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REVIEW

Viral Hepatitis: New Data on Hepatitis C Infection

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Viral hepatitis (VH) is almost as old as human beings, at least as old as known human history. However, the natural history and the epidemiology of the disease has undergone changes during the centuries and even recently we have been facing several new aspects. The estimated global prevalence is around 3-5%, which means that approximately 400 million patients are infected with hepatitis B virus[49] and that there are 170 million infections with hepatitis C virus.[62,63] The mortality figures are projected to show a 2- to 3-fold increase over the next two decades as hepatitis C virus-infected patients develop cirrhosis, which makes this the leading indication for liver transplantation.[4,6] These data point to the importance of VH being a significant public health problem worldwide.[65] The list of hepatotropic viruses is well known, including hepatitis A (HAV), B (HBV), C (HCV), D (HDV), E (HEV), G (HGV) and F (HFV). HGV and HFV are excluded from the present review, mainly because they are questionable in relation to the causation of liver disease. Our knowledge of HAV, HBV, HDV and HEV has accumulated over the last decade, so the present discussion is focused on HCV, which is currently generating considerable concern and controversy, and is the leading cause of chronic liver disease worldwide. The main questions to be discussed, are: the characterization of the agents' viral genotypes/subtypes, the viral-cell interaction, the pathogenesis of VH, the extrahepatic manifestations of viral infection and hepatocarcinogenesis. (Pathology Oncology Research Vol 9, No 4, 215–221)

Keywords: viral hepatitis, hepatitis C, chronic hepatitis

Characteristics of HCV, viral replication

The genetically complex HCV has recently been classified as a Hepacivirus of the Flaviviridae family.[12,17,27,58] The 9.6 kb single-stranded, positive-sense RNA genome encodes a single polyprotein of about 3,010 amino acids in length, which is processed by proteases into structural (at least three) and nonstructural (NS) (six) proteins (*Figure 1*). The function of NS proteins is not completely understood, but, certain aspects are being discovered. Recently we learned that NS5A probably mediates viral IFN-resistance and possibly regulates viral replication.[25,26] Based on the high level of sequence variation, HCV is classified into 6 major genotypes (1-6) and several subtypes (for a review see Bartenschlager and Lohmann[8]), having possible significance in both the route of transmission and the histological activity of viral hepatitis[24,38,48] *(Table 1).*

HCV attaches to the cell surface mainly via receptors (*Figure 2, Table 2*). However, attachment of HCV has been observed to lymphoid cells and red blood cells also.[36] CD81 seems to be a key molecule in the cell surface binding to E2,[44] a putative HCV receptor which belongs to the so called tetraspanin family. It has been shown, however, that HCV internalization is facilitated via LDL (low density lipoprotein) receptors[1] and the virus enters into the cell via endocytosis. More recently, a broadly expressed lipoprotein binding receptor, the human scavenger receptor class B type I was shown to serve as a receptor for HCV.[51] A recent report describes that HCV particles bind specifically to L-SIGN (CD209L) and DC-SIGN which function as capture receptors for HCV and play an important role in pathogenesis and liver tropism.[22]

HCV replicates in the cytoplasm of the hepatocytes. The majority of core protein (p21) is formed and can be located in the endoplasmic reticulum (ER), however, shorter

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Table 1. **Terminology relating to hepatitis C viral genomic heterogeneity**

Terminology	*Definition*	*Nucleotide similarity (%)*
Genotype (1-6)	Major genetic group based on similarity of nucleotide sequence	65.7 – 68.9
Subtype (a, b, etc.)	Genetically closely related viruses within of nucleotide sequence	76.9 – 80.1
Quasispecies	Complex of genetic variants within individual isolates	90.8 – 99

portions (p19, p16) of capside proteins are transported to the nucleus[17] *(Figure 2),* which might have effect on the genes related to cell proliferation, activating NFkB and STAT. A specific characteristic of the HCV is the high variability of its nucleotid sequence.[12,21,24,25] The viral RNA-dependent RNA polymerase is mainly responsible for this „inaccuracy", which leads to formation of quasi-species. The various core proteins are differently expressed in the HCV genotypes influencing, for example, the activation of NFkB.[23] The E2 region is the most variable region of the genome, which explains the „escape" of the viral protein from the neutralizing antibodies.

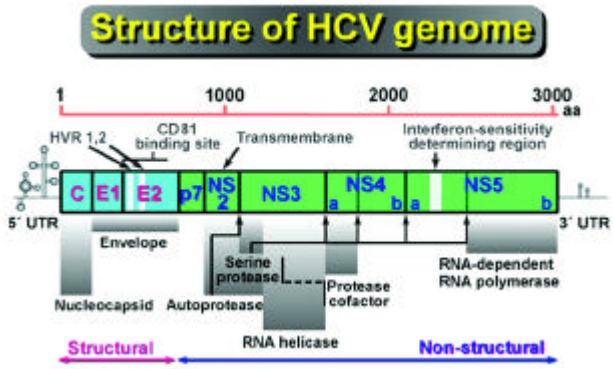

Figure 1*. Structure of HCV genome.*

Several studies have located the different viral proteins in the cytoplasm, mainly in association with or near the endoplasmic reticulum (*Figures. 2,3*). Based on confocal microscopic studies, it has been demonstrated that the HCV RNA replication involves specific intracellular lipid membranes.[7]

Very recently a new HCV protein, so called „F" protein, has been described.[13] The F protein received its name because of frameshifting – ribosomes shift from the normal („zero") reading frame to the –2/+1 reading frame – to generate a 17-kDa protein.[13] Antibodies to this protein can be detected during natural HCV infection. The F protein was found located at the ER as the core and other proteins, and is presumed to play role in viral morphogenesis and/or replication. The „slipperiness" of the HCV-1 frameshift signal raises the possibility that the F protein might be synthesized through multiple frameshifting events at multiple sites. This would explain the sequence heterogeneity of HCV.

Attachment is followed by entry into the cell; the virus is uncoated, exposing the positive-strand RNA genome (*Figures 2*). After translation, a single large polyprotein is produced, which is to be cleaved into structural and non-structural proteins. The positive-strand RNA serves as a template for generating a negative-strand RNA, which binding to the NS proteins forms a replicating complex producing further positive-strand RNA (for review see Chang et al[12]).

It is important to learn more about HCV structure and replication because gene therapy might provide a possibility for the treatment of HCV infection. RNA interference which blocks gene expession might provide a new approach, which at present has proved to be effective in tissue culture systems.[32,64]

The question is what do we see during HCV replication by light (LM) or electron microscopy (EM)? It is well documented that characteristic membrane changes of the endoplasmic reticulum (4 types of alterations) can be observed in chimpanzees infected by HCV,[54] which can not be seen in human biopsies. In human livers, however, several „virus-like" particles have been described, some measuring 50-60 nm in diameter, consisting of a dense

Table 2. **Receptors for HCV**

CD81[44]	tetraspanin family, high affinity for E_2 binding, isolate specific expressed in most cell types (required, but not sufficient)
LDL-R[1]	(low density lipoprotein receptor) mediate internalization via binding to virus- LDL particles
hSR-BT[51]	(human scavenger receptor class B type I) CD36 superfamily, E_2 binding, selective species specific
Others	?

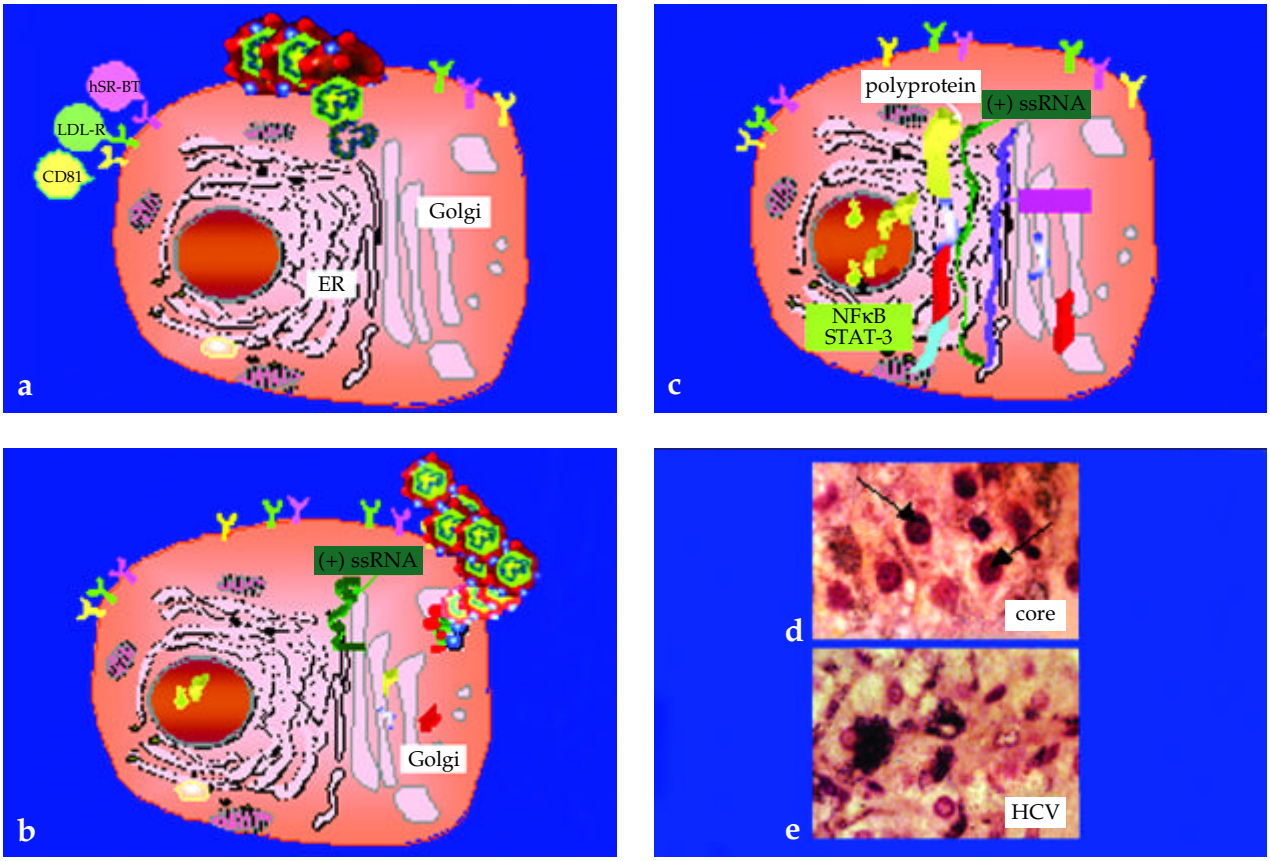

***Figure 2**. Replication cycle of HCV. **(a)** The virus attaches to the cell surface via receptors, internalization, uncoating in the cytoplasm. **(b)** A single polyprotein is formed, then cleaved into structural and nonstructural proteins. Parts of core protein (p16, p19) enter into the nucleus and might activate NFkB, STAT-3. (-)ssRNA is transcribed from the (+)ss RNA. **(c)** Viral assembly occurs in the Golgi-cisternae, then secreted. **(d,e)** Immunogold detection of core **(d)** and other **(e)** viral proteins. The core can be localized in the cytoplasm and the nucleus as well (arrows).*

core and covered by a lipid envelope.[30] A similar observation was published recently, describing particles lying free in the hyaloplasm.[16] Using anti-core antibodies and immunoelectronmicroscopy, positivity was detected at the endoplasmic reticulum membranes, the Golgi-system and the surface of lipid droplets.[7]

Pathogenesis and histopathological aspects of viral hepatitis

Several international consensus meetings have discussed the characteristics and definition of acute and chronic VH,[28] reviewed and updated even recently.[49] The major new knowledge in the pathogenesis of VH has been the recognition of the role of apoptosis[53] and very recently the significance of stem cells.[20]

The presence of apoptotic cells in acute VH, described as Councilman-like bodies, has been known for several decades. The appearance of eosinophilic apoptotic bodies, however, at the „interface", at the site of piecemeal necrosis in chronic hepatitis has been recognized only in the last few years[53] (*Figures 4*).

Several studies have shown increased expression of Fas (CD95) in virus-infected hepatocytes in human and chimpanzee livers[53] (*Figures 5*). Increased TGFβ1 – as another apoptosis inducing factor - in correlation with the activity of chronic hepatitis has been demonstrated as well.[40]

Very recently the role of stem cells in several diseases including VH has come into focus. Through normal proliferation, hepatocytes restore the liver, re-entering the cell cycle from the G_0 phase.[20] In mild or moderate parenchymal cell loss it is also thought of as the main response to restoration. However, in more severe damage the CK-7/CK-19 positive, so called „oval cells" or „ductular type cells" proliferate and probably differentiate into hepatocytes[37,41] (*Figures 6a,b*). A new marker for the stem cells has been published recently,[10] which partially overlaps with the CK-7/CK-19 positivity. Its significance will be known only in the future. The „third defense system" against cellular loss resides in the bone marrow. This

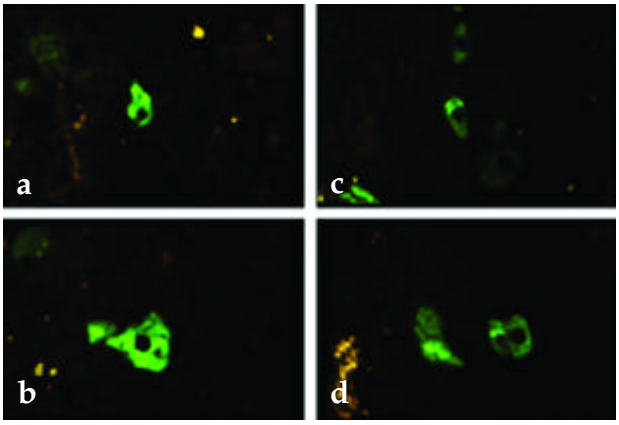

***Figure 3**. Immunofluorescence localization of HCV on frozen liver. Reaction with an antibody against the whole viral protein **(a, b)** and the core antigen **(c, d)**.*

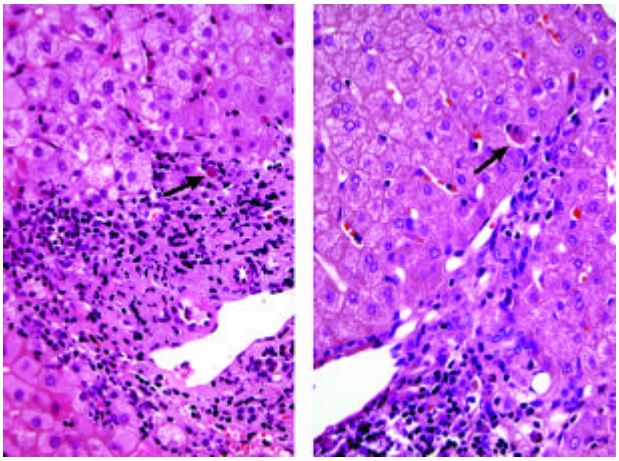

***Figure 4**. Apoptotic bodies (arrows) at the interface.*

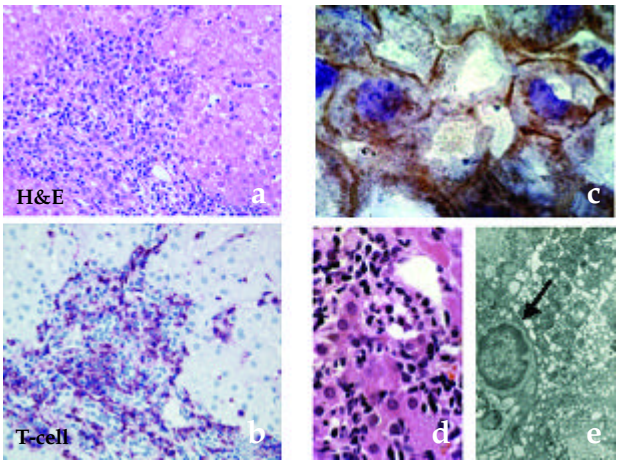

***Figure 5**. Close association of lymphoid cells and hepatocytes at the interface in CH-C **(a,b,d,e)**. Strong expression of CD95 (FAS) on the hepatocyte membranes after HCV infection **(c)**.*

haematopoetic stem cell population probably plays role in more significant regeneration.[3,34]

Major new knowledge has accumulated in understanding the pathogenesis of fibrosis and about the possibility to reverse the process.[47,61] Several changes have been recognized in the composition of the extracellular matrix, which might be a target for drug therapy.[18] An example of this is the decrease of decorin expression after IFN treatment.[31] New data indicate the relationship between genotypes of HCV and the histopathology of CH-C.[2] It has been demonstrated that HCV genotype 1b has a worse prognosis than other genotypes. The „well accepted" observation, however, that steatosis is significantly greater in association with HCV type 3a[38,57] might be questionable. Our study including 120 CH-C patients with genotype 1b and found the same percentage of steatosis as in a published series with HCV-3 genotype.[50] It seems to be proved that CH-C is associated with steatosis more often than CH of other etiology. The cause of this, however, is not clear, the interference of the viral core component with lipid metabolism has been suggested.[7]

The evaluation or scoring of the liver biopsy materials obtained from patients with CH have been revised several times in the last years. After the initial Knodell scoring,[33] the most widely used systems have been proposed by Ishak et al[29] and Scheuer et al.[56] The METAVIR cooperative study group published a similar reliable and useful evaluation system.[9] Comparison of the different scoring systems proved that the choice should be dictated by the preference of the team; the clinician and the pathologist.[49,55]

Extrahepatic manifestation of HCV infection

HCV is a hepatotropic virus, however, it has been demonstrated that it might replicate in lymphocytes and in certain macrophages.[39] Diseases associated with HCV infection are numerous (*Tables 3,4,5*). Our group has shown that HCV might attach to the surface of erythrocytes, becoming internalized: a newly recognized ‚hiding mechanism" for HCV and probably important in the transmission of the infection.[36] Several neurological disorders are associated with HCV infection (*Table 3*). Few studies have shown the presence of HCV-RNA in the central nervous system (CNS) and the periferal nerve tissue,[15] which might explain the neurological symptoms in CH-C. More recently negative strand HCV-RNA has been demonstrated by in situ hybridization in the glia cells, suggesting that HCV might even replicate in the CNS.[14] Dermatological manifestations of HCV infection have been detected as well[14,46] (*Table 4*). In one of our recent studies we detected positive strand HCV-RNA in altered skin lesions, not found at all in the normal areas.[46]

The mechanism of tissue alterations in the extrahepatic manifestation of HCV infection is not completely clear,

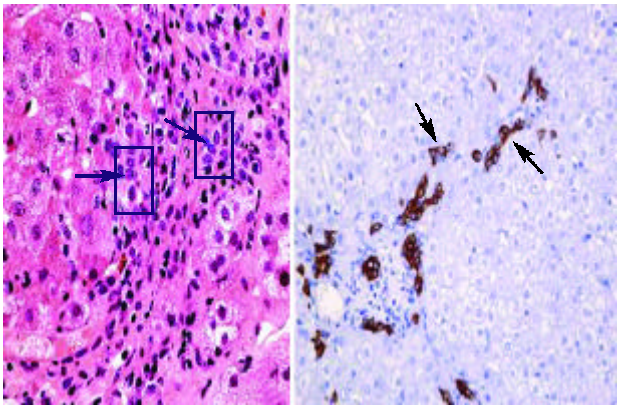

***Figure 6**. Ductular proliferation in CH-C. Stem cells have „oval" shape **(a)** and Ck-7 immun-positivity **(b)**.*

but several possibilities might exist. The deposition of viral antigen–antibody complexes has been shown in different vascular structures or autoantibody production, both causing vasculitis, glomerulonephritis, autoimmune thyroiditis, etc (for review see Pár et al[43]). Cryoglobulinemia in HCV patients is well known and the association with B-cell non-Hodgkin lymphomas has been suggested, too.[42]

HCV and hepatocarcinogenesis

Since the discovery and identification of HCV, data have proved an association between HCV and hepatocellular carcinoma (HCC).[11,35,59,60] In HBV-associated HCC, the pathomechanism of hepatocarcinogenesis is better understood (although not exactly clear), asthis is a DNA virus.[35] Based on the pathogenesis of HCV infection, however, the mechanism of HCC formation is more difficult to explain. As it has been shown, HCV is an RNA virus, replicated in the cytoplasm with no reverse transcriptase, so no integration occurs into the cell genome, in contrast to HBV infection.[35] HCV does not seem to be a directly cytopathic virus. The viral proteins expressed stimulate the host immune system, through which the death of infected hepatocytes occurs. This explains why activated T cells predominate in the inflammatory infiltrate and T and B lymphocytes and different antigen presenting reticulum cells are present in the portal tract, occasionally forming even lymphoid follicules. Besides, HLA I is expressed highly in hepatocytes, HLA I and II in T lymphocytes and HLA II in endothelial cells.[53]

The repeated necroinflammatory effects and cell death lead to hepatocyte proliferation, with acceleration of the cell cycle, as well as progressive accumulation of mutations and genomic instability.[45] Allelic imbalance has been shown to occur frequently in hepatitis-related HCC.[19]

A recent study[5] using cDNA microarray analysis has demonstrated that a total of 53 genes are consistently dysregulated in macroregenerative and dysplastic nodules in end-stage HCV-induced cirrhosis. The list of gene expression alters, including transcription factors and house-keeping genes, several growth factors and cytokines. Several previous studies showed the upregulation and increased expression of TGFα, IGF and changes in their receptors.[52]

HCV does not integrate into the genome of the hepatocytes. Several viral proteins, however, have been suggested to be associated with hepatocarcinogenesis, especially the core and NS5.[35,58] The data presently discussed suggest that besides HBV, HCV is also able to drive the hepatocytes in an accelerated cycle through increased virus induced apoptosis and proliferation. Depending on the host immune response and several viral factors, elimination of the infection or chronic

***Table 3.* Association of HCV and central nervous system**

• Fatigue
• Progressive encephalomyelitis
• Chronic sensory neuropathy
• Guillain-Barré syndrome
• Peripheral neuropathy
• Quality of life measurement
• Others

***Table 4.* Dermatological manifestation associated with HCV[14]**

• Vasculitis
• Pruritus
• Porphyria cutanea tarda
• Urticaria
• Erythema nodosum
• Granuloma annulare
• Lichen ruber planus
• Others

***Table 5.* Extrahepatic manifestation of HCV infection**

• Haematopoetic system
Lymphocytes, macrophages/monocytes
Aplastic anaemia
Autoimmune thrombocytopenia
B-cell lymhoma
• Association with erythrocytes
• Glomerulonephritis
• Skin alterations
• Arthritis, myalgia
• Endocrine system
• Central nervous system
• Others

inflammation may develop varying in intensity and propensity. Viral proteins such as HBx and HCV core protein may directly interfere with gene products responsible for cell proliferation and growth. The genomic integration of HBV-DNA may increase the genomic instability which favors the development of clones bearing genetic defects. The increased growth stimulus may help the clonal expansion of the damaged cells, finally leading to hepatocellular carcinoma.

HBV and HCV might therefore result in the development of hepatocellular carcinoma directly, interfering with the genome and different gene products, and in part indirectly, by means of increased cell proliferation – through chronic hepatitis and cirrhosis.

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