Liver Digest

A weekly update of PLRC happenings

June 13, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Shari Rogal

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- Faculty Highlights
- Funding Opportunity
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Faculty Highlights

Original Article:

Marron MM, **Miljkovic I**, Boudreau RM, Christensen K, Feitosa MF, Lee JH, Sebastiani P, Thyagarajan B, Wojczynski MK, Zmuda JM, Newman AB; Long Life Family Study. A novel healthy metabolic phenotype developed among a cohort of families enriched for longevity. Metabolism. 2019 May;94:28-38. doi: 10.1016/j.metabol.2019.01.010. Epub 2019 Jan 30. PubMed PMID: 30710575.

ABSTRACT

BACKGROUND: Long-lived individuals and their offspring have healthier metabolic characteristics than expected, such as more favorable levels of fasting glucose, insulin, and lipids than controls without longevity. Dysregulation in metabolic pathways has also shown to predict accelerated aging. Using information from the Long Life Family Study (LLFS), a multi-center study of two-generation families selected for exceptional longevity, we developed an indicator of healthy metabolism to determine whether metabolic health was more prevalent in a subset of LLFS families and whether it was heritable and associated with other metrics of healthy aging.

METHODS: A Latent Profile Analysis was applied to age- and gender-adjusted z-scores of fasting levels of glucose, insulin, triglycerides, and high-density lipoprotein cholesterol, body mass index, waist circumference, interleukin-6, and C-reactive protein. Families were defined as meeting the healthy metabolic phenotype if ≥2 and ≥50% of their offspring were classified into a latent subgroup with a profile of healthier metabolic markers than expected given age and gender relative to all LLFS offspring.

RESULTS: The log odds of being classified into the latent subgroup with a healthy profile of metabolic markers was heritable ($h2 = 0.40$, $p < 0.001$). Among

388 families, 39 (10%) met the healthy metabolic phenotype. Participants from these families had somewhat better cognition than those from remaining families. Proband-generation participants from families who met the healthy metabolic phenotype also had better pulmonary functioning and physical performance.

CONCLUSIONS: The better cognition, pulmonary function, and physical performance among probands from families with the healthy metabolic phenotype may indicate that this subset of LLFS families have a more extreme longevity phenotype than other LLFS families since cognitive, physical, and pulmonary function are top mortality predictors for older adults. Future work is needed to determine if rare or protective alleles confer a healthy metabolic phenotype in this subset of LLFS families with exceptional metabolism.

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

Faculty Accolade:

The Pharmacology and Toxicology program in the School of Pharmacy at the University of Wisconsin-Madison has honored **Dr. Gavin Arteel** with the distinction of 2019 Alumnus of the Year. The article released by the University of Wisconsin-Madison can be accessed at the link below, and it contains very nice references to the Pittsburgh Liver Research Center. Congratulations to Dr. Arteel!

https://pharmacy.wisc.edu/gavin-arteel-honored-as-2019-pharmtox-alumnus-of-the-year/

Original Article:

Yan J, Tung HC, Li S, Niu Y, Garbacz WG, Lu P, Bi Y, Li Y, He J, Xu M, Ren S, **Monga SP**, Schwabe RF, Yang D, **Xie W**. Aryl hydrocarbon receptor signaling prevents activation of hepatic stellate cells and liver fibrogenesis in mice. Gastroenterology 2019 Jun 3 [Epub ahead of print] PMID: 31170413.

ABSTRACT
BACKGROUND & AIMS: The role of aryl hydrocarbon receptor (AHR) in liver fibrosis is controversial, because loss and gain of AHR activity each lead to

liver fibrosis. The goal of this study is to investigate how the expression of AHR by different liver cell types, hepatic stellate cells (HSCs) in particular, affects liver fibrosis in mice.

METHODS: We studied the effects of AHR on primary mouse and human HSCs, measuring their activation and stimulation of fibrogenesis using RNA-seq analysis. C57BL/6J mice were given the AHR agonists TCDD or ITE, or carbon tetrachloride (CCl4), or underwent bile duct ligation. We also performed studies in mice with disruption of Ahr specifically in HSCs, hepatocytes, or Kupffer cells. Liver tissues were collected from mice and analyzed by histology, immunohistochemistry, and immunoblotting.

RESULTS: AHR was expressed at high levels in quiescent HSCs, but the expression decreased with HSC activation. Activation of HSCs from AHR-knockout mice was accelerated, compared to HSCs from wild-type mice. In contrast, TCDD or ITE inhibited spontaneous and transforming growth factor beta (TGFB)-induced activation of HSCs. Mice with disruption of Ahr in HSCs, but not hepatocytes or Kupffer cells, developed more severe fibrosis following administration of CCl4 or bile duct ligation. C57BL/6J mice given ITE did not develop CCl4-induced liver fibrosis, whereas mice without HSC AHR given ITE did develop CCl4-induced liver fibrosis. In studies of mouse and human HSCs, we found that AHR prevents TGFB-induced fibrogenesis by disrupting the interaction of SMAD3 with beta-catenin, which prevents the expression of genes that mediate fibrogenesis.

CONCLUSIONS: In studies of human and mouse HSCs, we found that AHR prevents HSC activation and expression of genes required for liver fibrogenesis. Development of non-toxic AHR agonists or strategies to activate AHR signaling in HSCs might be developed to prevent or treat liver fibrosis.

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

Original Article:

Davuluri G, Giusto M, Chandel R, Welch N, Alsabbagh K, Kant S, Kumar A, Kim A, Gangadhariah M, Ghosh PK, Tran U, Krajcik DM, Vasu K, DiDonato AJ, DiDonato J, Willard B, **Monga SP**, Wang Y, Fox PL, Stark GR, Wessely O, Esser KA, Dasarathy S. Impaired Ribosomal Biogenesis by Non-Canonical Degradation of β-catenin during Hyperammonemia. Mol Cell Biol. 2019 May 28. pii: MCB.00451-18. doi:

10.1128/MCB.00451-18. [Epub ahead of print] PMID:31138664

ABSTRACTIncreased ribosomal biogenesis occurs during tissue hypertrophy but whether ribosomal biogenesis is impaired during atrophy is not known. We show that hyperammonemia, which occurs in diverse chronic disorders, impairs protein synthesis as a result of decreased ribosomal content and translational capacity. Transcriptome analyses, real-time PCR and immunoblots showed consistent reduction in expression of the large and small ribosomal protein subunits (RPL, RPS) in hyperammonemic murine skeletal myotubes, HEK cells, and skeletal muscle from hyperammonemic rats and human cirrhotics. Decreased ribosomal content was accompanied by decreased expression of cMYC, a positive regulator of ribosomal biogenesis, as well as reduced expression and activity of β-catenin, a transcriptional activator of cMYC. However, unlike the canonical regulation of β-catenin via GSK3β-dependent degradation, GSK3β expression and phosphorylation were unaltered during hyperammonemia, and depleting GSK3β did not prevent ammonia-induced degradation of β-catenin. Overexpression of GSK3β-resistant variants, genetic depletion of IKKβ (activated during hyperammonemia), protein interactions and in vitro kinase assays showed that IKKβ phosphorylated β-catenin directly. Overexpressing β-catenin restored hyperammonemia-induced perturbations in signaling responses that regulate ribosomal biogenesis. Our data show that decreased protein synthesis during hyperammonemia is mediated via a novel GSK3β-independent, IKKβ-dependent impairment of the β-catenin-cMYC axis.

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

Original Article:
Gong S, Yan Z, Liu Z, Niu M, Fang H, Li N, Huang C, Li L, Chen G, Luo H, Chen X, Zhou H, Hu J, Yang W, Huang Q, Schnabl B, Chang P, **Billiar TR**, Jiang Y, Chen P. Intestinal Microbiota Mediates the Susceptibility to Polymicrobial Sepsis-Induced Liver Injury by Granisetron Generation in Mice. Hepatology. 2019Apr;69(4):1751-1767. doi: 10.1002/hep.30361. Epub 2019 Mar 5. PubMed PMID: 30506577.

ABSTRACT
Sepsis-induced liver injury is recognized as a key problem in intensive care units. The gut microbiota has been touted as an important mediator of liver disease development; however, the precise roles of gut microbiota in

regulating sepsis-induced liver injury are unknown. Here, we aimed to investigate the role of the gut microbiota in sepsis-induced liver injury and the underlying mechanism. Cecal ligation and puncture (CLP) was used to induce polymicrobial sepsis and related liver injury. Fecal microbiota transplantation (FMT) was used to validate the roles of gut microbiota in these pathologies. Metabolomics analysis was performed to characterize the metabolic profile differences between sepsis-resistant (Res; survived to 7 days after CLP) and sepsis-sensitive (Sen; moribund before or approximately 24 hours after CLP) mice. Mice gavaged with feces from Sen mice displayed more-severe liver damage than did mice gavaged with feces from Res mice. The gut microbial metabolic profile between Sen and Res mice was different. In particular, the microbiota from Res mice generated more granisetron, a 5-hydroxytryptamine 3 (5-HT3) receptor antagonist, than the microbiota from Sen mice. Granisetron protected mice against CLP-induced death and liver injury. Moreover, proinflammatory cytokine expression by macrophages after lipopolysaccharide (LPS) challenge was markedly reduced in the presence of granisetron. Both treatment with granisetron and genetic knockdown of the 5-HT3A receptor in cells suppressed nuclear factor kappa B (NF-κB) transactivation and phosphorylated p38 (p-p38) accumulation in macrophages. Gut microbial granisetron levels showed a significantly negative correlation with plasma alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels in septic patients. Conclusion: Our study indicated that gut microbiota plays a key role in the sensitization of sepsis-induced liver injury and associates granisetron as a hepatoprotective compound during sepsis development.

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

Funding Opportunity

Early-Stage Preclinical Validation of Therapeutic Leads for Diseases of Interest to the NIDDK (R01 Clinical Trial Not Allowed)

(PAR-19-294)

National Institute of Diabetes and Digestive and Kidney Diseases

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Pitt Ventures First Gear

If you've ever wondered how to begin taking your University research discovery to the marketplace, Pitt's Innovation Institute offers a six-session workshop called "First Gear" that helps guide researchers through the process. The next cohort will begin September 13, 2019, but applications are due by August 30. Please visit the website for more information:

https://www.innovation.pitt.edu/program-navigator/pitt-ventures-first-gear/

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