P-009

From cirrhosis to hepatocellular carcinoma: An investigation into hepatitis C viral oncogenesis using meta-analysis

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INTRODUCTION: Hepatitis C is a leading cause of chronic liver disease leading to cirrhosis and hepatocellular carcinoma (HCC). Even with the introduction of direct acting antivirals (DAAs), HCV incidence is increasing and its risks for HCC will likely persist. Despite advancements in treatment in HCC, the overall prognosis remains poor. Understanding the evolution and biology of HCC in HCV patients is of great interest and may pave the way for novel therapeutic avenues and better risk stratification.

METHODS: The Search Tag Analyze Resource for Gene Expression Omnibus (STARGEO) platform allows for meta-analysis of genomic signatures of disease and tissue. Through STARGEO we performed two separate meta-analyses on 357 HCV-related HCC tumor samples with 220 adjacent non-tumor samples as a control and 92 HCV-related cirrhotic liver samples with 53 healthy liver samples as a control. We then analyzed the signature in Ingenuity Pathway Analysis.

RESULTS: HCV-related cirrhosis analysis demonstrated LPS/IL-1 mediated inhibition of RXR function, LXR/RXR activation, sirtuin signaling, IL-10 signaling, and hepatic fibrosis/stellate cell activation as top canonical pathways. IL1B, TNF, and TGFB1 were top upstream regulators. Our analysis highlighted genetic changes that are involved in oncogenesis. Cellular morphologic and signaling changes were noted through upregulation of RGS1/2, WNT receptor FZD7, the TGFB1-induced gap junction gene GJA1, and the zinc finger transcription factor repressor SNAI2. Apoptosis was inhibited through downregulation of OMA1. Metabolic dysfunction was noted through downregulation of SCLY and CBS. Lastly, immune modulation was seen through IL10 signaling and upregulation of the prostaglandin receptor PTGER4, which has been shown to impair cytotoxic T cell function. HCV-related HCC analysis showed FXR/RXR and LXR/RXR signaling, LPS/IL1-mediated inhibition of RXR activation, and melatonin degradation as top canonical pathways. ERBB2, TP53, PPARA, and calcitriol were top upstream regulators. We found upregulation of recently described oncogenic "pseudogenes" DUXAP10 and NMRAL2P and of established tumorigenic genes such as CRNDE, CTHRC1, FAM83D, and GPC3. We also noted upregulation of canonical β-catenin/TCF targets AXIN2, LEF1, SP5, and DKK1 that was not upregulated in our HCV cirrhotic analysis.

CONCLUSION: Our results illustrated the genetic changes in the setting of chronic HCV infection and cirrhosis that predispose patients to developing HCC. Some of these changes, such as LXR/FXR signaling and tumor immune evasion, persist from the cirrhotic to carcinoma stage. The other changes, such as canonical β-catenin/TCF signaling, characterize what pathways and genes may drive progression from cirrhosis to HCC and may serve as potential therapeutic targets and biomarkers. Our analysis offered limited overview of the immune landscape, but we aim to expand our analysis to investigate immune checkpoint markers in the future.

Keywords: hepatitis C virus, HCV, hepatocellular carcinoma, HCC, oncogenesis, cirrhosis

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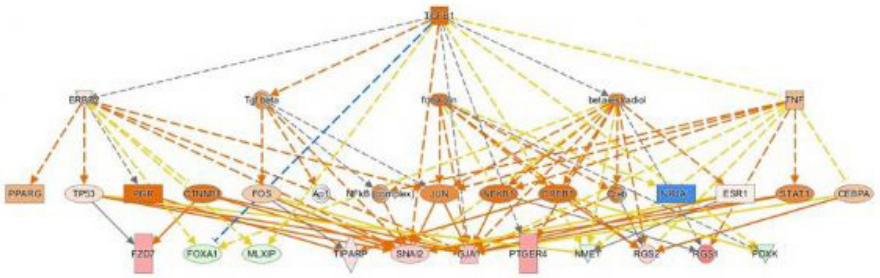
Pathologic Effects of TGFB1 in HCV-Related Cirrhosis



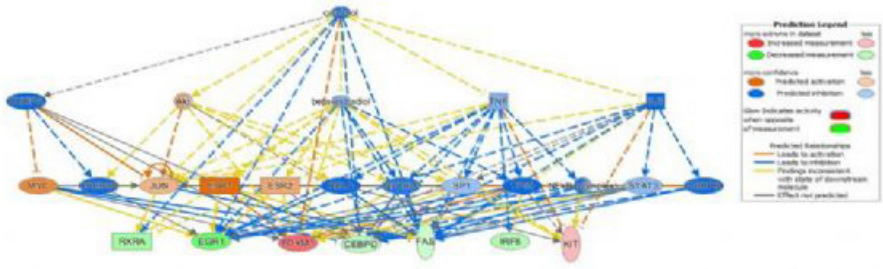
Search Tag Analyze Resource

A screen capture of how to use STARGEO. Relevant experiments can be searched and samples from those experiments can be tagged using the regex function, as shown.

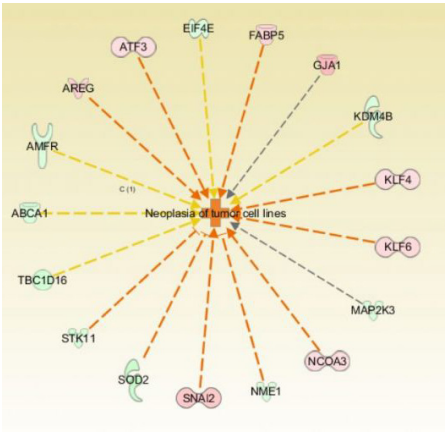
Table of Top Upregulated and Downregulated Genes

Top Upregulated				Top Downregulated			
HCV-Cirrhosis		HCV-HCC		HCV-Cirrhosis		HCV-HCC	
RGS1	0.834	DUXAP10	1.185	OMA1	-0.527	LINC01093	-2.258
PTGER4	0.581	NMRAL2P	1.130	SAA2	-0.313	CNDP1	-2.062
FZD7	0.552	CRNDE	1.125	LRIF1	-0.252	CLEC4G	-1.928
RGCC	0.524	AKRB10	1.090	CCDC69	-0.228	OIT3	-1.816
GJA1	0.416	CTHRC1	1.073	WWP1	-0.227	CLRN3	-1.814
DAB2	0.385	GPC3	1.072	SCLY	-0.211	TTC36	-1.763
APOLD1	0.323	FAM83D	0.985	KIAA0100	-0.194	CLTRN	-1.649
SNAI2	0.321	COX7B2	0.978	CBS/CBSL	-0.192	ADGRG7	-1.624
SAMSN1	0.312	KRT23	0.967	POMGNT1	-0.189	HHIP	-1.599
RGS2	0.282	RBM24	0.952	SEC4D	-0.186	CNTN3	-1.520

Possible Mechanistic Effects of Calcitriol in HCV-Related HCC



Genes Involved in Neoplastic Change in HCV-Related Cirrhosis



Top Canonical Pathways Identified by IPA