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EDITORIAL

Identifying New Epigenetic Drivers of Liver Fibrosis

Liver fibrosis is the wound healing response to repeated injury that occurs in most chronic liver diseases and results in excessive accumulation of extracellular matrix. The development of advanced fibrosis is a key determinant of liver-associated morbidity and mortality.[1] Patients with advanced fibrosis (Metavir degree F3/F4) are prone to develop liver decompensations and hepatocellular carcinoma and are at risk of liver-related morbidity and mortality. Currently, the only effective therapy to slow the progression or even regress liver fibrosis is the removal of the cause of liver disease (ie, weight loss in nonalcoholic steatohepatitis, elimination of viral hepatitis, and so forth). In the past 2 decades, the cellular and molecular basis of liver fibrosis have been partially uncovered.[2] Experimental studies using animal models with repeated liver injury as well as cultured hepatic stellate cells (HSCs)—the main fibrogenic cell type in the injured liver—have uncovered a number of molecular mechanisms responsible for HSC activation and extracellular matrix accumulation. Most drug therapies proven to be effective in rodents have not been successfully tested in human beings. Therefore, there is a clear need for translational studies to identify new druggable molecular targets. Among novel pathogenic mechanisms, the advance of molecular methods in recent years has allowed the uncovering of changes in genome-wide epigenetic regulation in liver fibrosis.

Recent translational studies in human livers strongly have indicated that hepatic fibrosis is associated with aberrant DNA methylation, changes in histone modifications, and expression of specific microRNAs. In vivo experimental studies have identified potential mechanisms through which these epigenetic changes regulate fibrogenesis. A role for DNA methylases (DNA Methyl Transferase 1 and DNA Methyl Transferase 3a), histone methyl-transferases (ASH1, MLL1, and JMJD1A), and noncoding RNAs (microRNA-29, microRNA-21, MEG3, PVT1, and long non-coding RNA p21) recently was described.[3] In particular, enhancer of zeste homologue 2 (*EZH2*), a histone-lysine N-methyltransferase enzyme that methylates the lysines 9 and 27 of histone 3 (Histone 3 Lysine 9 and Histone 3 Lysine 27), mediates Methyl-CpG Binding Protein 2-induced HSC activation in experimental liver fibrosis.[4] In addition to liver fibrosis, EZH2 has a role as an oncogene in several preclinical models of hematologic cancer. Several EZH2 inhibitors are being studied in phase I and II clinical trials (tazemetostat, CPI-1205, MAK683, and SHR2554).

In the present issue of *Cellular and Molecular Gastroenterology and Hepatology*, Martin-Mateos et al[5] add another important piece to this puzzle. They performed an unbiased RNA sequencing study during the activation process of human primary HSCs. The epigenetic regulation of gene transcription by the 2 most studied agonists for these cells (ie, transforming growth factor β1 [TGFβ1] and platelet-derived growth factor β) was assessed using state-of-the-art techniques. The investigators found that TGFβ1 specifically increased the expression and the transcriptomic signature of EZH2, an effect not observed in other histone-lysine N-methyltransferase enzymes. By using pharmacologic and small interfering RNA–mediated approaches, the investigators showed how TGFβ1-mediated HSC activation depends on the presence of EZH2 levels. In fact, EZH2 inhibition resulted in attenuated TGFβ1-induced transcriptional activation of key fibrogenic genes (ie, COL1A1, ASMA, and fibronectin). Moreover, overexpression of EZH2 was able to recapitulate TGFβ1-mediated HSC activation. These gain- and loss-of-function experiments were confirmed by the increase or decrease in H3K27 methylation using chromatin immunoprecipitation assays. Importantly, the inhibition of EZH2 by the small molecule GSK-503 strongly reduced the degree of liver fibrosis and attenuated HSC activation in 2 experimental models.

Further studies should address the specific role of the TGFβ–EZH2 axis in HSC activation and the resulting fibrogenesis. First, TGFβ1 signaling in HSC is complex and multiple pathways converge into SMAD2/3 nuclearization and target gene activation.[2] The specific involvement of different TGFβ1-induced signaling pathways and SMAD proteins in TGFβ1-mediated EZH2 expression needs to be elucidated. Second, it is possible that the effects of TGFβ1 on epigenetic reprogramming depends on the HSC phenotype (ie, quiescent vs myofibroblastic).[6] In quiescent HSC, TGFβ1 inhibits cell proliferation and induces fibrogenic gene expression by the formation of Smad complexes. In contrast, activated myofibroblastic HSC are partially resistant to TGFβ1. Further studies should investigate whether targeting EZH2 in livers with advanced fibrosis and massive accumulation of myofibroblastic HSCs is effective in promoting fibrosis resolution. Third, the EZH2 methyl-transferase domain modulates the methylation of nonhistone proteins. It therefore is plausible that part of the beneficial effects of targeting the TGFβ1–EZH2 axis are H3 lysine methylation–independent.

In conclusion, the current study provides evidence for a role of the TGFβ–EZH2 axis in HSC activation and liver fibrogenesis. These results support the current paradigm that epigenetic changes play a major role in liver fibrosis. GSK-503, currently in preclinical development, represents a potential novel approach for pharmacologic intervention, along with other EZH2 inhibitors that are being tested for different tumors. Targeting the epigenetic drivers of HSC activation represents a promising approach to reverse advanced fibrosis. The experience of these experimental drugs in oncology could be

very useful before they are tested in patients with chronic liver diseases.

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Conflicts of interest
The authors disclose no conflicts.


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