transplant Candidates"

Sponsored by
Thomas E. Starzl Transplantation Institute
University of Pittsburgh School of Medicine
Department of Surgery, Division of Transplantation
Center for Continuing Education in the Health Sciences

PLRC Seminar Series

Tue, 05/07/2019 -
12:00 to 13:00
1104 Scaife

Yasuko Iwakiri, PhD

Associate Professor of Medicine
Internal Medicine, Digestive Diseases

Yale School of Medicine

Lymphatics in the Liver

This activity has been approved for AMA PRA Category 1 Credit. #6242 Liver Center Seminars.
Pizza will be provided.
**This seminar will not be available via Webinar.

PLRC Seminar Series
Thu, 05/09/2019
12:00 to 1:00 p.m.
Eye and Ear Boardroom - 5th floor

Mo R. Ebrahimkhani, MD

Assistant Professor, School of Biological and Health Systems Engineering
Arizona State University

Next Generation Liver Organoids to Parse Human Development and Disease

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

**This seminar will not be available via Webinar.

PLRC Conversation on HCC:
Local Opportunities for Translation and Innovation

June 18, 2019
4:00-8:00 p.m.
LHAS Auditorium, 7th floor Montefiore
Dinner and drinks will be served
RSVP to Ann Vinski (vinskiam@upmc.edu) by June 4

Because we will be ordering catering for this event, we need all RSVPs no later than June 4, 2019. Thank you!

Session 1: Surveillance and Diagnosis

- Surveillance of HCC: Role of Hepatologist – Andres Duarte-Rojo
- Role of Imaging in HCC Diagnosis – Amir Borhani
- Role of Pathologist in HCC Diagnosis and Classification – Michael Nalesnik

Session 2: Current State of Therapies

- Non-transplant Surgical Management of HCC – David Geller
- Liver transplantation for HCC – Abhi Humar
- Medical Management of HCC – Nathan Bahary
- Role of Interventional Radiologist in HCC Management – Paula Novelli

Session 3: Fundamental Research in HCC

- Lymphocyte specific protein-1 as a biomarker for HCC – George Michalopoulos
- Beta-catenin mutations and precision medicine in HCC – Paul Monga
- Therapies for HCC based on novel fusion genes in HCC – Jianhua Luo

Faculty Highlights

Original Article:

Jiang Y, Feng D, **Ma X**, Fan S, Gao Y, Fu K, Wang Y, Sun J, Yao X, Liu C, Zhang H, Xu L, Liu A, Gonzalez FJ, Yang Y, Gao B, Huang M, Bi H. Pregnane X Receptor Regulates Liver Size and Liver Cell Fate by Yes-Associated Protein Activation in Mice. Hepatology. 2019 Jan;69(1):343-358. doi: 10.1002/hep.30131. Epub 2018 Dec 17. PubMed PMID: 30048004; PubMed Central PMCID: PMC6324985.

ABSTRACT

Activation of pregnane X receptor (PXR), a nuclear receptor that controls xenobiotic and endobiotic metabolism, is known to induce liver enlargement, but the molecular signals and cell types responding to PXR-induced

hepatomegaly remain unknown. In this study, the effect of PXR activation on liver enlargement and cell change was evaluated in several strains of genetically modified mice and animal models. Lineage labeling using AAV-Tbg-Cre-treated Rosa26EYFP mice or Sox9-CreERT , Rosa26EYFP mice was performed and Pxr-null mice or AAV Yap short hairpin RNA (shRNA)-treated mice were used to confirm the role of PXR or yes-associated protein (YAP). Treatment with selective PXR activators induced liver enlargement and accelerated regeneration in wild-type (WT) and PXR-humanized mice, but not in Pxr-null mice, by increase of cell size, induction of a regenerative hybrid hepatocyte (HybHP) reprogramming, and promotion of hepatocyte and HybHP proliferation. Mechanistically, PXR interacted with YAP and PXR activation induced nuclear translocation of YAP. Blockade of YAP abolished PXR-induced liver enlargement in mice. Conclusion: These findings revealed a function of PXR in enlarging liver size and changing liver cell fate by activation of the YAP signaling pathway. These results have implications for understanding the physiological functions of PXR and suggest the potential for manipulation of liver size and liver cell fate.

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

Review Article:
Kelly B, **Squires JE**, Feingold B, Hooper DK, **Mazariegos GV**. Quality initiatives in pediatric transplantation. Curr Opin Organ Transplant. 2019 Feb;24(1):64-72. doi: 10.1097/MOT.0000000000000595. PubMed PMID: 30516579.

ABSTRACT
PURPOSE OF REVIEW: Pediatric transplantation faces unique challenges in implementing dynamic quality improvement measures because of proportionally smaller volumes compared to adults, logistics of being integrated successfully within larger or complex hospital systems, lack of adult-affiliated transplant centers, varying focus in prioritization of relevant outcome metrics, and potential lack of sufficient resources.

RECENT FINDINGS: To address these challenges, multiinstitutional collaborations have developed which have proven increasingly effective in driving awareness and quality improvement measures to supplement regulatory efforts in the pediatric population. Relevant work from the Pediatric Heart Transplant Society and Studies in Pediatric Liver Transplantation will be

highlighted. The introduction of learning networks such as the Improving Renal Outcomes Collaborative and the Starzl Network for Excellence in Pediatric Transplantation have further focused on continuous learning initiatives in renal and liver transplantation using collaboration and patient informed measures.

SUMMARY: Optimal transplant performance improvement is fully integrated into health delivery at all points of the patient pathway. Progress in performance improvement will require ongoing integration of big data solutions, improved patient engagement and technology solutions.

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

Original Article:

Aguilar-Bravo, B., Rodrigo-Torres, D., Ariño, S., Coll, M., Pose, E., Blaya, D., Graupera, I., Perea, L., Vallverdú, J., Rubio-Tomás, T., Dubuquoy, L., Armengol, C., Lo Nigro, A., Stärkel, P., Mathurin, P., **Bataller, R.**, Caballería, J., José Lozano, J., Ginès, P. and Sancho-Bru, P. (2019), Ductular Reaction Cells Display an Inflammatory Profile and Recruit Neutrophils in Alcoholic Hepatitis. Hepatology, 69: 2180-2195. doi:10.1002/hep.30472

ABSTRACT

Chronic liver diseases are characterized by the expansion of ductular reaction (DR) cells and the expression of liver progenitor cell (LPC) markers. In alcoholic hepatitis (AH), the degree of DR expansion correlates with disease progression and short-term survival. However, little is known about the biological properties of DR cells, their impact on the pathogenesis of human liver disease, and their contribution to tissue repair. In this study, we have evaluated the transcriptomic profile of DR cells by laser capture microdissection in patients with AH and assessed its association with disease progression. The transcriptome analysis of cytokeratin 7-positive (KRT7+) DR cells uncovered intrinsic gene pathways expressed in DR and genes associated with alcoholic liver disease progression. Importantly, DR presented a proinflammatory profile with expression of neutrophil recruiting C-X-C motif chemokine ligand (CXC) and C-C motif chemokine ligand chemokines. Moreover, LPC markers correlated with liver expression and circulating levels of inflammatory mediators such as CXCL5. Histologically, DR was associated with neutrophil infiltration at the periportal area. In order to model the DR and

to assess its functional role, we generated LPC organoids derived from patients with cirrhosis. Liver organoids mimicked the transcriptomic and proinflammatory profile of DR cells. Conditioned medium from organoids induced neutrophil migration and enhanced cytokine expression in neutrophils. Likewise, neutrophils promoted the proinflammatory profile and the expression of chemokines of liver organoids. Conclusion: Transcriptomic and functional analysis of KRT7+ cells indicate that DR has a proinflammatory profile and promote neutrophil recruitment. These results indicate that DR may be involved in the liver inflammatory response in AH, and suggest that therapeutic strategies targeting DR cells may be useful to mitigate the inflammatory cell recruitment in AH.

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

Original Article:

Möhring T, Karch A, Falk CS, Laue T, D'Antiga L, Debray D, Hierro L, Kelly D, McLin V, **McKiernan P**, Pawlowska J, Czubkowski P, Mikolajczyk RT, Baumann U, Goldschmidt I. Immune Status in Children Before Liver Transplantation-A Cross-Sectional Analysis Within the ChilsSFree Multicentre Cohort Study. Front Immunol. 2019 Jan 25;10:52. doi: 10.3389/fimmu.2019.00052. eCollection 2019. PubMed PMID: 30740106; PubMed Central PMCID: PMC6357985.

ABSTRACT

Background: Both, markers of cellular immunity and serum cytokines have been proposed as potential biomarkers for graft rejection after liver transplantation. However, no good prognostic model is available for the prediction of acute cellular rejection. The impact of underlying disease and demographic factors on immune status before pediatric liver transplantation (pLTx) is still poorly understood. We investigated expression of immune markers before pLTx, in order to better understand the pre-transplant immune status. Improved knowledge of the impact of pre-transplant variables may enhance our understanding of immunological changes post pLTx in the future. **Methods**: This is a cross-sectional analysis of data from the ChilSFree study, a European multicentre cohort study investigating the longitudinal patterns of immune response before and after pLTx. Immune cell counts and soluble immune markers were measured in 155 children 1-30 days before pLTx by TruCount analysis and BioPlex assays. Results were logarithmised due to skewed distributions and then compared according to age, sex, and diagnosis using t-

tests, ANOVAs, and Tukey post-hoc tests. The association between immune markers at time of pLTx and patients' age was assessed using a fractional polynomial approach. Multivariable regression models were used to assess the relative contribution of each factor. **Results**: Sex had no effect on immune status. We found strong evidence for age-specific differences in the immune status. The majority of immune markers decreased in a log-linear way with increasing age. T and B cells showed a sharp increase within the first months of life followed by a log-linear decline in older age groups. Several immune markers were strongly associated with underlying diagnoses. The effects of age and underlying disease remained virtually unchanged when adjusting for each other in multivariable models. **Discussion**: We show for the first time that age and diagnosis are major independent determinants of cellular and soluble immune marker levels in children with end-stage liver disease. These results need to be considered for future research on predictive immune monitoring after pLTx.

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

Funding Opportunities

Limited Competition Cohort Studies of HIV/AIDS and Substance Abuse (U01 Clinical Trial Not Allowed)

(RFA-DA-20-005)

National Institute on Drug Abuse

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