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Commentary

Fighting liver fibrosis to reduce mortality associated with chronic liver diseases: The importance of new molecular targets and biomarkers

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The past 30 years have seen major progress in the knowledge and management of liver disease. Unfortunately, millions of people worldwide still suffer from chronic hepatic illness. The incidence and prevalence of fibrosis, leading to cirrhosis, which may predispose people to liver cancer, is key to understanding the burden of liver disease. Liver fibrosis can be induced by nonalcoholic liver disease (40%), hepatitis B virus (30%), hepatitis C virus (15%), and harmful alcohol consumption (11%) [1]. Fibrosis and cirrhosis represent the end stage of liver pathology and thus are indicative of the associated mortality. The projection of cirrhosis and liver cancer until 2030 clearly shows that these hepatic pathologies are increasing as an international cause of death [1]. However, no antifibrotic therapy has been approved to date.

The activation or transdifferentiation of hepatic stellate cells (HSCs), which are the major drivers of liver fibrogenesis, is the most important step triggering the deposition of exacerbated amounts of extracellular matrix (ECM) proteins. Cell type and target-specific pharmacological intervention to therapeutically induce the deactivation of HSCs will enable more effective and less toxic precision antifibrotic therapies [2]. In this regard, the role of collagen triple helix repeat containing 1 (CTHRC1) protein, which is involved in many physiological and pathological processes [3,4], in the activation of HSCs was investigated by Li et al. [5]. Interestingly, they found, for the first time, that CTHRC1 is an important regulator of hepatic fibrogenesis. CTHRC1 protein is secreted by HSCs and was found to be significantly upregulated in fibrotic liver tissues derived from chronically thioacetamide or CCl_4-treated rodents. Moreover, CTHRC1 induced the transdifferentiation of HSCs to the active ECM secreting type and increased the contractile and migratory ability of the activated HSCs through the TGF-β pathway. The authors also found that CTHRC1 bound to a noncanonical Wnt receptor in a competitive manner, thus promoting the contractility of HSCs. They corroborated their results by administering CCl_4 or TAA to CTHRC−/− mice and found that fibrosis was less evident in these mice than in littermate controls; moreover, a monoclonal antibody against CTHRC1 suppressed hepatic ECM deposition in WT mice treated with these chemical inductors of fibrosis. In summary, Li, et al. found, for the first time, that CTHRC1 is a new regulator of liver fibrosis that acts by modulating TGF-β signaling [5]. TGF-β is a potent pro-fibrogenic factor that plays a fundamental role in fibrogenesis, mainly by inducing HSC activation, and therefore, anti-fibrotic therapies have been focused on the inhibition of this factor. Unfortunately, this approach is associated with undesired effects because TGF-β plays important roles as in cell proliferation, recognition, differentiation and apoptosis [6]. In this scenario, the most important implication of the results by Li et al. is that CTHRC1 could be a promising therapeutic target to arrest the fibrotic process in chronic liver disease with fewer side effects that direct blockade of TGF-β. In addition, CTHRC1 may be a potential biomarker for monitoring fibrosis or the response of a given antifibrotic therapy.

However, it is known that ROS may modulate many proinflammatory and profibrogenic pathways [7,8]. Therefore, from a basic perspective, the role of oxidative stress on the expression of CTHRC1 and the consequent fibrosis upregulation should be investigated. Interestingly, many antioxidants acting at several levels have been reported to attenuate the fibrogenic process [9,10]; therefore, the question of whether these antioxidants produce their antifibrotic effect through downregulation of CTHRC1 arises. Moreover, it is generally accepted that necrosis leads to fibrosis; in this sense, the role of inflammation on the expression of CTHRC1 may be of interest to basic researchers in the field of hepatology. For example, information on the relationship between the expression of NF-κB, a master proinflammatory factor, and the consequent production of proinflammatory cytokines on the expression of CTHRC1 may be of interest to further characterize this new mediator of fibrogenesis. Interestingly, there is a relationship between oxidative stress, inflammation and fibrosis. Therefore, researchers can find an almost unexplored area of investigation opened by the report by Li et al. [5] because there are several questions that need to be answered to illuminate the molecular mechanisms by which these three pathways interact. Indeed, there is controversy regarding the role of ROS in the activation of NF-κB and the pathways involved in the induction of profibrogenic mediators by proinflammatory cytokines. It is noteworthy that basic knowledge on the interaction of these pathways will lead, in the long-term, to more regulatory points of necrosis and fibrosis that may become alternative pharmacological targets to fight these diseases that presently lack effective treatments.

Perhaps the most interesting (and useful) clinical perspective is the search for drugs blocking CTHRC1 signaling to provide effective and safe therapeutic options to treat fibrosis, as the lack of these treatments is currently a major challenge for clinicians who treat patients with chronic liver diseases who eventually die as a consequence of untreated disease.

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Disclosure

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