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Gut-liver cross talk: Role of toll-like receptors in liver fibrogenesis and development of hepatocellular carcinoma

Mostafa El Awady
National Research Center, Egypt

The increase in intestinal barrier permeability due to bacterial over growth, viral infection or heavy fat or alcohol intake is associated with excessive release of several pathogen associated molecular patterns into the portal circulation such as LPS, FFA or viral CpG containing nucleic acids. The subsequent binding of these factors to toll like receptors in the liver activates downstream intracellular signaling pathways resulting in innate immunological, molecular and pathological responses in liver cells ending with fibrogenesis, and hepatocarcinogenesis. We examined the expression profiling of 168 genes related to fibrogenesis and IFN induced genes in a hundred patients chronically infected with HCV type 4. Those patients suffer different stages of liver fibrosis (F0-F4) as well as HCC. The transcriptome data were compared with twenty healthy subjects proven to have normal liver functions and undetectable viral hepatitis markers. The studied array included TLR, IFN stimulated genes, inflammatory cytokines, chemokines and their receptors, adhesion molecules, extracellular matrix proteins, Metalloproteinases, growth factors and signal transduction mediators. Based on the initial explorative study few genes were selected for validation based on fold changes, statistical significance, their relation to chronic liver disease and novelty. The validation included analyses of expression profiles at both RNA and protein levels. Members of innate immune responses and their transcription factors such as TLR and NFkB were clearly up regulated in fibrosis. Chemokines and their receptors involved in hepatic stellate cell activation were also up regulated in fibrosis. The role of SMAD genes in directing the dialogue between TGFB and TLR signaling has been confirmed. The roles of matrix Metalloproteinases and their tissue inhibitors in fibrogenesis as well as the roles of inflammatory cytokines IL1 A & B and TNFα in inflammation of Kupffer cells were confirmed in the current profiling. Besides, 11 genes whose roles are not directly related to TLR signaling were found differentially regulated in fibrosis. *THBS1, TGIF1, STAT1, STAT6, SERPINH1* were up regulated. While *IL5, ITGB3, ITGB1, ITGA2, ITGAV* and *SERPINA1* were down regulated. The current study provides gene signatures associated with liver fibrosis and HCC as well as transcriptome data on mechanisms of HCV related liver disease.

Biography

Mostafa El Awady is a Professor of Molecular Genetics and Biochemistry at the National Research Center, Cairo, Egypt. He obtained his PhD in Biochemistry in 1981 and received several Postdoctoral fellowships in South Western Med. School Dallas TX, Liver Research Center, Albert Einstein College of Medicine NY and University of North Carolina Chapel Hill (1981-1993). He was the Dean of Genetic Engineering Research Institute Mubarak Science Park Alexandria, President of the Division of Genetic Engineering at NRC. He has been granted several state awards for his accomplishments in science. He has published over 100 articles in peer reviewed journals in molecular biology of genetics and viral diseases. His current interests include development of prophylactic vaccine against HCV and exploration of novel therapeutic targets and prognostics of chronic liver disease.

mkawady49@yahoo.com