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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Sphingosine Kinase 1 – A Therapeutic Opportunity for Alleviating Liver Fibrosis?

Liver fibrosis (LF) is a clinical manifestation of underlying liver disease and metabolic disorders, where functional liver tissue is replaced by non-functional collagen fibers arising from the extracellular matrix. It is an escalating concern, as the incidence of LF is surging due to rising prevalence of alcoholic liver disease and metabolic dysfunction-associated steatotic liver disease.[1,2] LF is reversible; however, many patients suffer from this condition unnoted, until it deteriorates into liver cirrhosis and liver cancer.[3] Moreover, even when diagnosed in time, there is lack of effective treatments, leaving diet control as the only means to mitigate this condition.[4] LF is frequently associated with chronic liver inflammation; hence, understanding how the immune response contributes to LF progression is key to developing therapeutic interventions. The liver is inundated with macrophages, with 90% of total macrophages in the human body found within it, where they play essential roles in infection control and tissue repair.[5] During LF, naïve (M0) macrophages polarize towards pro-inflammatory (M1) or anti-inflammatory (M2) cell fates.[6] Despite their seemingly contrasting influences, both M1 and M2 macrophages promote LF. Inflammation-promoting cytokines, such as interleukin-1 and interleukin-6, are released by M1 macrophages, and they drive the hepatic injury that induces fibrosis pathogenesis.[7] M2 macrophages secrete transforming growth factor-beta, the most potent inducer of fibrogenesis, facilitating the transformation of hepatic stellate cells into extracellular matrix-accumulating myofibroblasts.[7] Hence, understanding the mechanisms driving macrophage infiltration and differentiation during LF could reveal therapeutic windows to limit the disease progression.

In a previous issue of *Cellular and Molecular Gastroenterology and Hepatology*, Ding et al[8] have highlighted sphingosine kinase 1 (SphK1) as a central mediator of macrophage recruitment during LF, and of their polarization towards M1 and M2 cell fates (Figure 1). Using SphK1 knockout ($SphK1^{-/-}$) mice in the carbon tetrachloride-induced LF model, the authors demonstrated that the lack of SphK1 alleviated the disease and was accompanied by reduced hepatic macrophage recruitment and M1/M2 polarization. Without SphK1, the carbon tetrachloride-damaged liver secreted less macrophage-recruiting chemokines, such as CCL2, thus limiting the macrophage infiltration. This is in line with their prior work revealing that SphK1 signaling in Kupffer cells and hepatic stellate cells drove liver fibrosis development and progression via a CCL2-CCR2 axis.[9] Furthermore, through single-cell RNA sequencing of liver tissue from 6 patients with liver fibrosis and 3 healthy donors, the authors identified monocytes and macrophages as the highest expressors of SphK1. Bone

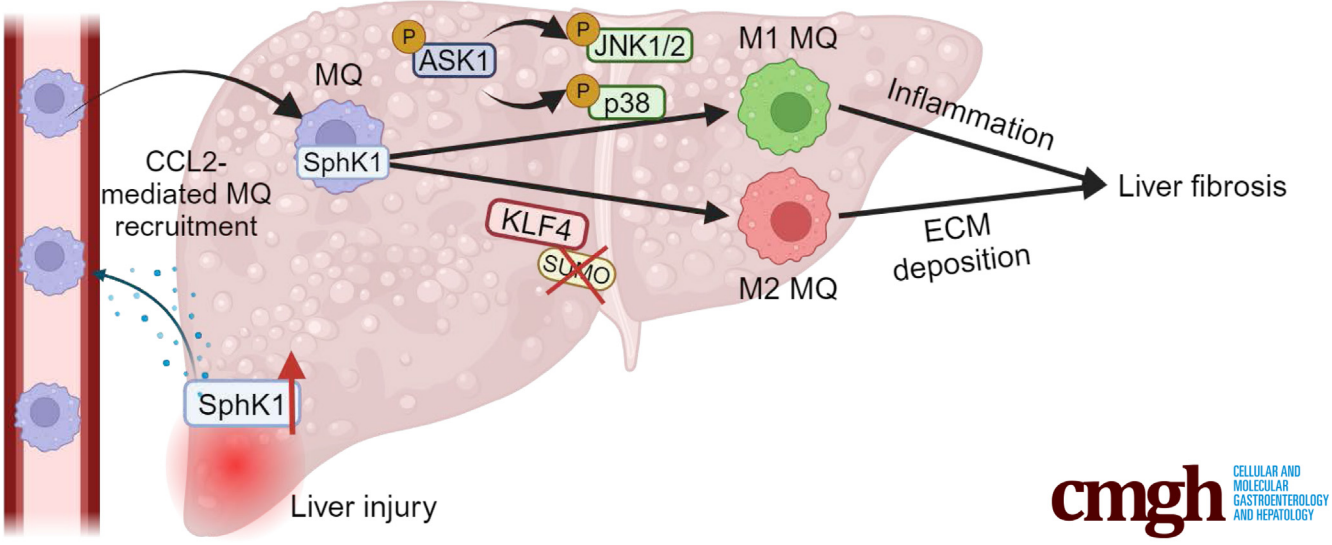

Figure 1. SphK1 drives macrophage recruitment and polarization to aggravate LF. LF, where functional liver tissue is replaced by non-functional collagen fibers, typically precedes more detrimental liver diseases such as liver cirrhosis and liver cancer. Understanding the key drivers of LF is crucial for improving its treatment options, and M1 and M2 macrophages (MQs) have previously been implicated as such. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Ding et al[8] identify SphK1 as the key factor responsible for macrophage infiltration during LF, and for their development into M1 and M2 MQs. Macrophages of both polarizations potentially aggravate LF. Created in BioRender.com

marrow chimeras were used to investigate the role of SphK1 within these cells during LF. Although the loss of SphK1 did not disrupt their liver-infiltrating abilities, SphK1$^{-/-}$ macrophages displayed impaired M1/M2 polarization. Specifically, this study showed that SphK1 promoted M1 polarization through activating ASK1-JNK1/2-p38 signaling pathways, whereas M2 polarization was supported through SphK1 suppressing the de-SUMOylation of KLF4. Altogether, this work has revealed the important role SphK1 in liver fibrogenesis and suggests that disrupting the SphK1 pathways is a potential therapeutic target for the treatment of LF.

In summary, the findings presented by Ding et al are of interest and advance our understanding of LF, as the detrimental roles and mechanisms of SphK1 in the liver are elucidated. Discovering pathways responsible for the detrimental polarization of macrophages during LF is important, as autologous macrophage therapy for liver diseases is being investigated.[10] However, given the conflicting natures of M1 and M2 macrophages, how the upregulation of both populations by SphK1 results in the unified progression of LF is unclear. Further work is needed to unravel the spatiotemporal dynamics of M1 and M2 macrophages during the progression of LF, alongside changes in SphK1 expression. Nevertheless, this work lays the foundation for additional therapeutic research into controlling harmful macrophage development during LF.

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Conflicts of interest
The authors disclose no conflicts.


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