infections, contributes to various pathologies such as liver fibrosis, cirrhosis, and the development of HCC (72). Cirrhosis is sometimes a component of the study design of clinical trials for anti-HCV drugs. In one trial, cirrhosis was one of the exclusion criteria (73). In another clinical trial, subjects with cirrhosis were permitted to enroll in the trial, but they were required to be stratified according to the presence or absence of cirrhosis (74). Chronic inflammation can result in cirrhosis of the liver as well as liver cancer, that is, HCC. The damage that is caused by the immune system to the liver is separate from, and in addition to, that caused by the virus alone (75,76,77,78).

b. Stellate Cells, Fibrosis, and Cirrhosis

In patients with chronic HCV infections about 20% develop cirrhosis. Progression to cirrhosis takes about 20–50 years. Cirrhosis of the liver is staged according to the Metavir system, with F1 indicating portal fibrosis without septa, F2 portal fibrosis with few septa, F3 septal fibrosis without cirrhosis, and F4 cirrhosis. The Metavir score evaluates data from a liver biopsy (79,80). Dienstag (81) and Ramadori and Bernhard (82) provide accounts of the distinction between portal fibrosis and septal fibrosis.

Hepatic stellate cells are involved in HCV-induced liver fibrosis. The stellate cells reside in the liver in areas called the space of Disse. Stellate cells, which represent about 5–8% of the cells of the liver, are distinguished in that they are rich in vitamin A and store nearly 80% of retinoids of the human body in their lipid droplets in the cytoplasm (83). HCV-infected hepatocytes release transforming growth factor-beta1 (TGF-beta-1) and other profibrogenic factors which, in turn, activate stellate cells.

[72]Spengler U, et al. Between Scylla and Charybdis: the role of the human immune system in the pathogenesis of hepatitis C. World J. Gastroenterol. 2013;19:7852–66.

[73]Gane EJ, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N. Engl. J. Med. 2013;368:34–44.

[74]Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N. Engl. J. Med. 2014;370:1889–98.

[75]Cruise MW, Lukens JR, Nguyen AP, Lassen MG, Waggoner SN, Hahn YS. Fas ligand is responsible for CXCR3 chemokine induction in CD4 + T cell-dependent liver damage. J. Immunol. 2006;176:6235–44.

[76]Cruise MW, Melief HM, Lukens J, Soguero C, Hahn YS. Increased Fas ligand expression of CD4 + T cells by HCV core induces T cell-dependent hepatic inflammation. J. Leukoc. Biol. 2005;78:412–25.

[77]Urbani S, Amadei B, Fisicaro P, et al. Heterologous T cell immunity in severe hepatitis C virus infection. J. Exp. Med. 2005;201:675–80.

[78]Bertoletti A, Maini MK. Protection or damage: a dual role for the virus-specific cytotoxic T lymphocyte response in hepatitis B and C infection? Curr. Opin. Immunol. 2000;12:403–8.

[79]Muir AH. Cirrhosis in hepatitis C virus-infected patients: a review for practitioners new to hepatitis C care. Top. Antiviral Med. 2014;22:685–89.

[80]Boursier J, et al. Comparison of fibrosis degree classifications by liver biopsy and non-Invasive tests in chronic hepatitis C. BMC Gastroenterol. 2011;11:132 (13 p).

[81]Dienstag JL. The role of liver biopsy in chronic Hepatitis C. Hepatology 2002;36:S151–S160.

[82]Ramadori G, Bernhard S. Portal tract fibrogenesis in the liver. Lab. Inv. 2004;84:153–9.

[83]Brody T. Nutritional biochemistry. 2nd ed. San Diego, CA: Academic Press; 1999. p. 555–7.