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Integrative omics analysis identifies candidate alleles and pathways underlying human hepatic fibrogenesis and fibrosis

Zhipeng Liu[1], **Jingmei Lin**[2], **Naga Chalasani**[2] and **Wanqing Liu**[1]
[1]Purdue University, USA
[2]Indiana University School of Medicine, USA

Background: The genetic basis underlying liver fibrosis remains largely unknown. Quantitative sirius red staining and expression of alpha-smooth muscle actin (α-SMA) are accurate and reliable markers for liver fibrosis and fibrogenesis, respectively.

Aims: To identify genetic alleles and underlying pathways associated with hepatic fibrogenesis and fibrosis at the genome-wide level.

Methods: We conducted a genome-wide association study (GWAS) by examining the associations between 533,687 single-nucleotide polymorphisms (SNP) and the measurements of hepatic fibrogenesis (α-SMA staining) and fibrosis (Sirius red staining) in human liver samples collected from donors without heavy alcohol consumption or viral hepatitis (n=123). Following the GWAS, an expression quantitative trait loci (eQTLs) analysis was conducted to examine the relationship between candidate SNPs ($p<10^{-4}$) and gene expression levels in the same sample set of liver tissues, by focusing on the genes in the region of ±1Mbp of each candidate SNP locus. The significant ($p<0.05$) eQTL-controlling genes were then examined in an enrichment analysis to identify molecular pathways using Ingenuity Pathway Analysis package.

Results: At the $p<10^{-4}$ level, we identified 71 and 73 candidate loci potentially affecting the fibrosis and fibrogenesis, respectively. Among which, 52 candidate loci for fibrosis and 58 loci for fibrogenesis were significant eQTLs of their nearby genes. Pathway analyses of these genes indicated that Macrophage Migration Inhibitory Factor (MIF)-mediated Glucocorticoid Regulation (p=0.003), MIF Regulation of Innate Immunity (p=0.005), and Endothelin-1 Signaling (p=0.009) were the top three pathways involved in the collagen accumulation, while Eumelanin Biosynthesis ($p= 7.2 \times 10^{-5}$), Glutathione Redox Reactions (p=0.001), and VEGF Signaling (p=0.002) for stellate cell activation. Interestingly, the MIF-mediated Glucocorticoid Regulation (p=0.004) and MIF Regulation of Innate Immunity pathways were also significantly associated with α-SMA expression (p=0.006).

Conclusion: Our study identified candidate alleles and pathways strongly associated with hepatic fibrogenesis and fibrosis. The MIF signaling pathway may play a critical role in liver fibrosis.

Biography

Zhipeng Liu is a Graduate student at Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, USA.

liu1449@purdue.edu

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