The process by which hepatitis C virus (HCV) enters cells has been difficult to study because of a lack of in vitro systems for HCV propagation. Several widely distributed potential receptors have been identified, none of which provides an explanation for HCV hepatotropism.

Three recent studies have demonstrated the binding of DC-SIGN (dendritic cell specific intercellular adhesion molecule grabbing non-integrin) and DC-SIGNR (DC-SIGN related molecule) to the HCV envelope protein E2. DC-SIGN and DC-SIGNR were originally described as human immunodeficiency virus (HIV) binding molecules, able to adsorb HIV to the surface of cells and facilitate the infection of DC-SIGN/DC-SIGNR positive cells or adjacent cells. DC-SIGN and DC-SIGNR are not HIV entry receptors.

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In normal tissues, dendritic cells (DCs) express DC-SIGN. DC-SIGNR shows more restricted distribution, being limited to hepatic sinusoidal endothelium, lymph node sinus endothelium, and placental capillary endothelium. This distribution could potentially explain HCV hepatotropism. Here, we present new data regarding the expression of DC-SIGN and DC-SIGNR in HCV induced liver disease.

**METHODS/RESULTS**

Needle biopsies or explant sections of HCV infected liver, with no concurrent HBV or HIV infection (Ishak stages 3 (n = 10) and 5 (n = 10)), and HCV negative normal liver (n = 3) were immunostained for DC-SIGN (using polyclonal rabbit serum (with preimmune rabbit serum as a negative control)) and DC-SIGNR (using anti-DC-SIGN polyclonal chicken antibody (negative control), anti-DC-SIGN polyclonal chicken antibody incubated overnight with an excess of the peptide against which the antibody was raised), using methods described previously. Very few DC-SIGN-positive cells were present in normal liver or liver tissue at stages 3 and 5 fibrosis (fig 1A and B), suggesting that DC-SIGN does not play a major role in initiation or propagation of HCV infection. However, because DCs are migratory cells, it is possible that DC-SIGN positive DCs carry adsorbed HCV particles into hepatic parenchyma, mediating initial HCV infection.

In contrast, DC-SIGNR is present on most hepatic sinusoidal endothelial cells in normal liver and in stage 3 HCV infected livers (fig 1C), whereas there is patchy loss in stage 5 disease (fig 1D and E). However, staining for the endothelial cell marker, von Willebrand factor, confirms the presence of endothelial cells lining all visible sinusoidal spaces even in stage 5 disease (fig 1F), suggesting that some endothelial cells lose DC-SIGNR expression. Therefore, DC-SIGNR may be in a unique position to capture blood borne HCV and potentiate efficient infection of underlying hepatocytes. However, the space of Disse and a basement membrane, which separate the sinusoidal endothelium from hepatocytes, may reduce the efficiency of hepatocyte infection following any DC-SIGNR mediated endothelial adsorption of HCV.

**DISCUSSION**

The patchy loss of DC-SIGNR during progression to stage 5 disease (fig 1D and E) may correlate with the previously described cirrhotic “capillarisation” of the sinusoids, during which there is an ultrastructural loss of sinusoidal fenestrations. Our previous work has shown that DC-SIGNR is expressed only on fenestrated endothelium. However, loss of DC-SIGNR in cirrhosis is unlikely to affect the course of HCV infection, because HCV infection of hepatocytes probably occurs at earlier stages.

In conclusion, we suggest that the expression of DC-SIGNR in HCV induced liver disease may play a role in potentiating hepatocyte infection with HCV.

**Take home messages**

- The human immunodeficiency virus binding lectin DC-SIGNR is expressed in hepatitis C virus (HCV) induced liver disease
- The expression of this lectin may play a role in potentiating hepatocyte infection with HCV

**Abbreviations:** DC, dendritic cell; DC-SIGN, dendritic cell specific intercellular adhesion molecule grabbing non-integrin; DC-SIGNR, dendritic cell specific intercellular adhesion molecule grabbing non-integrin related molecule; HCV, hepatitis C virus; HIV, human immunodeficiency virus
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Figure 1 Immunoperoxidase staining for DC-SIGN and DC-SIGNR in hepatitis C virus (HCV) infection. (A) DC-SIGN expressing cell (brown) with dendritic morphology (arrow) in a portal tract in HCV infected liver showing stage 3 fibrosis. Some hepatocytes are brown because of the presence of endogenous pigment, with similar appearances in the negative control. (B) A serial section of (A) was stained with paired preimmune rabbit serum. (C) Most of the hepatic sinusoids express DC-SIGNR (brown, arrows) in HCV infected liver showing stage 3 fibrosis. (D) There is patchy expression of DC-SIGNR on hepatic sinusoids (brown, arrows) in a cirrhotic (stage 5 fibrosis) HCV infected liver. Numerous lymphocytes are also present in this section and their nuclei avidly take up the dark blue haematoxylin counterstain. The area marked with a box is magnified in (E), where sinusoids expressing appreciable amounts of DC-SIGNR are marked with long arrows, whereas an area in which sinusoids express minimal DC-SIGNR is present between the arrowheads. (F) Von Willebrand factor (VWF) staining of case shown in (D) and (E) demonstrates VWF positive endothelial cells lining all sinusoids. All sections were immunostained with the indirect immunoperoxidase method and counterstained with haematoxylin.