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Genetics and epigenetics in the fibrogenic evolution of chronic liver diseases

Vincent Zimmer, MD, Senior Clinical Research Physician, Frank Lammert, MD, Professor, Head of Department *

Department of Medicine II, Saarland University Hospital, Saarland University, Kirrberger Str., 66421 Homburg, Germany

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Recent years have seen unprecedented progress in the identification and characterization of genetic information related to chronic liver diseases (CLDs). However, despite the conceptual benefit in early recognition of at-risk populations amenable to pre-emptive treatment and/or surveillance strategies, recent genomic research in the field has placed focus on unravelling the genetic architecture of disease susceptibility, while data on genetic markers anticipating an accelerated fibrogenesis in an individual are still limited. Likewise, sequence variation assigning rapid fibrogenic evolution common to CLDs irrespective of etiology are poorly defined aside from *PNPLA3* (adiponutrin) as a prominent exception. The emerging field of epigenetics in hepatology has mostly been studied under the perspective of gene regulation, less so as a heritable alteration in gene activity. In this article we will critically discuss recent findings in genomic hepatology with special focus on the (epi)genetic contribution to the fibrogenic evolution of CLDs.

Introduction

Liver fibrosis represents a final pathway, in principle, common to all chronic liver diseases (CLDs), such as viral, cholestatic or fatty liver diseases, and poses a significant burden of morbidity and mortality worldwide [1]. Hepatic stellate cell (HSC) activation characterized by retinoid loss is considered central to fibrogenesis as a common response to various injurious insults to the liver [2]. In the presence of continuous liver injury, a sustained wound-healing process is activated, resulting in

* Corresponding author. Tel.: +49 6841 1623201; fax: +49 6841 1623267.
E-mail addresses: vincent.zimmer@uks.eu (V. Zimmer), frank.lammert@uks.eu (F. Lammert).

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progressive accumulation of extracellular matrix (ECM) in the subendothelial space of Disse and distortion of parenchymal and vascular liver architecture by scar tissue. Nevertheless, in its pre-cirrhotic stage, the etiology and primary site of injury is of relevance to liver fibrogenesis [3]. In addition to activated HSCs representing a key and well characterized reservoir for fibrogenic myofibroblasts (MFB), other cell populations such as portal fibroblasts or bone-marrow derived cells provide a context-specific substrate for modulation of hepatic fibrogenesis. The clinical appreciation of individual variation in fibrogenesis dynamics and cirrhosis risk, most thoroughly investigated in patients with chronic hepatitis C virus (HCV) infection, has indicated a strong host genetic modulation in liver fibrosis independent of other appreciable environmental factors (concept of "*slow* versus *rapid fibrosers*") [4–6]. With the advent of modern genotyping and sequencing technologies, major progress has been achieved in the field of fibrosis genetics by the accelerated identification of genetic risk factors and modulators underlying the most diverse CLDs by virtue of genome-wide association studies (GWAS) [7,8]. The two recent top-hits in the field of hepatology, *IL28B* and *PNPLA3*, are prominent examples for pathobiological pathway identification by the hypothesis-free GWAS approach and its potential for risk assessment in clinical practice [9,10]. Even larger-scale mapping of genetic disease markers is expected to arise from continuous technical improvements in and the ever-decreasing costs related to next-generation sequencing technologies and the future opportunity of whole-genome sequencing, which has been facilitated by the refined characterization of human genomic variation via the *1000 Genomes Project* [11]. By contrast, the emerging field of epigenetics in CLDs is still in its infancy and may provide further clues to the heritable fraction of their fibrogenic evolution.

In this review, we will delineate novel findings and concepts in genetics and epigenetics with relevance to different CLDs, including recent human genetic data on cholestatic liver diseases, chronic HCV infection, and non-alcoholic fatty liver disease (NAFLD).

Host genetics in chronic liver diseases

Since the first GWAS on gallstone risk has been published in 2007 [12], more than 25 GWAS related to hepatobiliary diseases and/or quantitative traits have been published and have been instrumental in the dissemination of knowledge of genetic risk and, though less so, progression factors ("*modifier genes*"). Marked individual differences in fibrosis progression rates independent of environmental and other identified risk factors suggest a strong genetic determination of an individual's risk of progression to liver cirrhosis. Quantitative trait locus (QTL) mapping and GWAS are powerful tools to identify fibrosis-associated genes at the genome-wide scale in mice and men, respectively [13]. It is assumed that different CLDs may share common fibrosis risk genes, whereas others may be exclusive to distinct CLDs [14,15]. Genetic loci potentially common to all CLDs may include genes affecting (adapted from [16]):

- Hepatocellular apoptosis and necrosis, including *BCL-XL* and *Fas*
- Inflammatory and innate immune responses, such as *TNFα*, *IL-1β*, *IL-1RN*, *IL-6*, *IL-13*, *IFNγ*, *SOCS1*, *osteopontin*, *TLR4* and *DDX5*
- Profibrogenic cytokines, e.g., *TGFβ1* and *AGT*
- Matrix degradation (*TIMP1*) and regulation (*TGFβ1* and *MMP7*)
- ROS generation: *NADPH oxidase* and *SOD2*
- Chemotaxis: *CCL2*, *CCR5*, *CXCL9 or C5*

However, the focus of recent genetic research in the field has been placed on unravelling susceptibility loci associated with CLDs, while there is only limited data available in terms of genetic modulation of their natural courses (Table 1). Since the majority of genetic data has been derived from academic referral centres with the inherent potential of biasing towards more severe phenotypes compared to community-based populations, an overlap between true susceptibility and progression factors may arise. Similarly, current susceptibility loci represent logical candidates for subsequent studies that address their impact on the fibrogenic progression of CLDs.