But chronic injury to the liver can activate the stellate cells, resulting in the conversion of *stellate cells* into proliferative, *myofibroblast-like cells*, which produce molecules that result in fibrogenesis (84).

With this conversion, the molecules expressed by stellate cells include proteins of the extracellular matrix, such as collagen types I and III, fibronectin, and laminin (85,86).

During chronic liver injury, as in chronic HCV infections, normal collagen type IV is lost and replaced with collagen types I and III, as well as with other extracellular matrix proteins, such as elastin, hyaluronan, proteoglycans, and fibronectin (87). These changes impair the transport of nutrients and other solutes to the hepatocytes. Another change that impairs transport of nutrients to the hepatocyte is that the hepatocytes lose their microvilli (88). The term "scar deposition" may be used to refer to fibrosis of the liver, where the scar contains high levels of fibrillar collagen type I and type III. Cirrhosis is defined as an abnormal liver architecture, with "fibrotic septa" and altered vascularization (89).

The liver stands out from all other tissues by its ability to regenerate from and reverse fibrotic lesions. Thus, it is the case that fibrosis may be reversed. In other words, with treatment of HCV, it is the case that liver fibrosis may be reversed (90).

XIII. ONCOGENES AND GROWTH FACTORS

a. Introduction to Oncogenes and Growth Factors Relevant to HCC

HCC is a risk with chronic HCV infection. The risk for this type of cancer increases as liver fibrosis progresses, and once cirrhosis is established, the risk for this cancer is about 1−7% per year (91).

Hoshida et al. (92) and Whittaker et al. (93) provide lists of genes, mutations, enzymes, and signaling pathways that connect *chronic HCV* infections to eventual *HCC*. It is not yet known which components in these lists of genes, mutations, and such, are necessary or sufficient for the generation of HCC. But to

[84] Nishitsuji H, et al. Hepatitis C virus infection induces inflammatory cytokines and chemokines mediated by the cross talk between hepatocytes and stellate cells. J. Virol. 2013;87:8169−78.

[85] Bandyopadhyay S, et al. Hepatitis C virus infection and hepatic stellate cell activation downregulate miR-29: miR-29 overexpression reduces hepatitis C viral abundance in culture. J. Inf. Dis. 2011;203:1753−52.

[86] Elpek GO. Cellular and molecular mechanisms in the pathogenesis of liver fibrosis: an update. World J. Gastroenterol. 2014;20:7260−76.

[87] Albanis E, Friedman SL. Antifibrotic agents for liver disease. Am J. Transplant. 2006;6:12−9.

[88] Albanis E, Friedman SL. Antifibrotic agents for liver disease. Am J. Transplant. 2006;6:12−9.

[89] Mallat A, Lotersztajn S. Cellular mechanisms of tissue fibrosis. 5. novel Insights into liver fibrosis. Am. J. Physiol. Cell Physiol. 2013;305:C789−C799.

[90] Zeisberg M, Kalluri R. Cellular mechanisms of tissue fibrosis. 1. common and organ-specific mechanisms associated with tissue fibrosis. Am. J. Physiol. Cell Physiol. 2013;304:C216−C225.

[91] Hoshida Y, et al. Pathogenesis and prevention of hepatitis C virus-induced hepatocellular carcinoma. J. Hepatol. 2014;61:S79−S90.

[92] Hoshida Y, et al. Pathogenesis and prevention of hepatitis C virus-induced hepatocellular carcinoma. J. Hepatol. 2014;61:S79−S90.

[93] Whittaker S, et al. The role of signaling pathways in the development and treatment of hepatocellular carcinoma. Oncogene 2010;29:4989−5005.