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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 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, carcinomembrontic antigen cellular adhesion molecule-1 (CEACAM-1) may be increased in cirrhotic patients, which inhibits the activity of CSF3R (Fig. 1).8,9

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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 \textit{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. 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. 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.

**Conflict of interest**

AKS has been an associate editor of \textit{Journal of Clinical and Translational Hepatology} since 2017. The other authors have no conflict of interests related to this publication.

**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.

**References**

[1] Ellis EL, Mann DA. Clinical evidence for the regression of liver fibrosis. J Hepatol 2012;56(5):1171–1180. doi:10.1016/j.jhep.2011.09.024, PMID:2245903.

[2] Paczkowska E, Kucia M, Kozierska D, Halasa M, Safranow K, Masiuk M, et al. Clinical evidence that very small embryonic-like stem cells are mobilized into peripheral blood in patients after stroke. Stroke 2009;40(4):1237–1244. doi:10.1161/STROKEAHA.108.535062, PMID:19246697.

[3] Marot A, Singal AK, Moreno C, Dellerete P. Granulocyte colony-stimulating factor for alcoholic hepatitis: A systematic review and meta-analysis of randomised controlled trials. JHEP Rep 2020;2(5):100139. doi:10.1016/j.jheprep.2020.100139, PMID:32775975.

[4] Fang H, Liu A, Sun J, Kitz A, Dirsch O, Dahmen U. Granulocyte colony-stimulating factor induces lipopolysaccharide (LPS) sensitization via upregulation of LPS binding protein in rat. PLoS One 2013;8(2):e56654. doi:10.1371/journal.pone.0056654, PMID:23473199.

[5] Sharma M, Kulkarni A, Sasikala M, Kumar P, Jaggaiahgari S, Pendugula K, et al. Long-term Outcome of Autologous Hematopoietic Stem Cell Infusion in Cirrhosis: Waning Effect over Time. J Clin Transl Hepatol 2020;8(4):385–395. doi:10.14218/ICTH.2020.00052, PMID:33447521.

[6] Haque MN, Al-Mahatab M, Das DC, Mohammad NS, Mamun AA, Khan MSI, et al. Effect of Granulocyte Colony-stimulating Factor and Erythropoietin on Patients with Acute-on-chronic Liver Failure. Euroasian J Hepatogastro-enterol 2020;10(2):64–67. doi:10.5005/jp-journals-10018-1330, PMID:33511067.

[7] Arab JP, Sehrawat TS, Simonetto DA, Verma VK, Feng D, Tang T, et al. An
Ayares G. et al: G-CSF and liver disease

Open-Label, Dose-Escalation Study to Assess the Safety and Efficacy of IL-22 Agonist F-652 in Patients With Alcohol-associated Hepatitis. Hepatology 2020;72(2):441–453. doi:10.1002/hep.31046, PMID:31774566.

[8] Kim WM, Huang YH, Gandhi A, Blumberg RS. CEACAM1 structure and function in immunity and its therapeutic implications. Semin Immunol 2019;42:101296, doi:10.1016/j.smim.2019.101296, PMID:31604530.

[9] Hosomi S, Chen J, Baker K, Chen L, Huang YH, Olszak T, et al. CEACAM1 on activated NK cells inhibits NKG2D-mediated cytolytic function and signaling. Eur J Immunol 2013;43(9):2473–2483. doi:10.1002/eji.201242676, PMID:23696226.

[10] Bihari C, Baweja S, Shasthry SM, Lal D, Negi P, Thangariyal S, et al. CEACAM-1 Induced CSF3-receptor Downregulation in Bone Marrow Associated With Refractory Neutropenia in Advanced Cirrhosis. J Clin Transl Hepatol 2022;10(1):53–62. doi:10.14218/JCTH.2021.00331.