LETTER TO THE EDITOR

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Suv39h1: Targeting epigenetics to treat liver fibrosis

A recent study published in *Gut* by Kong et al. revealed that a suppressor of variegation 3–9 homologue 1 (Suv39h1)-driven epigenetic mechanism is involved in the regulation of hepatic stellate cell (HSC) to myofibroblast transition, resulting in liver fibrosis (Figure 1A).[1] Remarkably, the authors also found that Suv39h1 can be successfully inhibited with a small-molecule natural product isolated from Chaetomium fungi belonging to thiodiketopyrazine complexes, namely chaetocin, leading to the attenuation of liver fibrosis.

Liver fibrosis represents a dynamic pathological process characterized by immune cell infiltration and inflammation, as well as the aberrant deposition of excess extracellular matrix (ECM) components, which are secreted by liver myofibroblasts, within the liver tissue as result of a continuous reparative response to a plethora of injurious stimuli. This ever-going process leads to accumulating abnormalities in liver architecture and function, progressing to end-stage liver diseases, such as cirrhosis and hepatocellular carcinoma (HCC).[2] Multiple studies suggest that liver myofibroblasts are mainly derived from activated HSCs and that the HSC to fibrogenic myofibroblast transition is the rate-limiting step in liver fibrosis.[3–5] With this in mind and given that there is a lack of therapeutic interventions for liver fibrosis, focusing on the HSC-myofibroblast transition as a target and developing strategies to block this transition may generate the most promising treatments in patients with fibrotic livers.

Interestingly, Kong et al. uncovered an important and targetable signalling axis in HSC-myofibroblast transition, which entails transforming growth factor beta (TGF-β), CCAAT enhancer binding protein beta (C/EBPβ), Suv39h1 and heme oxygenase 1 (HMOX1). In a nutshell, the authors' data indicate that when a quiescent HSC becomes stimulated by pro-fibrogenic growth factors, such as TGF-β, downstream intracellular signalling causes C/EBPβ to induce the gene expression of Suv39h1, which in turn downregulates, in an epigenetic manner via histone 3 lysine 9 trimethylation (H3K9me3), the gene expression of HMOX1, not allowing the latter to mediate its antifibrotic effects and, thus, promoting liver fibrosis (Figure 1B). The translational potential of this work by Kong et al. is based on the finding showing that administration of a small-molecule compound, chaetocin, was able to potently inhibit Suv39h1 and successfully mitigate liver fibrosis in a relevant mouse model.

However, as the authors note, there are some limitations with this work that hinder the translation of its findings into clinical practice. For example, it was observed that pharmacological inhibition of Suv39h1 by chaetocin differed from genetic knockdown of *Suv39h1* in terms of transcriptomic changes, hinting to potential off-target effects of the drug. Notwithstanding, while in HSC- and myofibroblast-specific *Suv39h1* knockout mice there was no significant difference with respect to liver injury and inflammation when compared to control, in chaetocin-treated mice, both liver injury and inflammation were reduced. Therefore, chaetocin appears to not only dampen liver fibrogenesis, but also liver injury and inflammation, effects that are beneficial in the setting of liver fibrosis. Perhaps, it would be worth investigating the molecular underpinnings of these 'positive off-target effects' of chaetocin to gain a better understanding of its mechanism of action.

Regarding the therapeutic potential of targeting Suv39h1 in patients with liver fibrosis, further research is needed to identify and validate new generation Suv39h1 inhibitors that are more target-selective and less toxic. Along these lines, a selective Suv39h1 inhibitor, ETP69 (a chaetocin A analog), and its successful application in treating memory loss in aged rodents has been reported.[6] Additionally, two other recent studies on colon cancer used the chemically synthesized small-molecule compound F5446 to more potently and selectively inhibit Suv39h1, resulting in enhancement of effector gene expression in tumour-infiltrating cytotoxic T lymphocytes to suppress colon tumour growth, and suppressing human colon tumour xenograft growth in vivo, respectively.[7,8] Exploring these Suv39h1 inhibitors for the intervention of liver fibrosis would be intriguing. Finally, another therapeutic aspect that demands further probing in liver fibrosis is the combination of Suv39h1 inhibitors with other epigenetically acting drugs (e.g. C/EBPβ inhibitors), small-molecule compounds disrupting Suv39h1-gene-specific transcription factor interactions, TGF-β targeting agents or mechanotherapeutics that target the mechanobiological features (i.e. ECM, mechanotransduction signalling cascades) of liver fibrosis (Figure 1C).[9–12]

Future investigations should augment our multidisciplinary efforts by fusing data from omics technologies (genomics, epigenomics, transcriptomics, proteomics, metabolomics) with advances in computer-aided drug design (computational chemistry, molecular modelling) methods and drug delivery systems (micelles, nanoparticles). Only then will we have an opportunity to combat the intricate and dynamic realm of liver fibrosis and its complications in the clinical setting.
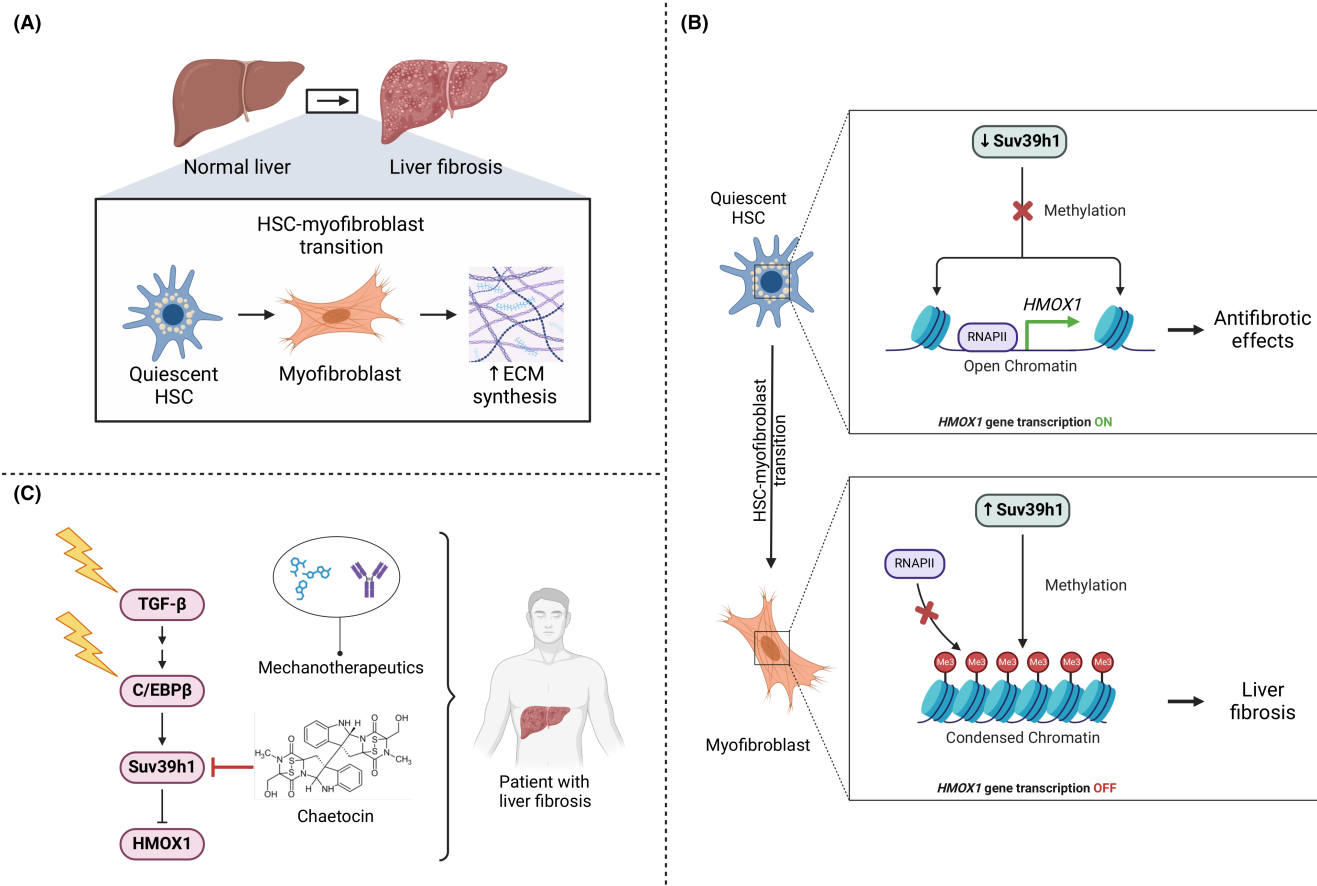
FIGURE 1 Suv39h1 is a key regulator of HSC-myofibroblast transition, which promotes liver fibrosis, and can be targeted with the small-molecule compound chaetocin. (A) In liver fibrosis, quiescent HSCs transdifferentiate into ECM-secreting myofibroblasts. (B) Downregulated Suv39h1 in quiescent HSCs is not able to methylate histones and, thus, repress the gene expression of HMOX1, allowing the latter to freely mediate its antifibrotic effects, whereas upregulated Suv39h1 during HSC-myofibroblast transition and in myofibroblasts functions to trimethylate histones (Me3) and, thus, repress the gene expression of HMOX1, not allowing the latter to mediate its antifibrotic effects, leading to liver fibrosis. (C) Signalling pathway involved in HSC-myofibroblast transition fostering liver fibrosis and its targetable components, including Suv39h1, C/EBPβ and TGF-β. Future therapeutic strategies against liver fibrosis may be based on combinatorial drug regimens, comprising Suv39h1 inhibitors with C/EBPβ and/or Suv39h1-recruited transcription factor inhibitors, TGF-β inhibitors or mechanotherapeutics that target the mechanobiological aspects (i.e. ECM, components of mechanotransduction signalling pathways) related to liver fibrosis. Thunder signs represent targeting. C/EBPβ, CCAAT enhancer binding protein beta; ECM, extracellular matrix; HMOX1, heme oxygenase 1; HSC, hepatic stellate cell; Me3, histone trimethylation; RNAPII, RNA polymerase II; Suv39h1, suppressor of variegation 3–9 homologue 1; TGF-β, transforming growth factor beta. This figure was created based on the tools provided by Biorender.com (https://biorender.com/).

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