Liver Digest

A weekly update of PLRC happenings

July 3, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Mordechai Rabinovitz

In this issue

PLRC Awarded NIH/NIDDK P30 Grant

It is our great pleasure to announce the successful funding of the Pittsburgh Liver Research Center (PLRC) by the NIH/NIDDK through a P30 mechanism. We are now one of the twenty NIDDK-designated Digestive Disease Research Core Centers and funded for 5 years. As you are aware, PLRC was formed in 2016 through generous support from UPMC & the University of Pittsburgh. Since its inception, we have brought together clinicians and scientists from various departments to build a thriving and collaborative community with common goals of improving outcome in patients with liver disease through a better understanding of the underpinnings of liver health and disease. This, in turn has been enabled through core services that provide exceptional, innovative and cutting edge technical support to the PLRC members. In addition, PLRC, through its Pilot and Feasibility program, has financially supported liver-related research especially in the labs of early stage investigators while providing longitudinal mentoring and career development. Likewise, this program supports multidisciplinary & collaborative, commercialization, as well as translational grants, through various mechanisms. Lastly, through its Enrichment program, PLRC provides continued educational activities for its members by hosting extramural and intramural speakers, while also fostering physician-basic scientist interactions and collaborations through innovative platforms.

To celebrate our first major success in obtaining extramural funding and to provide an opportunity to further understand the organization and functioning of the PLRC, we will organize an evening reception in August. Please keep an eye out for this invitation. In the meantime, if there are any questions or comments, please feel free to contact us.

Thank you for your support.

Faculty Highlights

Original Article:

Russell JO, Ko S, **Monga SP**, **Shin D**. Notch Inhibition Promotes Differentiation of Liver Progenitor Cells into Hepatocytes via sox9b Repression in Zebrafish. Stem Cells Int. 2019 Mar 12;2019:8451282. doi: 10.1155/2019/8451282. eCollection 2019. PubMed PMID: 30992706; PubMed Central PMCID: PMC6434270.

ABSTRACT

Liver regeneration after most forms of injury is mediated through the proliferation of hepatocytes. However, when hepatocyte proliferation is impaired, such as during chronic liver disease, liver progenitor cells (LPCs) arising from the biliary epithelial cell (BEC) compartment can give rise to hepatocytes to mediate hepatic repair. Promotion of LPC-to-hepatocyte differentiation in patients with chronic liver disease could serve as a potentially new therapeutic option, but first requires the identification of the molecular mechanisms driving this process. Notch signaling has been identified as an important signaling pathway promoting the BEC fate during development and has also been implicated in regulating LPC differentiation during regeneration. SRY-related HMG box transcription factor 9 (Sox9) is a direct target of Notch signaling in the liver, and Sox9 has also been shown to promote the BEC fate during development. We have recently shown in a zebrafish model of LPC-driven liver regeneration that inhibition of Hdac1 activity through MS-275 treatment enhances sox9b expression in LPCs and impairs LPC-to-hepatocyte differentiation. Therefore, we hypothesized that inhibition of Notch signaling would promote LPC-to-hepatocyte differentiation by repressing sox9b expression in zebrafish. We ablated the hepatocytes of Tg(fabp10a:CFP-NTR) larvae and blocked Notch activation during liver regeneration through treatment with γ-secretase inhibitor LY411575 and demonstrated enhanced induction of Hnf4a in LPCs. Alternatively, enhancing Notch signaling via Notch3 intracellular domain (N3ICD) overexpression impaired Hnf4a induction. Hepatocyte ablation in sox9b heterozygous mutant embryos enhanced Hnf4a induction, while BEC-specific Sox9b overexpression impaired LPC-to-hepatocyte differentiation. Our results establish the Notch-Sox9b signaling axis as inhibitory to LPC-to-hepatocyte differentiation in a well-established in vivo LPC-driven liver regeneration model.

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

Original Article:
Gérard C, Di-Luoffo M, Gonay L, Caruso S, Couchy G, Loriot A, Castven D, Tao J, Konobrocka K, Cordi S, **Monga SP**, Hanert E, Marquardt JU, Zucman-Rossi J, Lemaigre FP. Dynamics and predicted drug response of a gene network linking dedifferentiation with beta-catenin dysfunction in hepatocellular carcinoma. J Hepatol. 2019 Apr 4. pii: S0168-8278(19)30195-3. doi: 10.1016/j.jhep.2019.03.024. [Epub ahead of print] PubMed PMID: 30953666.

ABSTRACT

BACKGROUND & AIMS: Alterations of individual genes variably affect the development of hepatocellular carcinoma (HCC). Thus, we aimed to characterize the function of tumor-promoting genes in the context of gene regulatory networks (GRNs).

METHODS: Using data from The Cancer Genome Atlas, from the LIRI-JP (Liver Cancer - RIKEN, JP project), and from our transcriptomic, transfection and mouse transgenic experiments, we identify a GRN which functionally links LIN28B-dependent dedifferentiation with dysfunction of β-catenin (CTNNB1). We further generated and validated a quantitative mathematical model of the GRN using human cell lines and in vivo expression data.

RESULTS: We found that LIN28B and CTNNB1 form a GRN with SMARCA4, Let-7b (MIRLET7B), SOX9, TP53 and MYC. GRN functionality is detected in HCC and gastrointestinal cancers, but not in other cancer types. GRN status negatively correlates with HCC prognosis, and positively correlates with hyperproliferation, dedifferentiation and HGF/MET pathway activation, suggesting that it contributes to a transcriptomic profile typical of the proliferative class of HCC. The mathematical model predicts how the expression of GRN components changes when the expression of another GRN member varies or is inhibited by a pharmacological drug. The dynamics of GRN component expression reveal distinct cell states that can switch reversibly in normal conditions, and irreversibly in HCC. The mathematical model is available via a web-based tool which can evaluate the GRN status of HCC samples and predict the impact of therapeutic agents on the GRN.

CONCLUSIONS: We conclude that identification and modelling of the GRN provide insights into the prognosis of HCC and the mechanisms by which tumor-promoting

genes impact on HCC development.

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

Original Article:

Wang H, Lu J, Kulkarni S, Zhang W, Gorka JE, Mandel JA, **Goetzman ES**, **Prochownik EV**. Metabolic and oncogenic adaptations to pyruvate dehydrogenase inactivation in fibroblasts. J Biol Chem. 2019 Apr 5;294(14):5466-5486. doi: 10.1074/jbc.RA118.005200. Epub 2019 Feb 12. PubMed PMID: 30755479; PubMed Central PMCID: PMC6462518.

ABSTRACT

Eukaryotic cell metabolism consists of processes that generate available energy, such as glycolysis, the tricarboxylic acid (TCA) cycle, and oxidative phosphorylation (Oxphos), and those that consume it, including macromolecular synthesis, the maintenance of ionic gradients, and cellular detoxification. By converting pyruvate to acetyl-CoA (AcCoA), the pyruvate dehydrogenase (PDH) complex (PDC) links glycolysis and the TCA cycle. Surprisingly, disrupting the connection between glycolysis and the TCA cycle by inactivation of PDC has only minor effects on cell replication. However, the molecular basis for this metabolic re-equilibration is unclear. We report here that CRISPR/Cas9-generated PDH-knockout (PDH-KO) rat fibroblasts reprogrammed their metabolism and their response to short-term c-Myc (Myc) oncoprotein overexpression. PDH-KO cells replicated normally but produced surprisingly little lactate. They also exhibited higher rates of glycolysis and Oxphos. In addition, PDH-KO cells showed altered cytoplasmic and mitochondrial pH, redox states, and mitochondrial membrane potential (ΔΨM). Conditionally activated Myc expression affected some of these parameters in a PDH-dependent manner. PDH-KO cells had increased oxygen consumption rates in response to glutamate, but not to malate, and were depleted in all TCA cycle substrates between α-ketoglutarate and malate despite high rates of glutaminolysis, as determined by flux studies with isotopically labeled glutamine. Malate and pyruvate were diverted to produce aspartate, thereby potentially explaining the failure to accumulate lactate. We conclude that PDH-KO cells maintain proliferative capacity by utilizing glutamine to supply high rates of AcCoA-independent flux through the bottom portion of the TCA cycle while accumulating pyruvate and aspartate that rescue their redox defects.

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

Original Article:

Harmon DB, Mandler WK, Sipula IJ, Dedousis N, Lewis SE, Eckels JT, Du J, Wang Y, Huckestein BR, Pagano PJ, Cifuentes-Pagano E, Homanics GE, Van't Erve TJ, Stefanovic-Racic M, **Jurczak MJ**, **O'Doherty RM**, Kelley EE. Hepatocyte-Specific Ablation or Whole-Body Inhibition of Xanthine Oxidoreductase in Mice Corrects Obesity-Induced Systemic Hyperuricemia Without Improving Metabolic Abnormalities. Diabetes. 2019 Jun;68(6):1221-1229. doi: 10.2337/db18-1198. Epub 2019 Apr 1. PubMed PMID: 30936145.

ABSTRACT

Systemic hyperuricemia (HyUA) in obesity/type 2 diabetes facilitated by elevated activity of xanthine oxidoreductase (XOR), which is the sole source of uric acid (UA) in mammals, has been proposed to contribute to the pathogenesis of insulin resistance/dyslipidemia in obesity. Here, the effects of hepatocyte-specific ablation of Xdh, the gene encoding XOR (HXO), and whole-body pharmacologic inhibition of XOR (febuxostat) on obesity-induced insulin resistance/dyslipidemia were assessed. Deletion of hepatocyte Xdh substantially lowered liver and plasma UA concentration. When exposed to an obesogenic diet, HXO and control floxed (FLX) mice became equally obese, but systemic HyUA was absent in HXO mice. Despite this, obese HXO mice became as insulin resistant and dyslipidemic as obese FLX mice. Similarly, febuxostat dramatically lowered plasma and tissue UA and XOR activity in obese wild-type mice without altering obesity-associated insulin resistance/dyslipidemia. These data demonstrate that hepatocyte XOR activity is a critical determinant of systemic UA homeostasis, that deletion of hepatocyte Xdh is sufficient to prevent systemic HyUA of obesity, and that neither prevention nor correction of HyUA improves insulin resistance/dyslipidemia in obesity. Thus, systemic HyUA, although clearly a biomarker of the metabolic abnormalities of obesity, does not appear to be causative.

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

Funding Opportunity

AASLD Research & Career Development Awards

AASLD Foundation

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