

Hepatocyte growth factor (HGF): a predictor of outcome and response to therapy in hepatitis C?

Infection with hepatitis C virus (HCV) is currently the most common cause of chronic hepatitis in our country, with a prevalence approaching 3% (1) that is progressively increasing because of multiple factors. It results in a readily understandable social and healthcare problem since the risk for chronicity is around 80%; of these subjects, 10-25% will develop cirrhosis after 20-30 years with a resulting mortality risk from cirrhosis itself or the development of hepatocarcinoma. Currently, the management of HCV-related chronic hepatitis consists of combined pegylated interferon (PEG-IFN) and ribavirin (RBV). This regimen results in sustained virological response in 45-55% of patients with genotype 1, in nearly 65-70% of subjects with genotype 4, and in 75-90% of individuals with genotype 2 or 3.

A key fact for the outcome of chronic liver disease is fibrosis development. Liver fibrosis is defined as an accumulation of proteins –mainly collagen– in the extracellular matrix, which occurs in most chronic liver conditions and distorts normal architecture leading to portal hypertension and its complications (2). It is considered a highly complex tissue repair process where a number of cell types and proinflammatory cytokines play a role. During the last decade our understanding of cellular and molecular mechanisms leading to fibrogenesis have increased, particularly regarding the relevance of inflammation mediators, apoptosis, and especially the role of hepatic stellate cells (HSC), deemed the “cornerstone” in this complex process. In the course of chronic liver disease HSCs undergo a phenotypical transformation or “cell activation” characterized by their acquisition of functions typical of myofibroblasts, including cell contractility and both proinflammatory cytokine and extracellular matrix secretion. Activated HSCs migrate and proliferate in hepatocellular necrosis areas, where they deposit extracellular matrix and play a role in inflammatory cell recruitment. Thus, various growth factors, including platelet-derived growth factor (PDGF) and transforming growth factor type β (TGF β), as well as vasoactive substances (thrombin, angiotensin II, endothelin 1) contribute to activated HSC accumulation, and have therefore profibrogenic activity. In contrast, various cytokines such as interferón alfa and HGF are powerful inhibitors of HSC activation.

In addition, fibrogenesis is a process that includes not only an increase in collagen synthesis but also a marked decrease in collagen degradation. Major enzymes regulating this process include collagenases, whose activity is modulated by other enzymes designated tissue inhibitors of collagenases or tissue inhibitors of metalloproteinases (TIMPs). During fibrogenesis there is a relevant increase in TIMP expression, and therefore of collagenase activity inhibition. HSCs are the primary cell type involved in the synthesis of these enzymes. HSCs secrete huge amounts of

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TIMPs, thus precluding the degradation of secreted collagen and increasing its fibrogenic capacity.

In the development of HCV-related fibrosis the host's genetic background, including polymorphisms for some cytokines and vasoactive substances, seems more influential than viral factors (3).

Numerous experimental and clinical reports suggest that liver fibrosis is a potentially reversible process (4). However, whether the liver is equally capable of clearing away fibrotic tissue in all patients and whether this depends on liver disease stage is unknown.

The mechanisms of action of HGF are manifold and complex. In addition to a potential antifibrogenic effect through HSC inhibition, several studies have shown that HGF plays a role in hepatic cell regeneration phenomena (5-7). On the other hand, it seems to play a significant proangiogenic role in chronic viral liver disease through the action of proinflammatory cytokines and by stimulating VEGF synthesis (8).

Another process wherein HGF has been involved is the development of hepatocellular carcinoma (HCC), and a number of papers demonstrate its potential role both in its diagnosis (9) and prognosis (10,11). A prospective study in 99 patients with chronic hepatitis C, cirrhosis, and HCC revealed that all patients with serum HGF levels above 0.6 ng/ml had HCC regardless of alfa-fetoprotein (AFP) and des-gamma-carboxyprothrombin (DCP).

In this issue of *The Spanish Journal of Gastroenterology* Marín-Serrano et al. (12) discuss HGF levels in a group of 45 patients with chronic hepatitis C and 15 healthy control subjects, as well as changes in said levels following antiviral therapy. Their findings suggest that, despite HGF being a cytokine with powerful antifibrogenic effects, high serum HGF levels are associated with greater liver fibrosis, both when compared to biopsy and non-invasive fibrosis tests. Regarding the subgroup of patients receiving antiviral therapy, HGF levels were of no use in estimating treatment effectiveness when responders and non-responders were compared; however, this group was of limited size and treatment type was heterogeneous (20 patients on conventional interferon, 5 patients on peginterferon).

In summary, HGF is closely related to cell regeneration activation and liver fibrosis control phenomena by inhibiting HSCs. Furthermore, it has angiogenic activity and plays an as-yet unclear role in hepatocarcinoma development. Further studies in the future will elucidate the clinical relevance of measuring HGF levels for the diagnosis and follow-up of fibrosis and hepatocarcinoma.

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