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Liver Digest

A weekly update of PLRC happenings

September 12, 2019



PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Patrick McKiernan

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PLRC Meet and Greet

September 12, 2019

4:30-7:30 p.m.

University Club

Dinner Reception included.

4:30 - Drinks & Hors d'oeuvres

4:45-5:15 - Welcome, Center Overview, Q&A (Dr. Paul Monga)

5:30-6:00 - Core Directors' presentations - 5 minutes each

- 5:30-5:35 - Pilot & Feasibility (Dr. Gavin Arteel)
- 5:35-5:40 - Enrichment (Dr. Kari Nejak-Bowen)
- 5:40-5:45 - Advanced Cell & Tissue Imaging (Dr. Donna Stolz)
- 5:45-5:50 - Biospecimen Repository & Processing (Dr. Aatur Singhi, Dr. David Geller)
- 5:50-5:55 - Genomics & Systems Biology (Dr. Takis Benos, Dr. Jianhua Luo)

6:00-6:15 - Q&A

6:15-7:00 - Dinner

7:00-7:15 - Path Forward (Dr. Paul Monga)

7:15-7:30 - Q&A

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Review Article:

Ko S, Russell JO, Molina LM, **Monga SP**. Liver Progenitors and Adult Cell Plasticity in Hepatic Injury and Repair: Knowns and Unknowns. *Annu Rev Pathol*. 2019 Aug 9. doi: 10.1146/annurev-pathmechdis-012419-032824. PubMed PMID: 31399003.

ABSTRACT

The liver is a complex organ performing numerous vital physiological functions. For that reason, it possesses immense regenerative potential. The capacity for repair is largely attributable to the ability of its differentiated epithelial cells, hepatocytes and biliary epithelial cells, to proliferate after injury. However, in cases of extreme acute injury or prolonged chronic insult, the liver may fail to regenerate or do so suboptimally. This often results in life-threatening end-stage liver disease for which liver transplantation is the only effective treatment. In many forms of liver injury, bipotent liver progenitor cells are theorized to be activated as an additional tier of liver repair. However, the existence, origin, fate, activation, and contribution to regeneration of liver progenitor cells is hotly debated, especially since hepatocytes and biliary epithelial cells themselves may serve as facultative stem cells for one another during severe liver injury. Here, we discuss the evidence both supporting and refuting the existence of liver progenitor cells in a variety of experimental models. We also debate the validity of developing therapies harnessing the capabilities of these cells as potential treatments for patients with severe and chronic liver diseases.

For full text, please [click here](#).

Original Article:

Chen R, Zhu S, Zeng L, **Wang Q**, Sheng Y, Zhou B, Tang D, Kang R. AGER-Mediated Lipid Peroxidation Drives Caspase-11 Inflammasome Activation in Sepsis. *Front Immunol*. 2019 Aug 8;10:1904. doi: 10.3389/fimmu.2019.01904. eCollection 2019. PubMed PMID: 31440260; PubMed Central PMCID: PMC6694796.

ABSTRACT

Inflammasome activation can trigger an inflammatory and innate immune response through the release of cytokines and induction of pyroptosis. A dysfunctional inflammasome has been implicated in the development of human pathologies,

including sepsis and septic shock. Here, we show that advanced glycosylation end-product specific receptor (AGER/RAGE) is required for caspase-11 inflammasome activation in macrophages. A nuclear damage-associated molecular pattern (nDAMP) complex, including high-mobility group box 1, histone, and DNA, can promote caspase-11-mediated gasdermin D cleavage, interleukin 1 β proteolytic maturation, and lactate dehydrogenase release. The inhibition of AGER-mediated lipid peroxidation via arachidonate 5-lipoxygenase (ALOX5) limits caspase-11 inflammasome activation and pyroptosis in macrophages in response to nDAMPs or cytosolic lipopolysaccharide. Importantly, the pharmacologic inhibition of the AGER-ALOX5 pathway or global depletion (Ager -/-) or conditional depletion of AGER in myeloid cells (Ager Mye-/-) protects against lipopolysaccharide-induced septic death in poly(I:C)-primed mice. These data identify a molecular basis for caspase-11 inflammasome activation and provide a potential strategy to treat sepsis.

For full text, please [click here](#).

Original Article:

Roth K, Strickland J, Joshi N, Deng M, Kennedy R, Rockwell CE, Luyendyk JP, **Billiar TR**, Copple BL. Dichotomous Role of Plasmin in Regulation of Macrophage Function after Acetaminophen Overdose. *Am J Pathol*. 2019 Aug 2. pii: S0002-9440(19)30657-1. doi: 10.1016/j.ajpath.2019.07.003. PubMed PMID: 31381887.

ABSTRACT

Kupffer cells and monocyte-derived macrophages are critical for liver repair after acetaminophen (APAP) overdose. These cells produce proinflammatory cytokines and growth factors, and they phagocytose dead cell debris, a process that is critical for resolution of inflammation. The factors that regulate these dynamic functions of macrophages after APAP overdose, however, are not fully understood. We tested the hypothesis that the fibrinolytic enzyme, plasmin, is a key regulator of macrophage function after APAP-induced liver injury. In these studies, inhibition of plasmin in mice with tranexamic acid delayed up-regulation of proinflammatory cytokines after APAP overdose. In culture, plasmin directly, and in synergy with high-mobility group B1, stimulated Kupffer cells and bone marrow-derived macrophages to produce cytokines by a mechanism that required NF- κ B. Inhibition of plasmin in vivo also prevented trafficking of monocyte-derived macrophages into necrotic lesions after APAP overdose. This prevented phagocytic removal of dead cells,

prevented maturation of monocyte-derived macrophages into F4/80-expressing macrophages, and prevented termination of proinflammatory cytokine production. Our studies reveal further that phagocytosis is an important stimulus for cessation of proinflammatory cytokine production as treatment of proinflammatory, monocyte-derived macrophages, isolated from APAP-treated mice, with necrotic hepatocytes decreased expression of proinflammatory cytokines. Collectively, these studies demonstrate that plasmin is an important regulator of macrophage function after APAP overdose.

For full text, please [click here](#).

Commentary:

Scott MJ. The upside-downside nature of Vitamin D signaling in liver. *J Leukoc Biol.* 2019 Aug 5. doi: 10.1002/JLB.3CE0519-157R. PubMed PMID: 31379001.

For full text, please [click here](#).

Original Article:

Anna L. Lang, Austin M. Krueger, Regina D. Schnegelberger, Brenna R. Kaelin, Maxwell J. Rakutt, Liya Chen, **Gavin E. Arteel, Juliane I. Beier.** Rapamycin attenuates liver injury caused by vinyl chloride metabolite chloroethanol and lipopolysaccharide in mice. *Toxicol Appl Pharmacol.* 2019 Sep 6:114745. doi: 10.1016/j.taap.2019.114745. [Epub ahead of print]

ABSTRACT

Vinyl chloride (VC) is a prevalent environmental toxicant that is rapidly metabolized within the liver. Its metabolites have been shown to directly cause hepatic injury at high exposure levels. We have previously reported that VC metabolite, chloroethanol (CE), potentiates liver injury caused by lipopolysaccharide (LPS). Importantly, that study showed that CE alone, while not causing damage per se, was sufficient to alter hepatic metabolism and increase mTOR phosphorylation in mice, suggesting a possible role for the mTOR pathway. Here, we explored the effect of an mTOR inhibitor, rapamycin, in this model. C57BL/6J mice were administered CE, followed by rapamycin 1h and LPS 24h later. As observed previously, the combination of CE and LPS significantly enhanced liver injury, inflammation, oxidative stress, and metabolic dysregulation. Rapamycin attenuated not only inflammation, but also restored the metabolic phenotype and protected against CE+LPS-induced oxidative stress. Importantly, rapamycin protected against mitochondrial

damage and subsequent production of reactive oxygen species (ROS). The protective effect on mitochondrial function by rapamycin was mediated, by restoring the integrity of the electron transport chain at least in part, by blunting the deactivation of mitochondrial c-src, which is involved mitochondrial ROS production by electron transport chain leakage. Taken together, these results further demonstrate a significant role of mTOR-mediated pathways in VC-metabolite induced liver injury and provide further insight into VC-associated hepatic damage. As mTOR mediated pathways are very complex and rapamycin is a more global inhibitor, more specific mTOR (i.e. mTORC1) inhibitors should be considered in future studies.

For full text, please [click here](#).

Funding Opportunities

Myeloid-Derived Suppressor Cells (MDSCs) as Potential Therapeutic Targets in TB/HIV (R01 Clinical Trial Not Allowed)

(PAR-19-357)

National Institute of Allergy and Infectious Diseases

Myeloid-Derived Suppressor Cells (MDSCs) as Potential Therapeutic Targets in TB/HIV (R21 Clinical Trial Not Allowed)

(PAR-19-364)

National Institute of Allergy and Infectious Diseases



Our mailing address is:

Pittsburgh Liver Research Center
200 Lothrop St. | Pittsburgh, PA 15261