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## Unresolved issues in hepatitis C: The role of liver non-parenchymal cells and semaphorins

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### Editorial

With broad usage of direct acting antivirals (DAAs) the global epidemics of hepatitis C will probably come to an end in next 20 years.<sup>1,2</sup> The price of DAAs is still high in European countries and in USA, but it is plausible to assume that the availability of generic drugs will make the treatment possible for the majority of diagnosed patients. So we will be able to eliminate the virus without really understanding the pathophysiology of chronic infection, fibrogenesis and carcinogenesis. Substantial number of treated patients will therefore have to be followed up for cirrhosis and hepatocellular carcinoma.

There is growing evidence that liver non-parenchymal cells, specifically liver sinusoidal endothelial cells (LSEC) and Kupffer cells (KC), may play key roles in regulating immune responses and facilitating tolerance induction.<sup>3,4</sup> Previously published gene expression analyses have revealed new disease specific changes in gene expression, identified potential biomarkers of HCV infection and suggested a new mechanism of host cell-virus interaction that results in viral particle assembly, secretion and infectivity.<sup>5-9</sup> *In vitro* HCV JFH-1 infection studies have shown different gene expression repertoires; unlike macrophages that demonstrated a broad increase in IL1 $\beta$  and NF $\kappa$ B-responsive proinflammatory cytokines and chemokines, transcriptome changes in hepatocytes enable the replicative infection, while LSEC favor the transcription of immunomodulators that can silence the inflammatory reaction and favor fibrogenesis.<sup>5,7-10</sup> Multiple strategies by which HCV evades the surveillance of the host immune system are proposed and yet to be explained.

These *in vitro* cell cultures studies suggested the connection of *immune sema-*

*phorins* with HCV infection. Semaphorins are a class of secreted and membrane-bound proteins that regulate key cellular functions involved in cell-cell communication. The importance of semaphorins and plexins has been emphasized by their discovery in many organ systems including the nervous, epithelial, and immune systems as well as diverse cell processes including angiogenesis, embryogenesis and cancer.<sup>11,12</sup> Studies of plexins and semaphorins have revealed that several members of these families are involved in a series of immune cell interactions, which ultimately influence the outcome of the immune response and substantially influence the level of inflammation.<sup>11,12</sup> Interestingly, semaphorins play the opposite roles in innate versus adaptive immune response, amplifying inflammation while dampening T-cell proliferation and activation.<sup>11,13,14</sup> Although *immune semaphorins* are crucial to various phases of the immune response, so far semaphorins have not been linked with HCV infection.

Previously mentioned gene expression studies have linked several semaphorins with HCV infection: SEMA3C was shown to increase the production/secretion of several extracellular matrix components (fibronectin, elastin, collagen) and promoting factors (CTGF, IL6 and TGF- $\beta$ 1), and the expression of SEMA3C correlated positively with the degree of fibrosis in adipose tissue;<sup>15</sup> SEMA6B and SEMA6D might bind to and activate dendritic cells and increase type I interferon production.<sup>16</sup>

We have been able to show in our Croatian Science Foundation project *Infectomics study of the human liver non-parenchymal cells in chronic hepatitis C* that serum concentrations of secreted semaphorins are higher in HCV infected patients, and their serum concentration correlate with the degree of liver fibrosis.<sup>17</sup> Immunohistochemistry in transplanted livers revealed the absence of semaphorins in healthy livers in comparison with strong positivity in LSEC and KC in explanted cirrhotic HCV positive livers (Vince A., unpublished data). Furthermore, results of that research imply the usage of semaphorins as predictive markers of liver cirrhosis, stronger than APRI score and FIB4 test.<sup>17</sup> These results provide first evidence that semaphorins are involved in immune response to chronic HCV infection. This might have important clinical implications as well, since their concentration correlates with the extent of liver disease, they might be considered as new biomarkers of liver fibrogenesis.

Although the serum concentration of semaphorins in people who develop hepatocellular carcinoma should be evaluated fur-

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ther, recent studies showed that semaphorins that restrict cell migration and angiogenesis are often downregulated, while those that support cancer progression and metastatic spreading are frequently upregulated in other cancers.<sup>18</sup> It was also shown that blocking these molecules effectively reduce tumor angiogenesis and metastatic spreading in preclinical trials in mice.<sup>18-20</sup>

These data validate the identification of semaphorin signals as a potential biomarker of infection and fibrosis stage in chronic viral hepatitis and promising therapeutic targets in liver cancer.

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