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Invited critical review

Biomarkers of liver fibrosis: Clinical translation of molecular pathogenesis or based on liver-dependent malfunction tests

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Abstract

Background: Fibrosis is the excessive deposition and histological redistribution of extracellular matrix (ECM) in the tissue as consequence of chronic liver damage. It leads to progressive liver insufficiency, portal hypertension and ultimately to cirrhosis and primary liver cell carcinoma. There is a strong demand for reliable, organ- and disease-specific, non-invasive biomarkers of fibrosis and fibrogenesis to replace or to complement the invasive method of needle biopsy, which is afflicted with a high degree of sampling error.
Methods: A systematic literature search was performed using electronic databases and reference lists of relevant publications to ascertain studies with non-invasive biomarkers of liver fibrosis.
Results: Two classes of serum biomarkers can be differentiated: Class I markers are those, which reflect ECM turnover (fibrogenesis and fibrolysis) and/or fibrogenic cell changes, mainly of hepatic stellate cells, which are the dominant profibrogenic cell type in liver. They are mostly cost intensive, single laboratory tests and derive from the translation of fibrogenic mechanisms into clinical application. Examples are procollagen peptides, hyaluronan, and laminin. Class II biomarkers are based on algorithmic evaluation of commonly observed functional alterations of the liver that do not necessarily reflect ECM metabolism and/or fibrogenic cell changes. About 20 numerical scores or indices are reported for parameters, which are mostly routine laboratory tests and frequently multiparametric (panels). Among them fibrotest, hepascore, ELF-score have reached limited clinical application.
Conclusions: Up to now the impact of both classes of biomarkers for diagnosis and monitoring of fibrosis, fibrogenesis, and fibrolysis is limited. They cannot replace needle biopsy but some of them might be complementary in follow-up studies. Innovative methods like proteomics and glycomics to establish fibrosis-specific serum protein and glycosylation patterns, respectively, might have a high potential for diagnosis and monitoring of fibrogenesis.

Keywords: Liver fibrosis; Biomarkers; Serum markers; Fibrogenesis; Non-invasive diagnosis; Biochemical monitoring

Contents

Worldwide persistent high prevalence of hepatitis B (HBV) (estimated to be 300 million) and hepatitis C (HCV) infection (about 170 million) and increasing prevalence of non-alcoholic steatohepatitis (NASH) and fatty liver disease (NAFLD) and

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alcoholic steatohepatitis (ASH) are major causes of chronic inflammatory liver diseases resulting in the destruction of liver parenchyma and its replacement by scar tissue (Fibrosis). Rare etiologies are autoimmune hepatitis, parasitic infections (schistosomiasis), and genetic diseases such as hemochromatosis, α1-antitrypsin deficiency, Morbus Wilson, and others. Fibrosis is characterized by the excess deposition of extracellular matrix (ECM) involving molecular and histological re-arrangement of various types of collagens, proteoglycans, structural glycoproteins and hyaluronic acid (hyaluronan). It is a hallmark of liver cirrhosis and contributes significantly to the deleterious outcome of chronic liver diseases. The deposition of ECM in the space of Disse (perisinusoidal fibrosis), the generation of (incomplete) subendothelial basement membranes, and the strangulation of hepatocytes by a surrounding matrix impair not only the blood flow through the organ, but also the biosynthetic function of hepatocytes and the clearance capability of these and other cells, e.g. of clotting factors and transport proteins in the plasma, hormones, and ammonia. Thus, diagnosis, follow-up and therapeutic monitoring of fibrogenesis, i.e. the active process of generation of new connective tissue in diseased liver, is of great clinical importance. This was done in the past and is currently practiced mostly by the invasive procedure of needle biopsy and consecutive histological evaluation based on various numerical scoring systems (Knodell, Ishak, METAVIR, Scheuer, Desmet and others) leading to grading of necroinflammatory (in general the driving force of fibrogenesis) activity and staging (extent) of fibrosis [1]. However, this "gold standard" has many draw-backs beside of invasiveness (mortality rate $1{:}10^3$–$1{:}10^4$, severe complications in 0.57%) such as sampling error (only 1/50 000th of the liver mass is usually obtained), unreproducible sample quality depending on length and size of the tissue specimen (coefficient of variation 45–35%) and a histological evaluation strictly dependent on the experience of the pathologist. Overall a coefficient of variation of about 55% must be accepted. Therefore, the development of non-invasive, serum- or plasma-based biomarkers of fibrogenesis is an important goal, which might be reached by two, principally different approaches: Class I fibrosis markers are direct serum markers, which reflect extracellular matrix turnover and/or fibrogenic cell changes in the liver. They are mostly cost intensive, single laboratory tests, and hypothesis-driven, i.e. they are derived from the translation of pathogenetic mechanisms of fibrosis into clinical application. Class II fibrosis markers compile indirect serum markers based on algorithmic evaluation of commonly observed functional alterations that do not necessarily reflect extracellular matrix metabolism (fibrogenesis or fibrolysis) and/or fibrogenic cell changes. These parameters are more or less cheap routine laboratory (liver) function tests, frequently multiparametric (panel markers), and not hypothesis-driven but based on empiric observations.

1. Basic principles of cellular and molecular pathobiology of liver fibrogenesis

The driving forces of fibrogenesis are in general liver cell injury (necrosis or apoptosis) with consecutive inflammatory reactions, which activate a special type of non-parenchymal

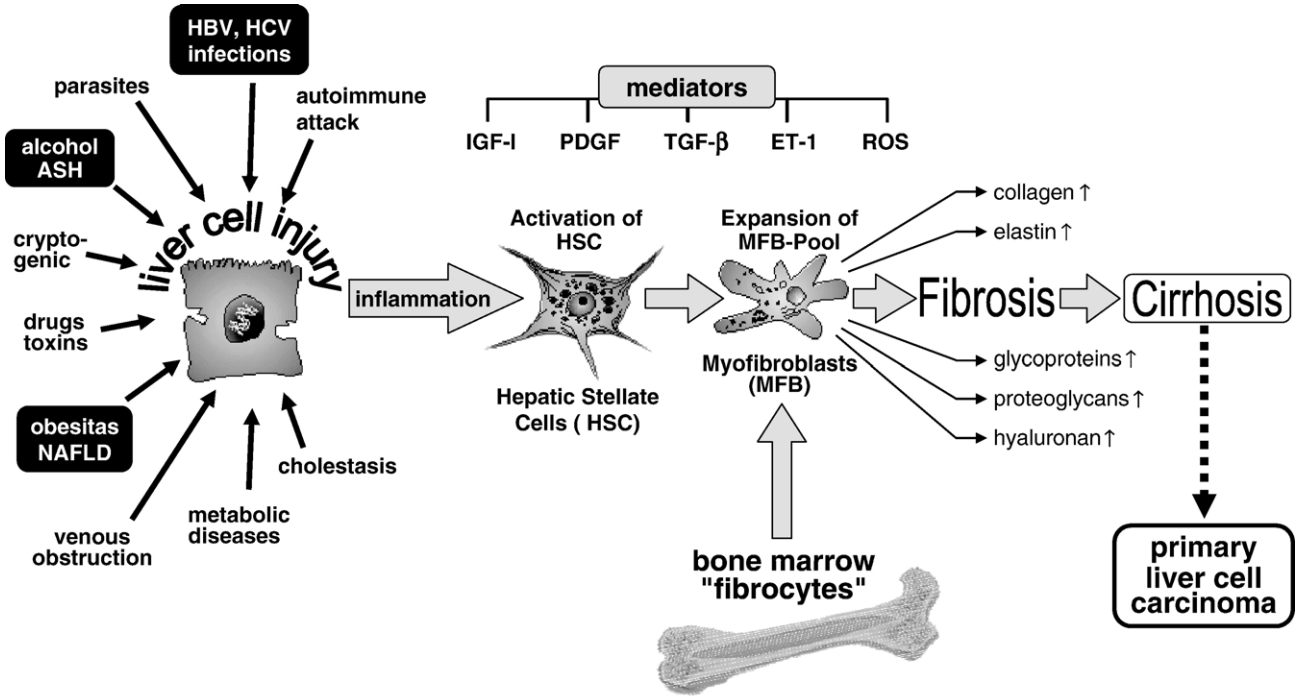

Fig. 1. Formal pathogenetic sequence of the fibrogenic activation of hepatic stellate cells (HSC) to myofibroblasts (MFB) leading to fibrosis and cirrhosis. The latter one can ultimately result in primary hepatocellular carcinoma. The potential contribution of bone marrow-derived fibrocytes to the extension of the pool of MFB and major mediators of transdifferentiation of HSC to MFB in damaged liver are illustrated. ASH, alcoholic steatohepatitis; ET-1, endothelin-1; IGF, insulin-like growth factor; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; TGF, transforming growth factor.