

A novel hypothesis for pathophysiology of hepatitis fibrosis in hepatitis C viral infection

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We present a novel hypothesis on the pathophysiology of Hepatitis fibrosis in hepatitis C viral (HCV) infection which takes into account the possibility that fibrosis in HCV infection in its pre-cirrhotic phase is a defensive mechanism to encapsulate the invading HCV and prevent further dissemination. This theory contrasts the idea that fibrosis in HCV infection is an ineffective complication. A presentation of the complex bidirectional interactions of the fibrosis in the space of Disse during this process is illustrated. Finally, based on this hypothesis, a novel therapeutic regimen is considered.

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Introduction

HEPATITIS C IS A WORLDWIDE chronic infectious disease. Most of the therapeutic strategies which have been introduced are based on the assumption that the body cannot eradicate the infection, and the end result is fibrosis, cirrhosis and finally may end with hepatocellular carcinoma (HCC). Accordingly the therapeutic regimen has been designed to use interferon alpha in combination with antiviral agent (ribavirin or telaprevir) for hepatitis C viral (HCV) infection. The outcome of this therapeutic regimen is not that much satisfactory as the response rate ranges from 40 to 70% (1, 2).

In this presentation a new hypothesis is presented, where the hepatic fibrosis in its early phases, is always in a continuous dynamic action being reversible, such phenomenon could be considered as a defensive mechanism rather than being a complication of the disease. Such hepatic fibrosis during the early phases of the disease try hard to encapsulate the invading virus preventing its dissemination to other lobules or lobes of the liver. During such encapsulation the natural immune and apoptotic mechanisms might succeed to get over such infection. According to this new hypothesis, some detailed sequences in the cascade of the process have to be illustrated.

Hepatic fibrosis is a long-term consequence of chronic hepatitis virus infection and is characterized by excessive fibrous scarring of the liver. Hepatitis fibrosis is characterized by activation of the Hepatic Stellate cells (HSC), which are involved in synthesis of matrix proteinases and regulating matrix degradation (3–6).

In the acute phase of liver injury and as the liver fibrosis progress, there is an increase of expression of family enzymes namely, matrix metalloproteinases (MMPs) and then tissue metalloproteinase inhibitors (TIMP). It is quite established now, with evidences, that liver fibrosis is in continuous dynamic action and can be bidirectional i.e. progression and regression (7–8).

In the space of Disse (the extracellular space), matrix degradation occurs as a sequence of the action of Matrix Metalloproteinases (MMPase) which are secreted from the mature healthy stellate cells present in the space of Disse, and are released as proenzymes which are activated by a number of specific cell surface-associated, cleavage mechanism (9). These active enzymes are in turn inhibited by the family of tissue inhibitors of metalloproteinases (TIMPase1 to 4) (10, 11). By this balanced mechanism extracellular matrix degradation is closely regulated preventing inadvertent tissue damage (4).

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In normal liver, HSCs in the space of Disse are present in a quiescent, nonfibrogenic phenotype in a matrix composed of collagen IV, laminine, and proteoglycans. When the HSCs are activated, they are transformed to profibrogenic myofibroblast phenotype "Activated HSCs" (12).

To illustrate the sequences of the process of pathophysiology of liver fibrosis, especially those accompanying HCV infection, it is essential to breakdown these cascades step-wise to be able to overview the pathophysiological intervention of this complex orchestrated process (Fig.1).

To start with, once the virus invades the hepatocytes, the damaged hepatocytes release of reactive oxygen species (ROS) and secrete fibrogenous factor (cxc chemokines, kc and MIP-2). Accordingly, oxidative stress takes place (8, 12–14) and the liberated hepatocytes components arouse tissue reactions releasing Hepatocyte Stimulating Factor (HSF), as well as other growth factors/cytokines (15–20).

The activated HSCs, then, lay down collagen I and through their aggregation they produce fibrosis (21) and start to release tissue Metalloproteinase inhibitors (TIMPase) to counteract the degradation of its product i.e. collagen I. (21–22) (Plate I).

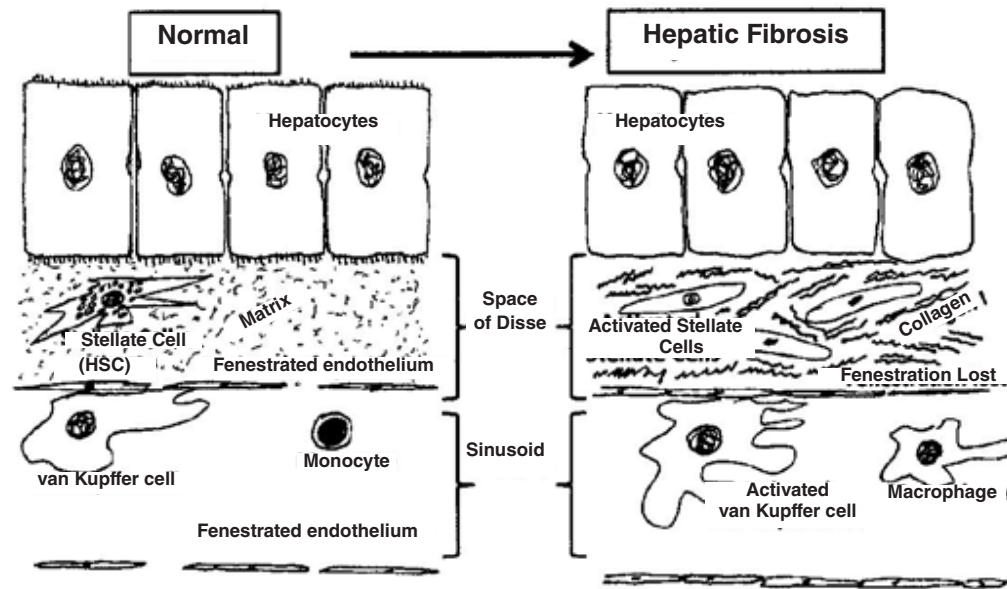


Figure 1 | Progress of Hepatic Fibrosis. Following the oxidative stress induced by HCV infection Stellate cells are activated and loose their vitamin E, iron stores, and transformed to myofibroblast laying down collagen I and the process of fibrosis starts. The hepatocytes loose their microvilli. The sinusoidal endothelial lining fenestration is lost.

The balance between these two opposing enzymes MMP and TIMP determine the process of fibrosis. Other opposing enzymes namely tissue plasminogen activator 1 (tPA1) and tissue plasminogen activator 1 inhibitor (tPAI-1) are released through the interaction between collagen degradation products (CDP) and fibrin degradation products (FDP) with van Kupffer cells and the sinusoidal endothelial cells releasing tPA-I (Plate I) (23, 24).

Plasmin is generated through the proteolytic cleavage of zymogens by plasminogen activator urokinase (μ PA) and tissue plasmin activator (tPA) (25, 26). In addition plasmin induces fibroblastic apoptosis in a time and dose dependant manner, in association with its proteolytic activity degrading the extracellular matrix protein (collagen I) as detected by the release of soluble fibronectin peptide (27, 28).

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hepatocellular proliferation, exerts a variety of other effects, regulating motility, tubule formation, and cytotoxicity in multiple cell types such as endothelium, macrophages, and fibroblasts (35).

As long as the virulence of HCV is taking place, this process of fibrinogenesis continues and the enzymes and their inhibitors are gradually depleted, till a steady state takes place, during which, the liver tries to limit the lesion produced by the invading virus. Certainly the balance between the two opposing mechanisms continues till the organ tissue lose its defensive mechanism, paving the way to the spread of the viral invasion, despite the additional role of the immune system which tries hard to limit or overcome the infection.

It seems that the viral infection, with its long lasting chronicity and the up and downs noticed in the serological and virological investigations, could be explained by such process of pathogenesis providing a new hypothesis for the Pathophysiology of hepatic fibrosis.

Competing interests

Authors declare no competing interest.

Conclusion

In conclusion this new outlook illustrating the pathophysiology of hepatic fibrosis in HCV infection and considering these above mentioned sequences closely and with evidences, one can provide novel therapeutic

measures putting into consideration the advantages of this natural morphological defensive mechanism. **H**

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