cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

FAP: Not Just a Biomarker but Druggable Target in Liver Fibrosis

Chronic liver injury is caused by various etiologies, including viral infections, alcohol abuse, metabolic disorders, cholestasis, and hepatotoxin exposure. Regardless of the multiple etiologies of injury, fibrosis is the most common characteristic of chronic liver diseases. Fibrosis ultimately may lead to hepatic cirrhosis, which is the 11th most common cause of death globally.[1] Despite the clear clinical need, there are no approved therapies to treat liver fibrosis. In chronic liver injury, continuous accumulation of extracellular matrix results in the progressive replacement of the liver parenchyma by fibrous scar tissue. Activated hepatic stellate cells/myofibroblasts are known as the main sources of extracellular matrix proteins in the injured liver. These cells produce fibrillar extracellular matrix proteins and release various cytokines and/or chemokines to induce crosstalk with inflammatory cells, thus forming a profibrogenic environment. Hence, activated hepatic stellate cells are regarded as one of the primary targets for treating fibrosis of the liver.

Fibroblast activation protein (FAP; also known as FAPα and seprase) is a type II integral membrane glycoprotein and serine protease of the dipeptidyl peptidase family. The expression of FAP in the healthy liver is nearly undetectable. In contrast, FAP is increased substantially in malignant and nonmalignant pathologic conditions. Its differential pattern of expression in disease supports the emerging role of FAP as a potential disease biomarker and a useful therapeutic target for drug development. In fact, FAP is a well-established marker of activated fibroblasts or cancer-associated fibroblasts because FAP is expressed specifically by fibroblasts in healing wounds or activates fibroblasts in the tumor stroma. Accordingly, FAP has attracted tremendous interest as a potential biomarker for cancer-associated fibroblast detection and as a druggable target for cancer therapy in recent years. However, the role of FAP in liver fibrosis remains underexplored. FAP is absent from the healthy adult liver, but is increased markedly in the fibrotic liver and desmoplastic stroma of hepatic tumors. A few early studies reported that FAP is expressed by activated hepatic stellate cells and its expression correlates positively with the severity of liver fibrosis,[2,3] suggesting a profibrotic role of FAP in liver disease. However, direct molecular and functional evidence of FAP in liver fibrosis is lacking. Functionally, FAP may contribute to hepatic stellate cell adhesion, migration, and apoptosis.[4] However, there is little overlap of FAP-expressing fibroblasts with myofibroblasts expressing α-smooth muscle actin (α-SMA), generally considered a marker of activated hepatic stellate cells.[5,6]

In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Yang et al[7] provide direct molecular evidence for the function of FAP and FAP-expressing fibroblasts in liver fibrosis. The investigators used a specific FAP inhibitor (FAPi) as a tool to study the function of FAP in 2 liver fibrosis mouse models, carbon tetrachloride (CCl_4)-induced parenchymal liver fibrosis and multidrug resistance protein 2 (Mdr2) null mice, which are a model of primary sclerosing cholangitis. In the CCl_4 model, FAP expression was up-regulated along with macrophage infiltration. FAPi treatment attenuated CCl_4-induced liver fibrosis with reduced hepatic stellate cell activation, total, and M2-type macrophage infiltration. Intriguingly, in contrast to the CCl_4-induced liver fibrosis model, Mdr2 null mice did not show such a strong reduction of fibrosis by FAPi. Nonetheless, FAPi treatment reduced α-SMA–positive myofibroblasts and collagen content in the portal area in Mdr2 null mice. These findings suggest that FAP modulates the activation of hepatic stellate cell and macrophage infiltration in liver fibrosis, and the magnitude of FAP effect depends on the etiology of liver disease.

The study further analyzed FAP expression in early vs advanced liver fibrosis using FAP reporter mice in which FAP-expressing cells express a red fluorescence protein. In early fibrosis, FAP is expressed in a very minor population of hepatic stellate cells. However, in advanced fibrosis, FAP is expressed more abundantly in glial fibrillary acidic protein, desmin, and collagen-expressing myofibroblasts. Intriguingly, FAP-expressing myofibroblasts do not overlap with α-SMA–expressing myofibroblasts. FAP-expressing myofibroblasts are found within thin fibrotic septa, while α-SMA–expressing myofibroblasts are seen in fibrotic areas. Thus, FAP-expressing fibroblasts may contribute to the fibroinflammatory response in a role distinct from that of α-SMA–expressing myofibroblasts. FAP may mediate fibrosis through both hepatic stellate cell activation and macrophage phenotype modulation. Therefore, targeting specific fibroblast subpopulations expressing FAP may offer a possible strategy to modulate inflammation and fibrogenesis.

This study shows the function of FAP in liver fibrosis, and expanded the therapeutic potential of FAPi to chronic liver disease. FAP directly contributes to the activated phenotype of fibroblasts and macrophages. However, its function likely is context-dependent and at least in part involves changes to macrophage phenotype. Thus, a better understanding of FAP actions in liver fibrosis and inflammation is further required for a successful translation of FAPi to clinical use.

JIEUN KIM
EKIHIRO SEKI
Department of Medicine
Cedars-Sinai Medical Center
Los Angeles, California

References

1. Asrani SK, Devarbhavi H, Eaton J, et al. Burden of liver diseases in the world. J Hepatol 2019;70:151–171.
2. Levy MT, McCaughan GW, Marinos G, et al. Intrahepatic expression of the hepatic stellate cell marker fibroblast activation protein correlates with the degree of fibrosis in hepatitis C virus infection. Liver 2002;22:93–101.
3. Levy MT, McCaughan GW, Abbott CA, et al. Fibroblast activation protein: a cell surface dipeptidyl peptidase and gelatinase expressed by stellate cells at the tissue remodelling interface in human cirrhosis. Hepatology 1999;29:1768–1778.
4. Wang XM, Yu DM, McCaughan GW, et al. Fibroblast activation protein increases apoptosis, cell adhesion, and migration by the LX-2 human stellate cell line. Hepatology 2005;42:935–945.
5. Shi Y, Kong Z, Liu P, et al. Oncogenesis, microenvironment modulation and clinical potentiality of FAP in glioblastoma: lessons learned from other solid tumors. Cells 2021;10:1142.
6. Kaps L, Schuppan D. Targeting cancer associated fibroblasts in liver fibrosis and liver cancer using nanocarriers. Cells 2020;9:2027.
7. Yang A-T, Kim Y-O, Yan X-Z, et al. Fibroblast activation protein activates macrophages and promotes parenchymal liver inflammation and fibrosis. Cell Mol Gastroenterol Hepatol 2023;15:841–867.

Correspondence
Address correspondence to: Ekihiro Seki, MD, PhD, Karsh Division of Gastroenterology and Hepatology, Department of Medicine, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Davis, Suite 2099, Los Angeles, California 90048. e-mail: Ekihiro.Seki@cshs.org.

Conflicts of interest
The authors disclose no conflicts.

Funding
This work is supported by National Institutes of Health grant R01DK085252 (E.S.).


Most current article

2352-345X
https://doi.org/10.1016/j.jcmgh.2022.12.018