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Editorial

Sending an SOS: Healing the Liver with the Bone Marrow

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Cirrhosis, an end stage of any chronic liver disease is a form of impaired regeneration leading to progressive diffuse hepatic fibrosis. The healthcare burden of cirrhosis is increasing, and it is currently the 13th leading cause of death globally. The progression of liver injury and fibrosis results in portal hypertension and hepatic insufficiency, which ultimately lead to complications of cirrhosis such as ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, variceal hemorrhage, hepatorenal syndrome, and hepatocellular carcinoma. Inflammatory signaling in response to noxious stimuli (e.g., alcohol, lipotoxicity, and hepatotropic viruses) and cross talk with hepatic stellate cells, resulting in their activation. The activated hepatic stellate cells stimulate fibrogenesis with laying down of collagen tissue. The mainstay of treatment recommendations in several guidelines on cirrhosis emphasize treatment and control of the risk factor and inciting stimulus. The recommendations are based on the hepatic regenerative potential in response to controlling the causative agent (e.g., alcohol abstinence, antiviral therapy, weight loss, and control of metabolic syndrome), with a potential for significant improvement in fibrosis and even reversal of cirrhosis.[1] In this regard, the bone marrow seems to have an important role, responding to peripheral tissue injury by increasing the innate immune response and tissue repair. However, cirrhotic patients tend to have cytopenia, and although it is usually attributed to splenomegaly, it may also result from concomitant bone marrow dysfunction.[2]

Granulocyte colony-stimulating factor (G-CSF), as its name suggests, can increase neutrophil production and hematopoietic stem cell mobilization, which in turn tap into the liver's regenerative properties. For example, the use of G-CSF in patients with acute-on-chronic liver failure (ACLF), hepatitis B virus infection, and alcohol-associated hepatitis (AH) has been shown to improve outcomes in hepatorenal syndrome, hepatic encephalopathy, and sepsis.[3] Conversely, G-CSF can induce sensitization to lipopolysaccharides, which can increase pathological gut-liver axis interactions and result in some of adverse outcomes.[4]

Similar proregenerative strategies, such as bone marrow-derived hematopoietic stem cells and mesenchymal stem cell transplantation have been shown to improve liver function in patients with cirrhosis. In one study, autologous CD34+ cell infusion combined with G-CSF improved liver function and Model for End-Stage Liver Disease (MELD) scores for up to 1 year. The benefits were not sustained for of 3 years, which the authors attributed to the ongoing progression of the underlying disease.[5] Alternatively, G-CSF combined with erythropoietin was shown to decrease 1-year mortality compared with standard of care in patients with decompensated cirrhosis ACLF.[6] Another interesting avenue is interleukin (IL)-22, with an evidence in murine models to induce regeneration in acute hepatitis, liver ischemia-reperfusion injury, and alcohol-induced liver disease. IL22 promotes the proliferation of liver stem cells and induces the expression of anti-apoptotic, anti-oxidative, proliferative and antibacterial genes in the hepatocytes. A phase 2b trial that explored the use of an IL22 analog (F-652) in 18 patients, nine with moderate and nine with severe AH, showed a significant decrease in MELD score, day 7 Lille score, cytokine inflammatory markers, and serum aminotransferases. The effects were associated with an increase in markers of regeneration at days 28 and 42 compared with baseline ($p<0.05$).[7]

G-CSF, produced by macrophages, endothelial cells, and bone marrow stromal cells, is encoded by the colony-stimulating factor 3 receptor (*CSF3R*) gene. However, cirrhotic patients may be refractory to G-CSF therapy leading to disturbances in CSF3R expression, microenvironment, or regulation. In particular, carcinoembryonic antigen cellular adhesion molecule-1 (CEACAM-1) may be increased in cirrhotic patients, which inhibits the activity of CSF3R (Fig. 1).[8,9]

In a study published in this issue, Bihari *et al*.[10] assessed the CSF3R status in cirrhotic patients and showed that they have lower levels of CSF3R but higher levels of CEACAM1. The authors performed bone marrow examination in 127 cirrhotic patients and 26 controls and profiled cirrhosis patients by measuring G-CSF, CSF3R, and CEACAM1 in the bone marrow and peripheral blood by qRT-PCR and immunohistochemistry. The results showed that a decline in CSF3R was associated with cirrhosis progression and a decrease in hematopoietic stem cells, neutrophils and CD34+ cells. Interestingly, there were no differences in CSF3R levels in the bone marrow and peripheral blood. Further, patients with lower CSF3R (both in bone marrow and peripheral blood) had higher rates of infection ($p=0.056$), including spontaneous bacterial peritonitis. The authors also confirmed that

Abbreviations: ACLF, acute-on-chronic liver failure; AH, alcohol-associated hepatitis; CEACAM-1, carcinoembryonic antigen cellular adhesion molecule-1; G-CSF, granulocyte colony-stimulating factor; MELD, Model for End-Stage Liver Disease.

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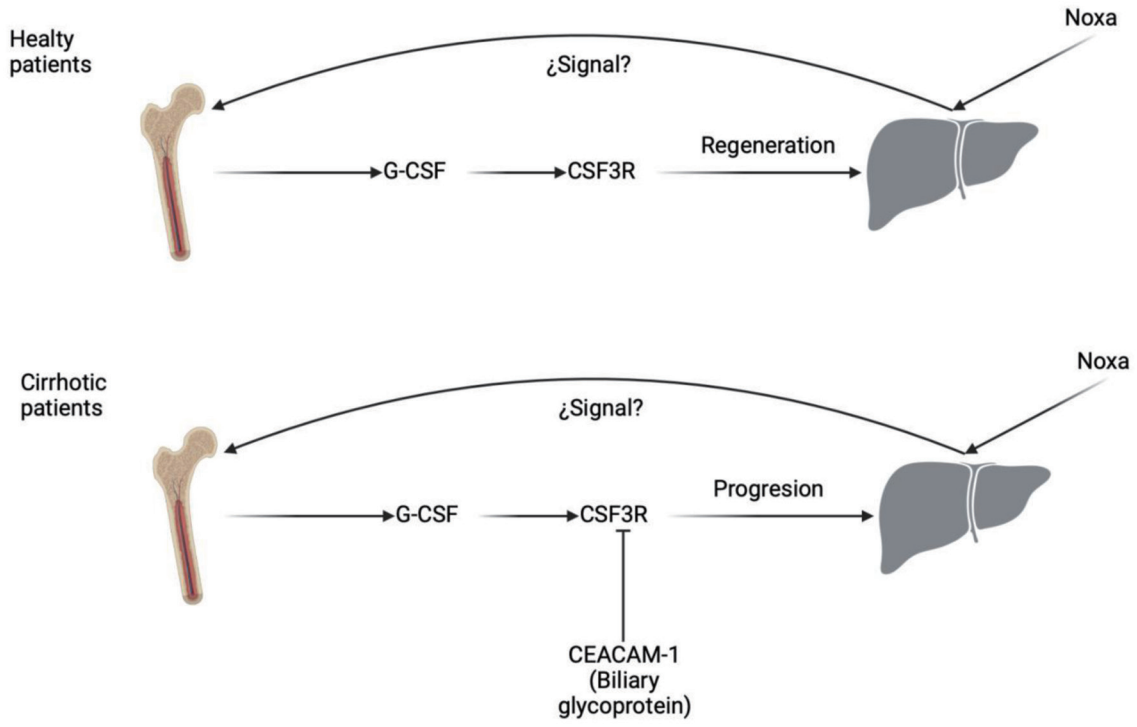

Fig. 1. Bone marrow signaling pathway in mediating hepatic regeneration. CEACAM-1, carcinoembryonic antigen cellular adhesion molecule-1; G-CSF, granulocyte colony-stimulating factor.

CEACAM1 was upregulated in cirrhosis patients, leading to CSF3R downregulation in bone marrow by lysosomal degradation. CEACAM1 levels in bone marrow and peripheral blood correlated with CSF3R levels ($p<0.001$). In contrast, G-CSF levels correlated positively with CEACAM1 ($p<0.001$) in bone marrow and in the peripheral blood. Finally in an *in vitro* study, the investigators showed that bone marrow mononuclear cultured cells from healthy controls without cirrhosis had a 28% mean reduction of CD34+CSF3R+ cells after 24 h treatment with CEACAM-1 compared with untreated cells ($p=0.031$). The study has several interesting implications. First, it highlights that other than portal hypertension, cytopenia in patients with cirrhosis may also be due to bone marrow dysfunction. Further, measuring CSF3R levels in the peripheral blood can help to identify patients who are not likely to respond to G-CSF treatment. If the findings are validated, this concept could be extended to studying thrombocytopenia in patients with cirrhosis.

It has been proposed that restoring bone marrow function may provide new therapeutic options for patients with cirrhosis.[10] As CEACAM-1 downregulates CSF3R and is positively correlated with G-CSF, inhibiting it may be a viable treatment option. That is important, as elevated G-CSF can induce hematopoietic stem cells to enter into refractory colony formation stages, which can further decrease bone marrow function. In summary, Bihari *et al*.[10] have shed light on the molecular mechanisms that lead to bone marrow dysfunction in patients with cirrhosis, and to an unexplored avenue of treatment that may impact patient survival. Further exploration of the relationship between G-CSF, its receptor CSF3R, and CEACAM-1 is warranted.

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Conflict of interest

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Author contributions

GA and JPA wrote the initial draft of the manuscript. AKS reviewed and finalized the draft. All the authors approved the final version of the manuscript.

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