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Liver Digest

A weekly update of PLRC happenings

June 6, 2019

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

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Featured Faculty - Dr. Shari Rogal

In this issue

Faculty Highlights

Original Article:

Poole LG, **Beier JI**, Torres-Gonzales E, Schlueter CF, Hudson SV, Artis A, Warner NL, Nguyen-Ho CT, Dolin CE, Ritzenthaler JD, Hoyle GW, Roman J, **Arteel GE**. Chronic + binge alcohol exposure promotes inflammation and alters airway mechanics in the lung. Alcohol. 2018 Nov 13. pii: S0741-8329(18)30080-6. doi: 10.1016/j.alcohol.2018.10.008. [Epub ahead of print]. PMID: 30445135.

ABSTRACT

INTRODUCTION: Alcohol use disorders are major risk factors for the development of and susceptibility to acute respiratory distress syndrome. Although these risks of alcohol consumption on the lung are well described, mechanisms by which alcohol abuse promotes acute lung injury are poorly understood. These gaps in our understanding are due, at least in part, to limitations of animal models to recapitulate human alcohol consumption. Recently, a new model of chronic plus binge alcohol exposure was developed that is hypothesized to better model drinking patterns of individuals with alcohol use disorders. Specifically, this paradigm models chronic consumption coupled with periodic bouts of heavy drinking. The impacts of this alcohol exposure regimen on the lung are uncharacterized. Therefore, the goal of this study was to examine lung injury and inflammation in a well-characterized experimental model of chronic + binge alcohol exposure.

METHODS: 10-week male C57Bl6/J mice were administered ethanol-containing (or isocaloric control) liquid diet for ten days, followed by a single ethanol gavage (5 g/kg). Lung inflammation and pulmonary function were assessed.

RESULTS: Ten days of ethanol-containing liquid diet alone (chronic) did not

detectably affect any variables measured. However, ethanol diet plus gavage (chronic + binge) caused neutrophils to accumulate in the lung tissue and in the bronchoalveolar lavage fluid 24 hours post-binge. This inflammatory cell recruitment was associated with airway hyper-responsiveness to inhaled methacholine, as indicated by elevated resistance, Newtonian resistance, and respiratory resistance.

CONCLUSIONS: Taken together, the novel findings reveal that ethanol alone, absent of any secondary inflammatory insult, is sufficient to produce inflammation in the lung. Although these changes were relatively mild, they were associated with functional changes in the central airways. This animal model may be useful in the future for identifying mechanisms by which alcohol abuse sensitizes at-risk individuals to lung injury.

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

Review Article:

Deng M, **Scott MJ**, Fan J, **Billiar TR**. Location is the key to function: HMGB1 in sepsis and trauma-induced inflammation. J Leukoc Biol. 2019 Apr 4. doi: 10.1002/JLB.3MIR1218-497R. [Epub ahead of print] Review. PubMed PMID: 30946496.

ABSTRACT

High mobility group box 1 (HMGB1) is a multifunctional nuclear protein, probably known best as a prototypical alarmin or damage-associated molecular pattern (DAMP) molecule when released from cells. However, HMGB1 has multiple functions that depend on its location in the nucleus, in the cytosol, or extracellularly after either active release from cells, or passive release upon lytic cell death. Movement of HMGB1 between cellular compartments is a dynamic process induced by a variety of cell stresses and disease processes, including sepsis, trauma, and hemorrhagic shock. Location of HMGB1 is intricately linked with its function and is regulated by a series of posttranslational modifications. HMGB1 function is also regulated by the redox status of critical cysteine residues within the protein, and is cell-type dependent. This review highlights some of the mechanisms that contribute to location and functions of HMGB1, and focuses on some recent insights on important intracellular effects of HMGB1 during sepsis and trauma.

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

Clinical Practice Guidelines:

Arab JP, Roblero JP, Altamirano J, Bessone F, Chaves Araujo R, Higuera-De la Tijera F, Restrepo JC, Torre A, Urzua A, Simonetto DA, Abraldes JG, Méndez-Sánchez N, Contreras F, Lucey MR, Shah VH, Cortez-Pinto H, **Bataller R**. Alcohol-related liver disease: Clinical practice guidelines by the Latin American Association for the Study of the Liver (ALEH). Ann Hepatol. 2019 May - Jun;18(3):518-535. doi: 10.1016/j.aohep.2019.04.005. Epub 2019 Apr 18.

ABSTRACT

Alcohol-related liver disease (ALD) is a major cause of advanced chronic liver disease in Latin-America, although data on prevalence is limited. Public health policies aimed at reducing the alarming prevalence of alcohol use disorder in Latin-America should be implemented. ALD comprises a clinical-pathological spectrum that ranges from steatosis, steatohepatitis to advanced forms such as alcoholic hepatitis (AH), cirrhosis and hepatocellular carcinoma. Besides genetic factors, the amount of alcohol consumption is the most important risk factor for the development of ALD. Continuous consumption of more than 3 standard drinks per day in men and more than 2 drinks per day in women increases the risk of developing liver disease. The pathogenesis of ALD is only partially understood and recent translational studies have identified novel therapeutic targets. Early forms of ALD are often missed and most clinical attention is focused on AH, which is defined as an abrupt onset of jaundice and liver-related complications. In patients with potential confounding factors, a transjugular biopsy is recommended. The standard therapy for AH (i.e. prednisolone) has not evolved in the last decades yet promising new therapies (i.e. G-CSF, N-acetylcysteine) have been recently proposed. In both patients with early and severe ALD, prolonged abstinence is the most efficient therapeutic measure to decrease long-term morbidity and mortality. A multidisciplinary team including alcohol addiction specialists is recommended to manage patients with ALD. Liver transplantation should be considered in the management of patients with end-stage ALD that do not recover despite abstinence. In selected cases, increasing number of centers are proposing early transplantation for patients with severe AH not responding to medical therapy.

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

Original Article:

Hachim D, Iftikhar A, LoPresti ST, Nolfi AL, Ravichandar S, Skillen CD, **Brown BN**. Distinct release strategies are required to modulate macrophage phenotype in young versus aged animals. J Control Release. 2019 May 17;305:65-74. doi: 10.1016/j.jconrel.2019.05.020. [Epub ahead of print] PubMed PMID: 31103676.

ABSTRACT

The role of innate immunity and macrophages in the host response to biomaterials has received renewed attention. A context-dependent spectrum of macrophage phenotypes are shown to affect tissue integration and performance of implanted biomaterials and medical devices. Recent studies by our group demonstrated that the host response in aged animals was characterized by delayed macrophage recruitment, differences in marker expression and a shifted pro-inflammatory (M1) response, associated with an unresolved host response in the long-term. The present work sought to study the effects of single and sequential cytokine delivery regimens in aged mice to restore delayed recruitment of macrophages and shift the inflammatory host response towards an M2-like phenotype, using MCP-1 (macrophage chemotactic protein-1) and IL-4 (interleukin-4), respectively. Implantation of cytokine-eluting implants showed a preserved response to MCP-1 in both young and aged animals, restoring delayed macrophage recruitment in aged mice. However, the response elicited by IL-4, sequential delivery of MCP-1/IL-4 and coating components was distinct in young versus aged mice. While single delivery of IL-4 did not counteract the high inflammatory response observed in aged mice, the sequential delivery of MCP-1/IL-4 was capable of restoring both recruitment and shifting the macrophage response towards an M2-like phenotype, associated with decreased implant scarring in the long-term. In young mice, sequential delivery was not as effective as IL-4 alone at promoting an M2-like response, but did result in a reduction of M1 macrophages and capsule deposition downstream. These results demonstrate that a proper understanding of patient/context-dependent biological responses are needed to design biomaterial-based therapies with improved outcomes in the setting of aging.

To access full text, please **click here**.

Meeting Report:

Lai JC, Sonnenday CJ, Tapper EB, Duarte-Rojo A, **Dunn MA**, Bernal W, Carey EJ, Dasarathy S, Kamath BM, Kappus MR, Montano-Loza AJ, Nagai S, Tandon P. Frailty in liver transplantation: An expert opinion statement from the American Society of Transplantation Liver and Intestinal Community of Practice. Am J Transplant. 2019;00:1-11. https://doi.org/10.1111/ajt.15392

ABSTRACT
Frailty has emerged as a powerful predictor of outcomes in patients with cirrhosis and has inevitably made its way into decision making within liver transplantation. In an effort to harmonize integration of the concept of frailty among transplant centers, the AST and ASTS supported the efforts of our working group to develop this statement from experts in the field. Frailty is a multidimensional construct that represents the end-manifestation of derangements of multiple physiologic systems leading to decreased physiologic reserve and increased vulnerability to health stressors. In hepatology/liver transplantation, investigation of frailty has largely focused on physical frailty, which subsumes the concepts of functional performance, functional capacity, and disability. There was consensus that every liver transplant candidate should be assessed at baseline and longitudinally using a standardized frailty tool, which should guide the intensity and type of nutritional and physical therapy in individual liver transplant candidates. The working group agreed that frailty should not be used as the sole criterion for delisting a patient for liver transplantation, but rather should be considered one of many criteria when evaluating transplant candidacy and suitability. A road map to advance frailty in the clinical and research settings of liver transplantation is presented here.

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

Statement from the Department of Health and Human Services

On June 5, 2019, the Department of Health and Human Services issued a statement regarding research involving human fetal tissue from elective abortions. The statement includes a link to the NIH's notice of intent to publish funding opportunities for "research to develop, demonstrate, and validate experimental models that do not rely on human fetal tissue from elective abortions."

The full statement is available on the HHS website (please click on link below).
https://www.hhs.gov/about/news/2019/06/05/statement-from-the-department-of-health-and-human-services.html

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Funding Opportunities

Immunobiology of Xenotransplantation (U01 Clinical Trial Not Allowed)
(RFA-AI-19-042)
National Institute of Allergy and Infectious Diseases

Immunobiology of Xenotransplantation (U19 Clinical Trial Not Allowed)
(RFA-AI-19-043)
National Institute of Allergy and Infectious Diseases

Adipogenesis, Adipocyte Function and Obesity Following HIV Infection, Antiretroviral Therapy, or Pre-Exposure Prophylaxis (R01 Clinical Trial Optional)
(RFA-DK-19-008)
National Institute of Diabetes and Digestive and Kidney Diseases

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