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Liver Digest

A weekly update of PLRC happenings

October 31, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Jianhua Luo

In this issue

Next Week's Seminar

The Connection Between Liver and Heart Disease
Thurs., 11/09/2019
5:00 - 9:00 p.m.
Ramada Hotel and Conference Center
Greensburg, PA

For program and registration information, please follow the link:
https://www.communityliveralliance.org/epidemics-in-liver-disease

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

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Upcoming Conference

2019 Annual Update in Medical Hepatology
December 7, 2019
University of Pittsburgh, University Club
The program and list of speakers is available **here**.
To register, please follow the link: https://cce.upmc.com/2019-annual-update-medical-hepatology

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:Hudson, Shanice V., Miller, Hunter A., Mahlbacher, Grace E., Saforo, Douglas, Beverly, Levi J., **Arteel**, **Gavin E.**, Frieboes, Hermann B. Computational/experimental evaluation of liver metastasis post hepatic injury: interactions with macrophages and transitional ECM. Scientific Reports volume 9, Article number: 15077 (2019)

ABSTRACT

The complex interactions between subclinical changes to hepatic extracellular matrix (ECM) in response to injury and tumor-associated macrophage microenvironmental cues facilitating metastatic cell seeding remain poorly understood. This study implements a combined computational modeling and experimental approach to evaluate tumor growth following hepatic injury, focusing on ECM remodeling and interactions with local macrophages. Experiments were performed to determine ECM density and macrophage-associated cytokine levels. Effects of ECM remodeling along with macrophage polarization on tumor growth were evaluated via computational modeling. For primary or metastatic cells in co-culture with macrophages, TNF-α levels were 5× higher with M1 vs. M2 macrophages. Metastatic cell co-culture exhibited 10× higher TNF-α induction than with primary tumor cells. Although TGFβ1 induction was similar between both co-cultures, levels were slightly higher with primary cells in the presence of M1. Simulated metastatic tumors exhibited decreased growth compared to primary tumors, due to high local M1-induced cytotoxicity, even in a highly vascularized microenvironment. Experimental analysis combined with computational modeling may provide insight into interactions between ECM remodeling, macrophage polarization, and liver tumor growth.

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

Review Article:
Dasyam AK, Shah ZK, Tirkes T, Dasyam N, **Borhani AA**. Cross-sectional imaging-based severity scoring of chronic pancreatitis: why it is necessary and how it can be done. Abdom Radiol (NY). 2019 Sep 11. doi: 10.1007/s00261-019-02218-6. Review. PubMed PMID: 31511956.

ABSTRACT

Chronic pancreatitis (CP) remains a diagnostic challenge as clinical symptoms are non-specific, histopathological appearances are varied and pathogenesis remains incompletely understood. Multiple classifications and grading systems have been proposed for CP, but none leverage the full capabilities of cross-sectional imaging modalities and are not

widely accepted or validated. CT and MRI/MRCP are useful in identifying a wide spectrum of histopathological changes in CP and can also assess exocrine reserve of pancreas. Advanced MRI techniques such as T1 mapping and extracellular volume fraction can potentially identify early CP. Cross-sectional imaging-based severity scoring can quantify CP disease burden and may have positive implications for clinicians and researchers. In this review, we discuss the need for cross-sectional imaging-based severity scoring for CP, role of CT, and MRI/MRCP in assessment of CP and how these modalities can be used to obtain severity scoring for CP. We summarize relevant information from recently published CT and MRI/MRCP reporting standards for CP, and from international guidelines for cross-sectional imaging and severity scoring for CP.

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

Original Article:
Merkel CD, Li Y, Raza Q, **Stolz DB**, Kwiatkowski AV. Vinculin anchors contractile actin to the cardiomyocyte adherens junction. Mol Biol Cell. 2019 Oct 1;30(21):2639-2650. doi: 10.1091/mbc.E19-04-0216. PubMed PMID: 31483697.

ABSTRACT
The adherens junction (AJ) couples the actin cytoskeletons of neighboring cells to allow mechanical integration and tissue organization. The physiological demands of intercellular adhesion require that the AJ be responsive to dynamic changes in force while maintaining mechanical load. These demands are tested in the heart, where cardiomyocyte AJs must withstand repeated cycles of actomyosin-mediated contractile force. Here we show that force-responsive cardiomyocyte AJs recruit actin-binding ligands to selectively couple actin networks. We employed a panel of N-cadherin-αE-catenin fusion proteins to rebuild AJs with specific actin linkages in N-cadherin-null cardiomyocytes. In this system, vinculin recruitment was required to rescue myofibril integration at nascent contacts. In contrast, loss of vinculin from the AJ disrupted junction morphology and blocked myofibril integration at cell-cell contacts. Our results identify vinculin as a critical link to contractile actomyosin and offer insight to how actin integration at the AJ is regulated to provide stability under mechanical load.

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

Original Article:
Zhao G, Zhang J, Nie D, Zhou Y, Li F, Onishi K, **Billiar T**, Wang JH. HMGB1 mediates the development of tendinopathy due to mechanical overloading. PLoS One. 2019 Sep 27;14(9):e0222369. doi: 10.1371/journal.pone.0222369. eCollection 2019. PubMed PMID: 31560698.

ABSTRACT
Mechanical overloading is a major cause of tendinopathy, but the underlying pathogenesis of tendinopathy is unclear. Here we report that high mobility group box1 (HMGB1) is

released to the tendon extracellular matrix and initiates an inflammatory cascade in response to mechanical overloading in a mouse model. Moreover, administration of glycyrrhizin (GL), a naturally occurring triterpene and a specific inhibitor of HMGB1, inhibits the tendon's inflammatory reactions. Also, while prolonged mechanical overloading in the form of long-term intensive treadmill running induces Achilles tendinopathy in mice, administration of GL completely blocks the tendinopathy development. Additionally, mechanical overloading of tendon cells in vitro induces HMGB1 release to the extracellular milieu, thereby eliciting inflammatory and catabolic responses as marked by increased production of prostaglandin E2 (PGE2) and matrix metalloproteinase-3 (MMP-3) in tendon cells. Application of GL abolishes the cellular inflammatory/catabolic responses. Collectively, these findings point to HMGB1 as a key molecule that is responsible for the induction of tendinopathy due to mechanical overloading placed on the tendon.

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

Original Article:
Vats R, Brzoska T, Bennewitz MF, Jimenez MA, **Pradhan-Sundd T**, Tutuncuoglu E, Jonassaint J, Gutierrez E, Watkins SC, Shiva S, **Scott M**, Morelli AE, Neal MD, Kato GJ, **Gladwin MT, Sundd P**. Platelet Extracellular Vesicles Drive Inflammasome-IL1β-dependent Lung Injury in Sickle Cell Disease. Am J Respir Crit Care Med. 2019 Sep 9. doi: 10.1164/rccm.201807-1370OC. PubMed PMID: 31498653.

ABSTRACT
RATIONALE: Intra-erythrocytic polymerization of hemoglobin S promotes hemolysis and vaso-occlusive events in the microvasculature of sickle cell disease (SCD) patients. Although platelet-neutrophil aggregates-dependent vaso-occlusion is known to occur in the lung and contribute to acute chest syndrome, the etiological mechanisms that trigger lung injury are largely unknown.

OBJECTIVES: To identify the innate-immune mechanism that promotes platelet-neutrophil aggregate-dependent lung vaso-occlusion and injury in SCD.

METHODS: In vivo imaging of the lung in transgenic humanized SCD mice and in vitro imaging of SCD patient blood flowing through a microfluidic system was performed. SCD mice were systemically challenged with nanogram quantities of lipopolysaccharide to trigger lung vaso-occlusion.

MAIN RESULTS: Platelet-inflammasome activation led to generation of IL-1β carrying platelet extracellular vesicles (EVs) that bind to neutrophils and promote platelet-neutrophil aggregation in lung arterioles of SCD mice in vivo and SCD human blood in microfluidics in vitro. The inflammasome activation, platelet EV generation and platelet-neutrophil aggregation were enhanced by the presence of lipopolysaccharide at a nanogram dose in SCD but not control human blood. Inhibition of the inflammasome

effector caspase-1 or IL-1β pathway attenuated platelet EV generation, prevented platelet-neutrophil aggregation, and restored microvascular blood flow in lung arterioles of SCD mice in vivo and SCD human blood in microfluidics in vitro.

CONCLUSIONS: These results are the first to identify that platelet-inflammasome dependent shedding of IL-1β carrying platelet EVs promote lung vaso-occlusion in SCD. The current findings also highlight the therapeutic potential of targeting the platelet-inflammasome dependent innate immune pathway to prevent acute chest syndrome.

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

Funding Opportunity

Limited Competition: Biospecimen Banks to support NCI National Clinical Trials Network (NCTN)(U24 Clinical Trial Not Allowed)
(RFA-CA-20-002)
National Cancer Institute

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