Liver Digest

A weekly update of PLRC happenings

March 7, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. David Whitcomb

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Next Week's Seminars

PLRC Seminar Series - 2018 Pilot and Feasibility Awardees

Tues, March 12, noon-1:30 pm

1103 Scaife

Three of the 2018-19 Pilot and Feasibility Awardees will present their work at this seminar.

Dong Hu, MD, PhD

Research Instructor, Department of Pathology, Division of Experimental Pathology

"A novel role of antiviral protein MAVS in high fat diet-induced hepatic insulin resistance"

Michael Jurczak, PhD

Assistant Professor of Medicine, Division of Endocrinology and Metabolism

"Exploring the role of hepatic mitophagy in the pathogenesis of NAFLD"

Ossama Kashlan, PhD

Assistant Professor of Medicine, Division of Renal-Electrolyte

"ENaC Regulation by Biliary Factors"

Pizza will be provided.

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

Call for Articles - Cells

*Dr. Ralf Weiskirchen, a Guest Editor of **Cells** (IF = 4.829), is arrangig a special issue entitled "Cellular and Molecular Mechanisms underlying the Pathogenesis of Hepatic Fibrosis." He is seeking contributions in the form of original research articles, reviews, or shorter perspective articles on all aspects related to the theme. The special issue is now open for submission.*

*Detailed information about this project can be found at: **https://www.mdpi.com/journal/cells/special_issues/hepatic_fibrosis***

Liver Cancer Conference - March 9

Community Liver Allicance Liver Cancer Conference
Saturday, March 9, 2019 | 7:30 a.m. - 3:00 p.m.
Wyndham Grand Hotel, Pittsburgh, PA
CME Accredited

*For schedule, speakers, and details, please visit the PLRC website: **http://www.livercenter.pitt.edu/livercancer-conference***

*To register, please visit the CLA website: **http://www.communityliveralliance.org/liver-cancerconference***

Liver-Themed Gut Club - May 2

***Dr. Fasiha Kanwal**, the division chief at Baylor, will speak at the May 2, 2019 Pittsburgh Gut Club accredited dinner/lecture series on "The Changing Epidemiology of Liver Cancer."*

Liver-related clinical and research trainees are invited to attend the lecture with fee-waived registration. All faculty are invited to attend as well but are required to pay to attend. But, they welcome your trainees as fee-waived participants.

To register for this event, please complete the registration form found in the brochure available on the here (trainees mark "fee waived" in the payment

*section), and scan (**joj2@pitt.edu**) or fax (412-578-9537) it to Joy Merusi by April 15th.*

Faculty Highlights

Original Article:

*Stahl EC, Haschak MJ, Popovic B, **Brown BN**. Macrophages in the Aging Liver and Age-Related Liver Disease. Front Immunol. 2018 Nov 30;9:2795. doi: 10.3389/fimmu.2018.02795. eCollection 2018. Review. PubMed PMID: 30555477; PubMed Central PMCID: PMC6284020.*

ABSTRACT

The number of individuals aged 65 or older is projected to increase globally from 524 million in 2010 to nearly 1. 5 billion in 2050. Aged individuals are particularly at risk for developing chronic illness, while being less able to regenerate healthy tissue and tolerate whole organ transplantation procedures. In the liver, these age-related diseases include non-alcoholic fatty liver disease, alcoholic liver disease, hepatitis, fibrosis, and cirrhosis. Hepatic macrophages, a population comprised of both Kupffer cells and infiltrating monocyte derived macrophages, are implicated in several chronic liver diseases and also play important roles in the homeostatic functions of the liver. The effects of aging on hepatic macrophage population dynamics, polarization, and function are not well understood. Studies performed on macrophages derived from other aged sources, such as the bone marrow, peritoneal cavity, lungs, and brain, demonstrate general reductions in autophagy and phagocytosis, dysfunction in cytokine signaling, and altered morphology and distribution, likely mediated by epigenetic changes and mitochondrial defects, that may be applicable to hepatic macrophages. This review highlights recent findings in macrophage developmental biology and function, particularly in the liver, and discusses the role of macrophages in various age-related liver diseases. A better understanding of the biology of aging that influences hepatic macrophages and thus the progression of chronic liver disease will be crucial in order to develop new interventions and treatments for liver disease in aging populations.

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

Review Article:

*Myers SP, Kulkarni SS, **Malik SM**, Tevar AD, Neal MD. Hernia Management in Cirrhosis: Risk Assessment, Operative Approach, and Perioperative Care. J Surg Res. 2019 Mar;235:1-7. doi: 10.1016/j.jss.2018.09.052. Epub 2018 Oct 23. Review. PubMed PMID: 30691782.*

ABSTRACT

BACKGROUND: The rising incidence of liver disease has complicated the management of common surgical pathologies. Hernias, in particular, are problematic given the shortage of high-quality data and differing expert opinions. We aim to provide a narrative review of hernia management in cirrhosis as a first step toward developing evidence-based recommendations for the care of these patients.

MATERIALS AND METHODS: A literature review using separate search strings was conducted for PubMed and Cochrane Central Register of Controlled Trials databases. Review articles, conference abstracts, randomized clinical trials, and observational studies were included. Articles without a focus on patients with end-stage liver disease were excluded. Manuscripts were selected based on relevance to perioperative risk assessment, medical optimization, surgical decision-making, and considerations of hernia repair in patients with cirrhosis.

RESULTS: The existing literature is varied with regard to focus and quality of data. Of the 4516 articles identified, 51 full-text articles were selected for review. In general, there is evidence to suggest that individuals with compensated cirrhosis may successfully undergo and benefit from hernia repair. Patients at high risk for decompensated cirrhosis may be best served by nonoperative management.

CONCLUSIONS: Carefully selected patients with cirrhosis may proceed with herniorrhaphy. A multidisciplinary approach is essential to provide high-quality care and improve outcomes.

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

Review Article:

*You M, **Arteel GE**. Effect of ethanol on lipid metabolism. J Hepatol. 2019*

Feb;70(2):237-248. doi: 10.1016/j.jhep.2018.10.037. Review. PubMed PMID: 30658725.

ABSTRACT

Hepatic lipid metabolism is a series of complex processes that control influx and efflux of not only hepatic lipid pools, but also organismal pools. Lipid homeostasis is usually tightly controlled by expression, substrate supply, oxidation and secretion that keep hepatic lipid pools relatively constant. However, perturbations of any of these processes can lead to lipid accumulation in the liver. Although it is thought that these responses are hepatic arms of the 'thrifty genome', they are maladaptive in the context of chronic fatty liver diseases. Ethanol is likely unique among toxins, in that it perturbs almost all aspects of hepatic lipid metabolism. This complex response is due in part to the large metabolic demand placed on the organ by alcohol metabolism, but also appears to involve more nuanced changes in expression and substrate supply. The net effect is that steatosis is a rapid response to alcohol abuse. Although transient steatosis is largely an inert pathology, the chronicity of alcohol-related liver disease seems to require steatosis. Better and more specific understanding of the mechanisms by which alcohol causes steatosis may therefore translate into targeted therapies to treat alcohol-related liver disease and/or prevent its progression.

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

Review Article:

*Molinari M, Sood P, Samra PB, Tevar A, Ganoza A, **Jonassaint N**, Puttarajappa C. Atrial fibrillation in renal or liver transplant recipients: A systematic review and meta-analysis. Transplant Rev (Orlando). 2019 Jan;33(1):29-38. doi: 10.1016/j.trre.2018.07.003. Epub 2018 Aug 9. Review. PubMed PMID: 30139706.*

ABSTRACT

BACKGROUND: The prevalence of atrial fibrillation (AF) in patients undergoing renal (RT) or liver transplantation (LT) has increased during the last decades. Yet, there is still uncertainty on the association between AF and patient and graft survival.

METHODS: Multiple electronic databases were searched using various combinations of keywords and MeSH terms pertinent to the exposure (AF), and

outcomes (graft and patient survival). Randomized or quasi-randomized controlled studies, cohort and case-control studies on adults with documented AF undergoing RT or LT were included. The quality of studies was assessed using the Newcastle-Ottawa Assessment Scale. When appropriate, data on the primary and secondary outcomes were pooled in a meta-analysis using the random-effect model. The Odds ratio was used for patients undergoing LT and the hazard ratio was used for patients who underwent renal transplantation.

RESULTS: A total of 50,362 publications were identified. Six studies, with a total of 136,331 patients, satisfied the inclusion criteria. LT was performed on 2861 patients and RT was performed on 133,470 recipients. Overall, AF affected 6652 (4.8%) transplant recipients. Among them, 153 received a LT and 6499 underwent RT. The OR for mortality after LT was 2.375 (95% CI; 1.532-3.682) (P = 0.000) in AF(+) recipients and the HR was 1.859 (95% CI; 1.031-3.354) (P = 0.039) after RT. The OR for graft loss in AF(+) after LT r was 1.088 (95% CI; 0.311-3.804) (P = 0.894) and the HR for graft loss was 1.632 (95% CI; 1.200-2.218) (P = 0.002) after RT.

CONCLUSIONS: To the best of our knowledge, this is the first systematic review and meta-analysis to explore the association between AF and patient and graft survival after RT or LT. Our findings suggest that the presence of AF is associated with inferior patient survival. For renal transplant recipients, AF is also associated with inferior graft survival.

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

Original Article:

Yu YP, Liu P, Nelson J, Hamilton RL, Bhargava R, ***Michalopoulos G****, Chen Q, Zhang J, Ma D, Pennathur A, Luketich J,* ***Nalesnik M****, Tseng G,* ***Luo JH****. Identification of recurrent fusion genes across multiple cancer types. Sci Rep. 2019 Jan 31;9(1):1074. doi: 10.1038/s41598-019-38550-6. PubMed PMID: 30705370; PubMed Central PMCID: PMC6355770.*

ABSTRACT

Chromosome changes are one of the hallmarks of human malignancies. Chromosomal rearrangement is frequent in human cancers. One of the consequences of chromosomal rearrangement is gene fusions in the cancer genome. We have previously identified a panel of fusion genes in aggressive prostate cancers. In this study, we showed that 6 of these fusion genes are present in 7

different types of human malignancies with variable frequencies. Among them, the CCNH-C5orf30 and TRMT11-GRIK2 gene fusions were found in breast cancer, colon cancer, non-small cell lung cancer, esophageal adenocarcinoma, glioblastoma multiforme, ovarian cancer and liver cancer, with frequencies ranging from 12.9% to 85%. In contrast, four other gene fusions (mTOR-TP53BP1, TMEM135-CCDC67, KDM4-AC011523.2 and LRRC59-FLJ60017) are less frequent. Both TRMT11-GRIK2 and CCNH-C5orf30 are also frequently present in lymph node metastatic cancer samples from the breast, colon and ovary. Thus, detecting these fusion transcripts may have significant biological and clinical implications in cancer patient management.

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

Funding Opportunities

Coulter - PLRC Joint Award

The University of Pittsburgh & UPMC Pittsburgh Liver Research Center (PLRC) is pleased to announce a new translational grant program in collaboration with the Coulter TPII Program (Coulter) at the University of Pittsburgh. In September of 2019, the PLRC/Coulter will award up to one $50,000 grant, aimed at developing the commercial potential of healthcare solutions that are based on innovative technologies related to liver health, including disease diagnosis, surgery, treatment, and public health. One-Page LOI Submission: Deadline – 5:00 p.m. Friday, March 15, 2019.

Modulating Intestinal Microbiota to Enhance Protective Immune Responses against Cancer (R01 Clinical Trial Not Allowed)

(PAR-19-198)

National Cancer Institute

Modulating Intestinal Microbiota to Enhance Protective Immune Responses against Cancer (R21 Clinical Trial Not Allowed)

(PAR-19-199)

National Cancer Institute

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