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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Inflammation Writes the Fibrogenic Code

Nonalcoholic steatohepatitis (NASH) is an increasingly common chronic liver disease and progression of NASH is associated with increased cirrhosis, liver failure, liver cancer, and mortality. One of the biggest factors associated with NASH progression and liver-related mortality is increased liver fibrosis, highlighting the importance of understanding the mechanisms regulating fibrosis and targeting them for treatment. One of the most potent profibrogenic signals is transforming growth factor beta 1 (TGFB1) and accordingly, increased expression and secretion of this cytokine is associated with NASH progression. The primary cellular source of TGFB1 in the liver is resident macrophages, also known as Kupffer cells. Although several stimuli, such as lipopolysaccharide (LPS), are known to induce TGFB1 synthesis in Kupffer cells it is unclear what cellular factors mediate this production.

Previous studies have suggested that N6-methyladenosie (m6A) methylation regulates expression of TFGB1 mRNA in cancer cells[1]; however, it is unclear if this mechanism also occurs in Kupffer cells. m6A methylation of mRNA regulates different stages of RNA-based gene expression, such as translation, stability, or splicing, depending on the recruitment of particular m6A "reader" proteins. Furthermore, the presence of m6A marks on mRNA is regulatable and reversible, with m6A marks being added or removed from mRNAs by "writer" and "eraser" proteins, respectively. Interestingly, m6A is known to play important roles in many cellular processes related to NASH, including inflammation,[2] lipid metabolism,[3] hepatic circadian rhythms,[4] and hepatocellular carcinoma progression.[5] Together, these findings suggest that m6A may play a role in TGFB1 regulation and NASH progression. However, little is known about the impact of m6A on the activation of Kupffer cells and the subsequent promotion of fibrosis.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Feng et al[6] demonstrate that high fat diet–induced NASH and LPS activation of Kupffer cells increase m6A methylation of the 5'UTR of TGFB1, and that this regulates the translation of TGFB1, thereby contributing to the progression of fibrosis. This is accomplished in LPS-stimulated Kupffer cells through increased transcription of the m6A writer enzymes, METTL3 and METTL14, by direct interaction between nuclear factor-κB and their promoter elements. Furthermore, they demonstrate that this increased methylation of the TGFB1 5'UTR and promoted its translation, possibly through a cap-independent mechanism. Importantly, by using combinations of siRNA and conditional null alleles they demonstrated that METTL3 and METTL14 were required for (1) LPS-induced methylation of TGFB1 mRNA, (2) LPS-induced synthesis and secretion of TGFB1, and (3) increased collagen fiber formation in both an ex vivo model and an in vivo CCl_4-induced fibrosis model.

Although this study mostly focused on the induction of m6A writers, the authors also found that high fat diet–induced NASH and LPS-activation decreased the expression of the m6A eraser protein, FTO. Common variants in FTO are strongly associated with obesity and type 2 diabetes susceptibility, with individuals homozygous for the risk allele having increased blood and hepatic glucose levels and increased adiposity.[7] Furthermore, FTO expression in the liver is known to be decreased by elevated blood glucose and insulin levels, consistent with the observation by Feng et al[6], that FTO expression is decreased in livers of rats on a high-fat diet. This result further supports the idea that m6A methylation plays an essential role in the liver's response to diet-induced injury.

Interestingly, the TGFB1 pathway is also known to activate m6A methylation through direct interaction of TGFB1-activated Smad2/3 with m6A writer complexes.[8] In stem cells, this promotes exit from pluripotency, thus allowing for the appropriate timing of differentiation. Although it is unclear if this same mechanism is operative in the liver, this raises the possibility that m6A-dependent production and secretion of TGFB1 by Kupffer cells may trigger induction of m6A methylation in other liver cell populations, such as stellate cells or hepatocytes. Therefore, depending on cell-type and condition, m6A may represent a dynamic mark of mRNA, which can regulate, and be regulated by, important hepatic repair pathways.

Overall, this study provides an interesting link between RNA methylation and regulation of TGFB1 production in the context of liver fibrosis, thus identifying a potential novel therapeutic target for controlling fibrosis progression. Interestingly, in addition to TGFB1, m6A methylation in many other mRNAs also changed in Kupffer cells, with the most common functions including inflammatory responses and metabolic pathways. This raises the possibility that therapies targeting m6A methylation may not only protect against TGFB1-mediated fibrosis, but might also reduce inflammation and rebalance metabolic processes that are dysregulated in NASH.

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Conflicts of interest
The authors disclose no conflicts.


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