2

Toll Like Receptors in Chronic Viral Hepatitis – Friend and Foe

Ruth Broering, Mengji Lu and Joerg F. Schlaak
University Hospital of Essen
Germany

1. Introduction

Chronic viral hepatitis caused by Hepatitis B virus (HBV), Hepatitis C virus (HCV) and Hepatitis D virus (HDV) infection is among the most frequent causes for liver related morbidity and mortality worldwide. In recent years, it has become clear that not only the adaptive but also the innate immune system is involved in the pathogenesis of these infections. The innate immune system represents the initial line of host defense against invading pathogens. Germline-encoded pathogen recognition receptors (PRR), that are able to recognize specific structures of microorganisms, are an important component of this system. Amongst these, Toll like receptors (TLR) are a family of PRR perceiving a wide range of microorganisms, including bacteria, fungi, protozoa and viruses. Hepatitis viruses have evolved evading strategies to subvert the innate immune system of the liver which is of relevance for understanding the mechanisms that lead to chronicity of these infections and to develop novel therapeutic approaches based on these findings. Thus, recent studies suggested that TLR-based therapies may represent a promising approach in the treatment in viral hepatitis. This chapter focuses on the role of local innate immunity of the liver in the pathogenesis of chronic viral hepatitis.

2. Innate immunity

It has been suggested that the innate immune system is of particular relevance in the early phase of viral and bacterial infections (Fearon and Locksley, 1996). PRR become activated immediately after exposure to infectious agents and activation of downstream signaling pathways leads to the expression of effector molecules that limit microbial replication (Biron, 1998; Epstein *et al.* 1996). PRR sense evolutionary highly conserved structures, so-called pathogen-associated molecular patterns (PAMPs). Within this process the TLR system is one of the main players (Medzhitov & Janeway, Jr., 2000; Medzhitov, 2001).

2.1 Toll like receptor system

Activation of the TLR system leads to the expression of pro-inflammatory (IL-6, IL-12, TNF-α,…) as well as anti-inflammatory cytokines (IL-10,…) by responsive cell types. TLR7, -8 and -9 additionally initiate Interferon-α (IFN-α) expression after binding of their specific ligands. Stimulation of TLR3 and -4 results in expression of IFN-β as well as immunoregulatory cytokines (Akira *et al.* 2006; Takeda & Akira, 2005).

TLRs are associated with cellular membranes and have a highly conserved cytosolic domain with similarity to the Interleukin-1 receptor and are therefore called Toll/IL-1 receptor (TIR). Binding of a specific pathogen-associated molecular pattern (PAMP) to these receptors leads to recruitment and activation of adapter molecules. All TLRs except TLR3 are able to activate the myeloid differentiation primary response gene 88 (MyD88). TLR2 and -4 integrate the TIR domain containing adapter protein (TIRAP) to active MyD88. MyD88-dependent signaling further involves Interleukin-1 receptor associated kinases 1 (IRAK1) and -4 (IRAK4) and Tumor necrosis factor (TNF) receptor associated factor 6 (TRAF6) to dissociate the Nuclear factor Kappa B (NFκB)-Inhibitor IκB. This is followed by translocation of NFκB into the nucleus and transcription of immunoregulatory genes (Takeda & Akira, 2005). MyD88 signaling additionally activates mitogen-activated protein kinases (MAPKs) which further activate AP-1 signaling resulting in cytokine expression. MyD88 signaling of endosomally located TLR7, -8 and -9 additionally promotes activation of Interferon regulatory factor 7 (IRF-7) which initiates the expression of IFN-α (Honda & Taniguchi, 2006).
TLR3 signaling is MyD88 independent. Activation of the TIR domain containing adaptor inducing IFN-β (TRIF) results in phosphorylation of IRF-3 followed by induction of IFN-β expression. TRIF additionally mediates activation of TRAF6 leading to translocation of NFκB as described before. TLR4 activates the toll-interleukin 1 receptor domain containing adaptor protein (TIRAP) to activate MyD88-dependent signaling as well as the TRIF-related adaptor molecule (TRAM) to enable TRIF dependent induction of IFN-β (Akira & Takeda, 2004; Honda & Taniguchi, 2006; Takeda and Akira, 2005) (Figure 1).

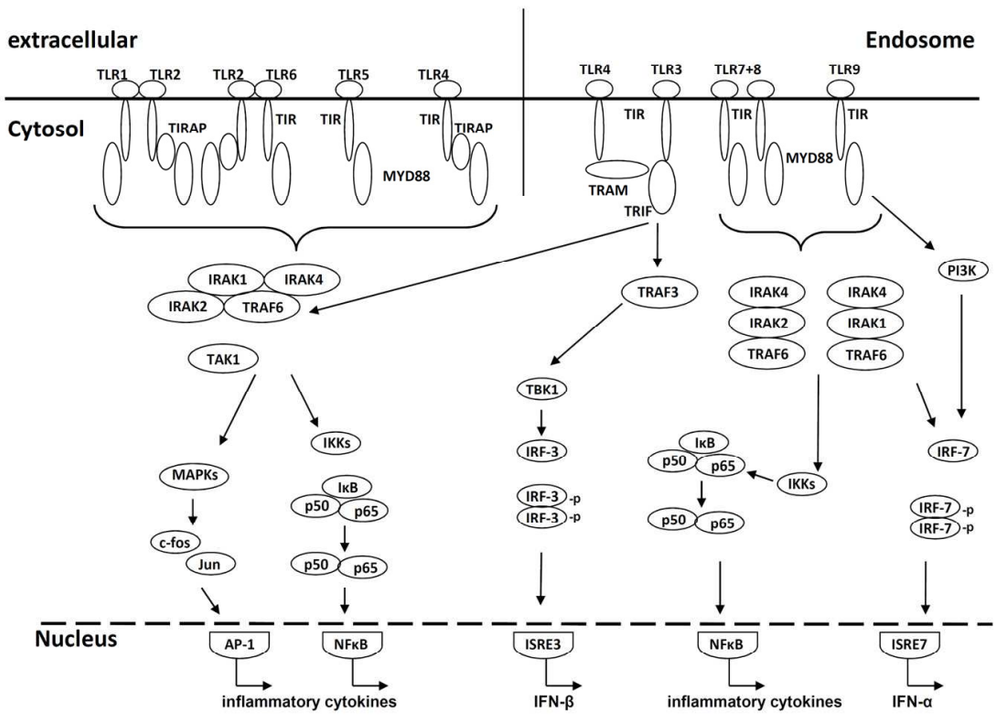


Fig. 1. Toll like receptor signaling
Activation of Toll like receptors leads to recruitment of the adaptor molecules MYD88, TIRAP, TRIF and TRAM. Downstream signaling involves TAK1, MAPKs, TRAF3, TBK1 and IKKs leading to nuclear translocation of transcriptions factors (AP-1, NFκB, IRF-3 or IRF-7) and subsequent transcription of inflammatory genes.

2.2 Local immune system of the liver

The liver represents an immunological organ in which blood from the gastrointestinal tract, enriched with nutrients and antigens, flows through sinusoids in close contact to antigen-presenting cells (APC) and lymphocytes (Figure 2). Physiological functions of the liver include protein synthesis and metabolism as well as removal of pathogens and antigens from the blood. This necessitates a locally regulated immune system. Efficient elimination of pathogenic microorganisms derived from the gastrointestinal tract must be accompanied by tolerance induction for a large number of harmless antigens to avoid unnecessary damage of hepatocytes that represent two third of the total liver cell population (Knolle & Gerken, 2000). The remaining cells consist of non-parenchymal liver cells (NPC) including Kupffer cells (KC), liver sinusoidal endothelial cells (LSEC), stellate cells, dendritic cells (DC) and intrahepatic lymphocytes.

It has been proposed that the liver is an organ of tolerance induction rather than induction of immunity. Therefore, the different types of APC may contribute in different ways to reach homeostasis of the local microenvironment (Racanelli & Rehermann, 2006). LSECs represent about 50% of the NPCs and form a fenestrated monolayer separating hepatocytes from the blood stream. LSECs are able to perform receptor-mediated endocytosis or phagocytosis with comparable efficacy as DCs. Processed peptides are loaded onto the major histocompatibility complex (MHC) class I and II molecules and are presented to passing lymphocytes. KCs represent approximately 20% of the NPC population of the liver, located in the hepatic sinusoids, where they are in close contact to the blood and passing lymphocytes. This exposed location enables Kupffer cells to take up antigens or debris from the blood stream and to induce inflammation or maintenance of tolerance (Sun *et al.* 2003).

2.3 The role of liver cells as part of the local innate immunity

TLR have recently been recognized to play an important role in the pathogenesis of chronic hepatitis. Activation of TLR signaling pathways results in an antiviral state of liver cells, thereby offering the possibility for the development of novel therapeutic strategies. Hepatocytes express TLRs and are able to respond to stimulation with TLR ligands. The expression of TLRs was demonstrated for primary human and murine hepatocytes as well as hepatoma cell lines including HepG2 and Huh7. The functionality of the TLR pathways in these cell systems was shown by analysis of cellular responses to various TLR ligands (Preiss *et al.* 2008; Thompson *et al.* 2009; Xia *et al.* 2008; Wu *et al.* 2007; Zhang *et al.* 2009; Broering *et al.* 2008).

Non-parenchymal liver cells; Kupffer cells; sinusoidal endothelial cells and hepatic stellate cells are important players to mount local innate and adaptive immune responses in the liver (Kimura *et al.* 2002; Knolle & Gerken, 2000). Studies regarding the diversification of TLR signaling pathways in NPC revealed that KC respond to all TLR ligands by producing TNF-α or IL-6. Only TLR3 and TLR4 activation leads to expression of IFN-β in KC. In addition, TLR1 and -8 ligands significantly upregulate MHC class II and costimulatory molecules. For TLR8-activated KC, high levels of T cell proliferation and IFN-γ production could be shown in mixed lymphocyte reactions (MLR). Similarly, LSEC respond to TLR3 ligands by producing IFN-β, to TLR1-4, -6 and TLR8-9 ligands by producing TNF-α, and to TLR3 and -4 ligands by producing IL-6. Interestingly, LSEC failed to stimulate allogeneic T cells in MLR despite significant upregulation of MHC class II and costimulatory molecules in response to TLR8 ligands (Wu *et al.* 2009). Taken together, NPC display a restricted TLR-

mediated activation profile when compared to 'classical' APCs which may also explain, at least in part, their tolerogenic function in the liver.

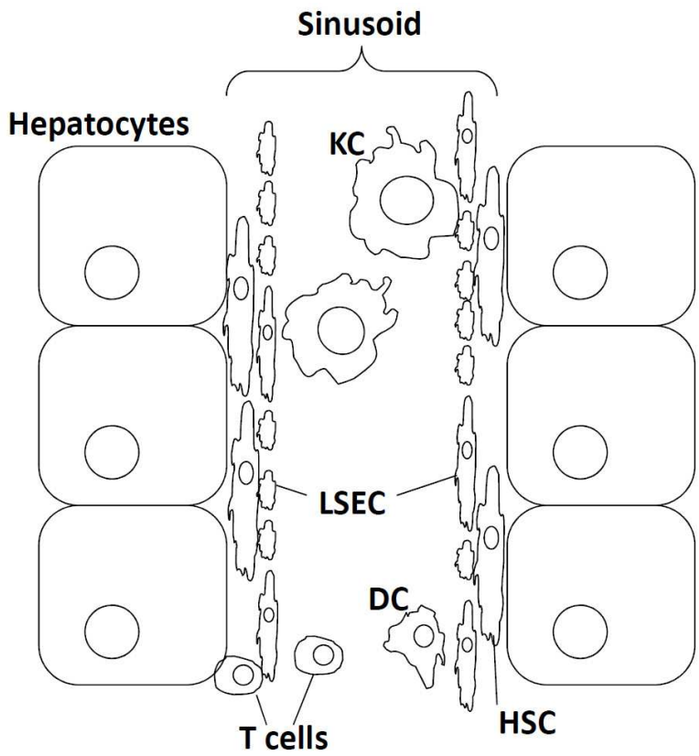


Fig. 2. Cell populations of the hepatic microenvironment
The hepatocytes are lined by the liver sinusoid endothelial cells (LSEC), preventing direct cell to cell contact to passing leucocytes, Kupffer cells (KC), dendritic cells (DC) or lymphocytes (T cells). Hepatic stellate cells (HSC) are located in the Space of Dissé between LSECs and hepatocytes.

3. Chronic viral hepatitis

Currently, five different human hepatitis viruses have been characterized: Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV) and hepatitis E virus (HEV). HAV is a single-stranded, unenveloped RNA virus encoding for a single polyprotein. HBV is a virus with a partially double stranded DNA genome that replicates through RNA intermediates. HCV is a single-stranded RNA virus coding for a polyprotein, which is cleaved into a capsid protein, two envelope proteins and 6 non-structural proteins. HDV is a defective RNA virus, similar to viroids, that only encodes the capsid antigen (delta antigen) and is dependent upon the HBV coinfection, in particular the surface protein (HBsAg), for production of infectious virus particles. HEV is a labile RNA virus, unrelated to the other known hepatitis viruses. Chronic infections of hepatitis viruses, that are caused by HBV, HCV and HDV in immunocompetent patients, are frequently associated with progression of fibrosis and the development of liver cirrhosis and primary hepatocellular carcinoma (Hayashi & Zeldis, 1993; Perrault & Pecheur, 2009; Wedemeyer & Manns, 2010; Aggarwal & Naik, 2009).

It has been suggested that the interaction between hepatitis viruses and the innate as well as the adaptive immune system determines the outcome of these infections. Thus, studies regarding specific interactions between viral proteins and components of the immune system may introduce important information about the establishment of chronic infection. Here, we focus on the role of non-parenchymal liver cells and hepatocytes as part of the innate immune system of the liver and their relevance in the pathogenesis of viral hepatitis.

3.1 Hepatitis B virus

Hepatitis B virus is a hepatotropic non-cytopathic DNA virus which belongs to the *Hepadnaviridae* family. An estimated 400 million people worldwide suffer from chronic HBV infection, reaching higher prevalence in Asia and Africa. Patients with chronic infections mostly remain asymptomatic while 10–30% of these individuals develop liver cirrhosis and liver cancer. Although the mechanisms that are involved in viral clearance and persistence are still not fully clarified, it is evident that cell-mediated immune responses play an important role for viral clearance as patients with chronic HBV infection usually fail to develop adequate HBV-specific immune responses. (Bertoletti & Gehring, 2006). Pegylated interferon *a* (IFN-*a*) and nucleos(t)ide analogues are used for therapy of chronic hepatitis B.

3.2 Hepatitis C virus

HCV, a member of the *Flaviviridae family, hepciviridae genius*, is a global health care problem as more than 2% of the world's population (170 million individuals) has been infected with the this hepatotropic virus (Alter, 2007). Infection with HCV leads to chronic hepatitis in 70-80% of the cases, thereby promoting serious hepatic disorders as liver cirrhosis and hepatocellular carcinoma (Di Bisceglie, 1997; Di Bisceglie, 1998). As a consequence, chronic HCV infection is a main indication for liver transplantation. Currently, standard of care is a combination therapy of pegIFN and ribavirin for patients infected with all 6 HCV genotypes (Manns *et al.* 2001), while addition of protease inhibitors have been licensed for the treatment of genotype 1 patients. Recently published clinical trials indicated that triple treatment with the protease inhibitors Telaprevir or Boceprevir in combination with pegIFN and ribavirin, compared to standard treatment with pegIFN and ribavirin alone, significantly improved sustained virologic response rates in naïve patients with HCV genotype 1 infection. In addition, these triple treatments resulted in significantly improved sustained response rates in patients with chronic HCV genotype 1 infection, who were nonresponders or relapsers to previous treatments (Bacon *et al.* 2011; Jacobson *et al.* 2011; Zeuzem *et al.* 2011; Poordad *et al.* 2011).

3.3 Hepatitis D virus

Hepatitis D virus (HDV) has primarily been identified as an additional antigen during HBV infection. It has been shown, that HDV only occurs in HBV infected patients, because it is using HBsAg as envelope protein, which is necessary for the cell entry of HDV (Rizzetto *et al.* 1977; Rizzetto *et al.* 1980). About 20 million HBV infected individuals are thought to be co-infected with HDV, occurring either as a superinfection of chronic HBV infection or a concomitant acute coinfection of HBV and HDV (Hadziyannis, 1997). The pathogenesis of HDV infection is only poorly understood. Whereas clinical observations identified that hepatitis D could be an immune-mediated disease process, specific clinical cases suggested that HDV induces cytopathic infections (Nakano *et al.* 2001). Chronic Hepatitis D is

associated with a severe course of hepatitis, frequently leading to rapid fibrosis progression and the development of hepatocellular carcinoma (Wedemeyer & Manns, 2010).

4. Interplay of forces

The local induction of type I IFNs (IFN-α, -β) during the early phase of infection with HBV and HCV (Bigger *et al.* 2001; McClary *et al.* 2000) is crucially important as they are thought to limit HBV as well as HCV replication (Frese *et al.* 2001; Guidotti *et al.* 1994) while induction of IFN-γ during progression of viral infection may additionally inhibit viral replication (Frese *et al.* 2002; Guidotti *et al.* 1996).

4.1 Innate immunity against HBV

The role of the innate immune system during the early phase of HBV infection has been investigated in different experimental systems. Wieland *et al*. investigated the transcriptome of the liver in three chimpanzees during the course of acute HBV infection (Wieland *et al.* 2004)**.** Their analysis focused on two diverse groups of cellular genes: those in the early phase are associated with the innate immune response, and those in the late phase are associated with the adaptive immune response that terminates infection. They demonstrated that this virus does not induce any genes during entry and expansion, leading the authors to suggest that HBV is a 'stealth virus' in the early phase of infection. By contrast, a large number of IFN-γ-regulated genes are expressed in the liver during viral clearance (Figure 3). This upregulation of IFN-γ-regulated genes in livers results from the adaptive T cell response as specific T-cells infiltrating the liver are major producers of IFN-γ (Wieland *et al.* 2004). Thus, HBV and HCV infections strongly differ in the early phase of infection, as HCV induces a strong IFN-α response in chimpanzees (Su *et al.* 2002).

There are data to suggest that HBV actively inhibits the induction of an early IFN response. Wu *et al.* showed a regulatory effect of TLR-activated KC and LSEC on the *in vitro* replication of HBV in a co-culture model utilizing HBV-Met cells (Pasquetto *et al.* 2002). TLR3- and TLR4-activated KC as well as TLR3-activated LSEC induced a MyD88-independent response inhibiting HBV replication. While HBV replicative intermediates were highly suppressed, viral mRNAs as well as secretion of HBsAg and HBeAg remained largely unchanged. The HBV suppressing effect mediated by TLR3 ligands was caused by IFN-β whereas TLR4-activated KC additionally induced undefined cytokines with antiviral activity (Wu *et al.* 2007).

Further studies included co-culture experiments with hepatocytes or NPC and HBV-Met cell supernatants, HBsAg, HBeAg as well as HBV virions resulting in abrogation of TLR-induced antiviral activity, correlating with decreased activation of IRF-3, NFκB and ERK1/2. In comparison to primary hepatocytes, HBV-infected HBV-Met cells did not induce antiviral cytokines upon TLR activation. TLR-induced expression of TNF-α and IL-6 was suppressed in the presence of high amounts of HBV. Accordingly, suppression of HBV replication by siRNA leads to activation or expression of pro-inflammatory transcription factors and cytokines (Wu *et al.* 2008). These data might explain why HBV does not induce a strong initial type I IFN response such as HCV and, therefore, behaves as a 'stealth virus' (Wieland *et al.* 2004).

Despite of the fact that HBV does not induce an IFN response during the early phase of infection, it can be recognized by liver resident cells, thereby activating innate immune

responses without IFN induction. Hoesel *et al.* recently showed that HBV is recognized by hepatic NPC, mainly by Kupffer cells, upon infection of primary human liver cells *in vitro*. Within 3 hours, these cells release inflammatory cytokines including IL-1β, -6, -8 and TNF-α without inducing an IFN response. NFκB-dependent IL-6 secretion of activated KC is able to control HBV gene expression and replication in hepatocytes at the level of transcription. IL-6 leads to activation of MAPKs exogenous signal-regulated kinase (ERK) 1/2 and c-jun N-terminal kinase resulting in decreased expression of two transcription factors (hepatocyte nuclear factor (HNF) 1α and HNF 4α) that are essential for HBV gene expression and replication (Hoesel *et al.* 2009).

A recent publication studied the full replication cycle of hepatitis B virus (HBV) in primary hepatocyte cultures that were isolated from the northern treeshrew (*Tupaia belangeri*). The Tupaia model has been used to investigate the effect of cytokines on HBV infection. Stimulation of HBV infected primary Tupaia hepatocytes with recombinant Tupaia TNF-α led to viral suppression while covalently closed circular DNA and viral RNA were still detectable leading to the conclusion that TNF-α may also control HBV infection (Xu *et al.* 2011).

Consistently, Zhang *et al*. demonstrated that activation of cellular pathways by TLR ligands leads to inhibition of hepadnaviral replication (Zhang *et al.* 2009). Using the model of woodchuck hepatitis virus (WHV) infected primary hepatocytes (PWH), Poly I:C and LPS stimulation resulted in upregulation of cellular antiviral genes and TLRs. LPS stimulation led to a pronounced reduction of WHV replication intermediates without a significant IFN induction while Poly I:C transfection resulted in the production of IFN and a highly increased expression of antiviral genes in PWHs and slight inhibitory effect on WHV replication. LPS could activate NFκB, MAPK, and PI-3k/Akt pathways in PWHs. Furthermore, inhibitors of MAPK-ERK and PI-3k/Akt pathways, but not those of IFN signaling pathways, were able to block the antiviral effect of LPS. These results indicate that IFN-independent pathways which activated by LPS are able to down-regulate hepadnaviral replication in hepatocytes (Zhang *et al.* 2009).

A direct activation of cellular pathways through the expression of cellular adaptors involved in signaling has similar effects like the stimulation with TLR ligands. Guo *et al.* determined the effects of PRR-mediated innate immune response on HBV replication in hepatoma cell lines. Plasmids expressing TLR adaptors, MyD88, TRIF, or RIG-I/MDA5 adaptor or interferon promoter stimulator 1 (IPS-1) were transfected into cells and led to dramatic reduction of the levels of HBV mRNA and DNA in hepatoma cells. Analysis of involved signaling pathways revealed that activation of NFκB is required for all three adaptors to elicit antiviral response in both HepG2 and Huh7 cells while activation of IRF-3 is only essential for induction of antiviral response by IPS-1 in Huh7 cells (Guo *et al.* 2009).

Although recent publications consistently confirmed the antiviral role of TLR-mediated innate responses of hepatic cells, the antiviral mechanisms that are induced by activation of the TLR system are not fully understood. IFN-β has been identified as the major antiviral factor produced by NPCs in response to TLR3 and 4 ligands (Wu *et al.* 2007). Wieland *et al*. showed that IFN-β inhibits hepatitis B virus (HBV) replication by non-cytolytic mechanisms that either destabilize pregenomic (pg)RNA-containing capsids or prevent their assembly. Using a doxycycline (dox)-inducible HBV replication system, IFN-β pretreatment led to production of replication-competent pgRNA-containing capsids. The turnover rate of preformed HBV RNA-containing capsids is not changed in the presence of IFN-β or IFN-γ.

These conditions further inhibited pgRNA synthesis. Thus, type I and II IFNs prevent the formation of replication-competent HBV capsids (Wieland *et al.* 2005). IL-6 was shown to activate cellular signaling pathways in PHHs including the MAPK pathway and inhibit the HBV gene transcription (Hoesel *et al.* 2009). In PWHs infected with WHV, LPS activates the MAPK pathway and reduce the WHV replication, but unable to deplete WHV transcripts (Zhang *et al.* 2009). Future studies are necessary to clarify the mechanisms involved in TLR-mediated anti-HBV actions.

As TLR-mediated immune responses down regulate HBV replication, HBV developed mechanisms to counteract these antiviral functions. Hepatocytes and Kupffer cells isolated from liver biopsies of patients with chronic hepatitis B (CHB) showed significantly decreased expression of TLR2 on hepatocytes, KCs and peripheral monocytes in patients with HBeAg-positive CHB in comparison with HBeAg negative CHB and controls (steatosis patients). The level of TLR4 expression did not significantly differ between these groups. Hepatic cell lines harboring a recombinant baculovirus encoding HBV significantly reduced TNF-α expression as well as phospho-p38 kinase expression in the presence of HBeAg. Within the absence of HBeAg, HBV replication was associated with upregulation of the TLR2 pathway resulting in increased TNF-α expression (Visvanathan *et al.* 2007). Consistent with these findings, the TLR expression was significantly suppressed in liver tissue and PBMC of woodchucks chronically infected with WHV, assuming an important role of TLR2 during hepadnaviral infection and pathogenesis (Zhang *et al.* unpublished). HBV additionally blocked the gene expression of MyD88, an essential adaptor molecule in TLR-mediated innate immune responses. The terminal protein (TP) domain of the HBV polymerase was described to be responsible for this antagonistic activity. It is supposed that the HBV polymerase inhibits IFN-inducible MyD88 expression by blocking the nuclear translocation of STAT1 and therefore representing a general inhibitor of IFN signaling (Wu *et al.* 2007).

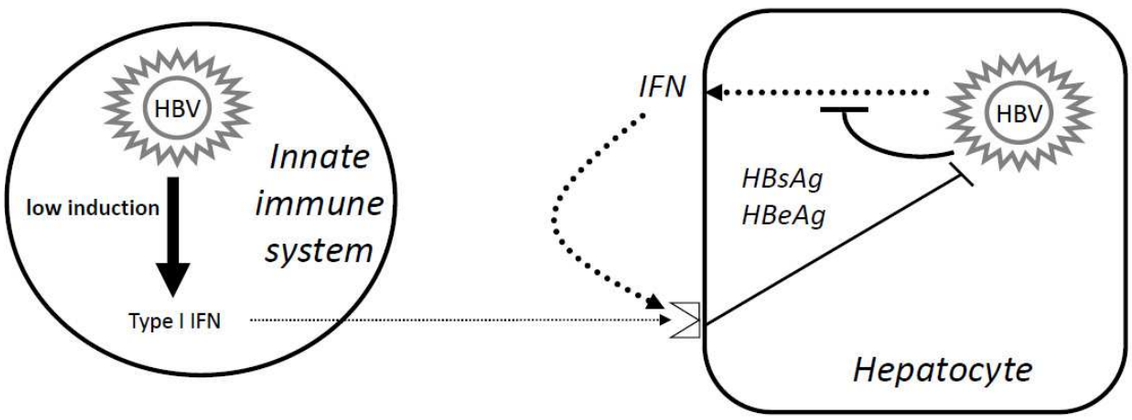


Fig. 3. Role of the innate immunity during pathogenesis of HBV
HBV infection only induces a weak type I IFN response. HBsAg or HBeAg inhibit endogenous expression of IFNs in the early phase of infection .Activated cells of the innate immune system may still produce type I IFNs , therefore limiting viral replication.

Isogawa *et al.* examined the ability of different TLRs to effect HBV replication *in vivo*. HBV transgenic mice have been injected with single doses of TLR2, -3, -4, -5, -7 and -9 ligands.

With the exception for TLR2, all of the ligands suppressed HBV replication in the liver in an IFN-α/-β-dependent manner (Isogawa *et al.* 2005). The potential of these TLR ligands to provoke the expression of antiviral cytokines at the site of HBV replication, leads to suggestion that TLR activation represents a powerful tool for novel therapeutic strategies in the treatment of chronic HBV infection.

4.2 Innate immunity against HCV

Standard treatment of HCV infection is the combination of pegylated type I IFN and ribavirin. Interferons are antiviral cytokines, produced after activation of the innate immune system during virus infection. Secretion of IFN leads neighbouring cells to switch to an 'antiviral state' and resists viral infection. Thus, an important role of the innate immune system is to limit viral replication and spread as well as to promote and orchestrate subsequent adaptive immune reactions. While the mechanisms that are utilized by the innate immune system to control HCV infection are not well defined, it is generally accepted that IFN signaling is likely to be involved. Viral proteins are able to potently activate the innate immune system. Nevertheless, HCV developed different mechanisms to evolve cellular, antiviral and innate immune responses, reflecting the adaptation to its host.

Molecular patterns within the 5′ as well as the 3′ non-translated region (NTR) of the HCV genome have been identified as retinoic acid inducible gene I (RIG-I) activating PAMPs. RIG-I is a well characterized PRR sensing and affecting HCV replication. Binding of viral double stranded RNA to the cytosolic RNA helicase RIG-I recruits the mitochondria-associated CARDIF protein, which induces IKKε/TBK1 kinases-mediated IRF-3 phosphorylation and thereby induces IFN-β expression. It is supposed that HCV RNA initiates IFN-β secretion in a RIG-I-dependent manner through its 5′ and 3′ NTR secondary structure (Saito *et al.* 2007; McCormick *et al.* 2004; Sumpter, Jr. *et al.* 2005). It has been additionally demonstrated that TLR3 is able to detect HCV structures in cultured hepatoma cells, leading to activation of IRF-3 and expression of ISGs, which limit HCV replication. The HCV motif that triggers TLR3 signaling remains to be characterized (Wang *et al.* 2009). It is suggested that RIG-I and TLR3 represent independent signaling pathways that are involved in IRF-3- and NFκB-mediated antiviral state during HCV infection (Alexopoulou *et al.* 2001; Yoneyama *et al.* 2004) (Figure 4).

In defiance of this immune activation HCV is able to subvert the antiviral activity of the innate immune system. Recent data suggested that the viral NS3/4A serine protease of the Hepatitis C virus may enable its persistent infection. The NS3/4A protein causes specific proteolysis of the TRIF adaptor molecule downstream the TLR3 signaling. It has been demonstrated that the viral NS3/4A protease additionally leads to disruption of RIG-I signaling. Therefore the viral NS3/4A protease cleaves CARDIF and abrogates IKKε/TBK1-mediated IFN-β secretion (Li *et al.* 2005; Foy *et al.* 2005; Foy *et al.* 2003; Breiman *et al.* 2005; Vilasco *et al.* 2006).

Broering *et al.* and Wang *et al.* investigated the antiviral capacity of TLR-activated KC, LSEC and HSC against HCV. Despite the expression of all TLRs, murine KC and LSEC only suppressed HCV replication in a co-culture model after activation of TLR3 and -4 which were mediated by IFN-β only (Broering *et al.* 2008). Similar results were obtained for murine HSC. Here, IFN-β was responsible for the antiviral activity of TLR3-stimulated HSC, whereas additional cytokines of undefined nature seem to be involved in the TLR4-mediated antiviral effect. In case of human HSC, only TLR3 stimulation led to production of

antiviral cytokines. HCV suppression was related to the upregulation of ISGs and RIG-I in target cells (Wang *et al.* 2009).

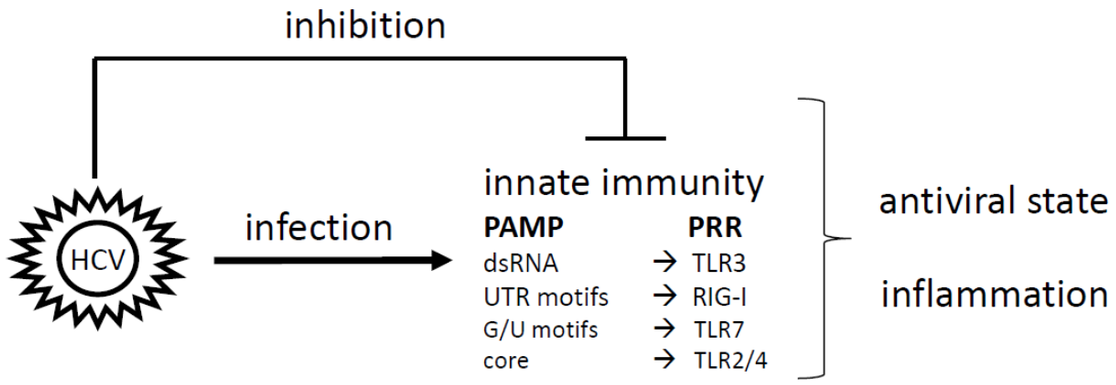


Fig. 4. HCV triggers innate immunity
Different structures of the hepatitis C virus can be detected by the innate immune system. This leads to cytokine secretion and induction of an antiviral state as well as inflammation processes. The virus developed evading strategies to subvert this antiviral state.

Recently established HCV cell culture models (Lindenbach *et al.* 2005; Wakita *et al.* 2005; Zhong *et al.* 2005) lead to the generation of infectious HCV particles. Zhang *et al.* generated cell culture derived HCV particles to study their immunomodulatory effects on freshly isolated PBMCs and pDCs obtained from healthy blood donors. While complete HCV particles were not able to induce cytokine production, purified HCV RNA led to immune stimulation, accompanied by enhanced TLR7 activation. It was suggested that the HCV RNA genome contains G/U-rich motifs which have immune-stimulatory capacity. It is hypothesized that HCV particles are digested by endosomal proteases, the uncoated viral genomes and therefore the G/U-rich motifs mediate TLR7 activation (Diebold *et al.* 2004; Jurk *et al.* 2002). Lee *et al.* additionally revealed an interaction between TLR7 and HCV, wherein TLR7 mediates interferon secretion as well as interferon-independent immune responses (Lee *et al.* 2006). Further analysis indicated a higher prevalence of single nucleotide polymorphisms (SNP) in TLR7 of patients chronically infected with HCV. These SNPs significantly correlates with the progression of liver fibrosis in patients with chronic HCV infection (Schott *et al.* 2007).
Another mechanism of HCV to evade the attack of the innate immune system targets TLR7. A significant decrease in TLR7 expression was shown in the presence of HCV *in vitro* and *in vivo* (Chang *et al.* 2010). It was proposed that HCV directly interferes with the transcriptional regulation of TLR7 mRNA. HCV replication level directly correlates with TLR7 expression, as reconstitution of TLR7 expression levels were achieved upon viral suppression. Despite this decrease in TLR7 mRNA in HCV-replicating cells, increased activation of IRF-7 was detected. This indicates that other PRR induce nuclear translocation of IRF-7 in HCV replicating cells (Chang *et al.* 2010).
Innate immunity is additionally activated by the HCV core protein leading to inflammation but failing to induce antiviral cytokines (Dolganiuc *et al.* 2004; Feldmann *et al.* 2006). Other studies have described that synthetic lipopeptide-complexes of the HCV core protein mediate the innate immune response through TLR2 and TLR4 (Duesberg *et al.* 2002). In

addition, an increased expression of some TLRs as well as inflammatory cytokines was shown in PBMC of chronically infected HCV patients (Sato *et al.* 2007).
Dolganiuc *et al.* identified pre-activated monocytes in patients with chronic hepatitis C. In this study, increased IFN-γ, endotoxin and HCV core protein seemed to modulate monocyte functions, resulting in the generation of MyD88/IRAK complexes, NFκB activation and increased expression of TNF-α. These findings lead the authors to suggest that LPS, HCV core protein and IFN-γ extend the activation of inflammatory monocytes/macrophages indicating a loss of TLR tolerance. These observations additionally lead to the assumption, that both host- as well as virus-derived factors influence macrophages to mediate persistent inflammation during chronic HCV infection (Dolganiuc *et al.* 2007).

4.2.1 Interferon response; friend or foe?

Elevated hepatic ISG expression in HCV infected chimpanzees as well as in patients was identified as a virus induced type I IFN response (Bigger *et al.* 2001; Bigger *et al.* 2004; Helbig *et al.* 2005). As already discussed HCV developed evading strategies to subvert the innate immune system. While infected cells are not able to sense the virus and subsequently secrete IFNs, it is supposed that the increased ISG expression during HCV infection is induced by an activated local innate immune system. Activation of the innate immune system, NPCs in particular, results in the expression and secretion of IFN-β. Type I IFNs bind to their cell surface receptor leading to conformational changes, which activate the Janus kinase - Signal Transducers and Activators of Transcription (JAK–STAT) signaling pathways. Downstream phosphorylation of STAT-1 and STAT-2 recruits a third factor (IRF-9) forming the transcription-complex ISG factor-3 (ISGF-3). ISGF-3 translocates into the nucleus and interacts with IFN stimulated response elements (ISRE) in the promoter regions of ISGs. Expression of selected ISGs may result in HCV eradication in acute hepatitis C infection (Bigger *et al.* 2001). However, progression of persistent HCV infection can be established due to escape strategies against the immune system which may also be responsible for non-response to therapies that are based upon the administration of exogenous IFNs (Sato *et al.* 2007).
A subgroup of ISGs has been described to directly suppress HCV replication. Protein kinase R (PKR) for example, phosphorylates the alpha subunit of the eukaryotic initiation factor (eIF)-2 leading to suppression of translational processes (Gale, Jr. *et al.* 1999; Pflugheber *et al.* 2002). The RNA-specific adenosine deaminase 1 (ADAR1) binds to dsRNA resulting in destabilization of secondary structures (Taylor *et al.* 2005). The antiviral function of 2′-5′ oligoadenylate synthetases (2′-5′ OAS) is mediated by the activation of the latently expressed endoribonuclease RNaseL, which induce degradation of viral and cellular RNA (Silverman, 1994; Zhou *et al.* 1997). ISG56 is an IRF-3 responsive gene that blocks one of the eIF3 subunits resulting in inhibition of translation (Wang *et al.* 2003; Hui *et al.* 2003; Terenzi *et al.* 2005). Additional ISGs affecting HCV replication have been identified during IFN therapy including MxA, ISG 6–16 and Viperin. The mechanisms of action of these host factors are still unclear (Bigger *et al.* 2004; Helbig *et al.* 2005; Suzuki *et al.* 2004).
HCV evolved mechanisms to influence this type I IFN response induced by the JAK–STAT signaling. The HCV polyprotein has been described as a strong inhibitor of IFN-α-induced signaling, as it impairs ISGF3 DNA binding. This effect is mediated by an increase in STAT1–protein inhibitor of activated STAT1 (PIAS1) association, resulting in the decreased transcriptional activity of ISGF3 through hypomethylation of STAT1 (Blindenbacher *et al.*

2003; Heim *et al.* 1999). In addition, also HCV core protein effects JAK-STAT signaling. The core protein induces STAT1 degradation, inhibits STAT1 activation/phosphorylation and increases the induction of suppressor of cytokine signaling (SOCS) proteins (Bode *et al.* 2003; Lin *et al.* 2005; Lin *et al.* 2006). Furthermore, the core protein suppresses the binding capacity of ISGF3 to the ISRE, resulting in decreased expression of anti-HCV effective ISG (de Lucas *et al.* 2005). Moreover, HCV proteins directly inhibit the antiviral action of selected ISGs. The envelope protein E2 and the non-structural protein NS5A have been reported as antagonists of PKR, leading to the disruption of translation control by IFNs (Gale, Jr. *et al.* 1998; Taylor *et al.* 1999).

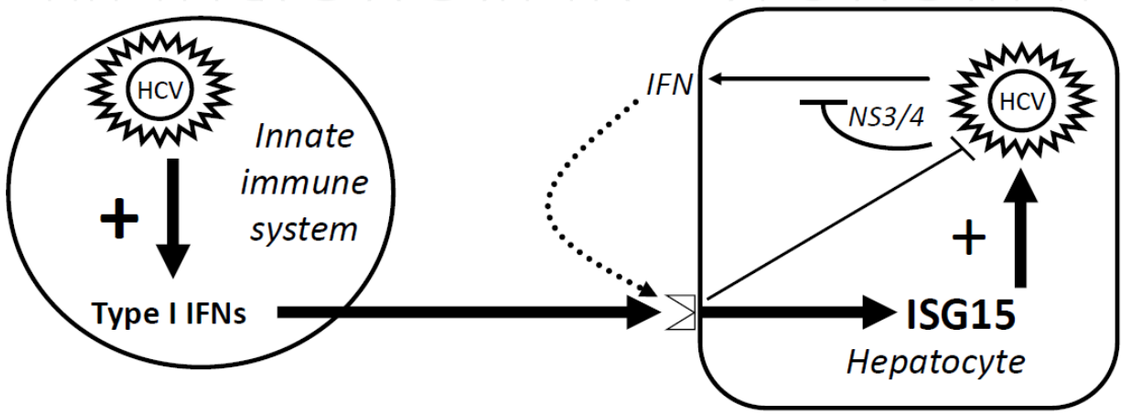


Fig. 5. Role of the innate immunity in the pathogenesis of HCV infection
HCV may directly induce type IFNs, while viral proteins like NS3/4 can inhibit endogenous expression of IFNs. Activated cells of the innate immune system might still produce type I IFNs resulting in increased ISG15 expression in infected cells and therefore promoting HCV replication.

The local type I IFN response induced by HCV seems to be paradox, as these interferons can inhibit HCV replication. In addition, patients that are non-responders to IFN-based therapies have highly elevated expression levels of a subset of ISGs compared to patients who cleared the virus (Asselah *et al.* 2008; Chen *et al.* 2005). ISG15, an ubiquitin-like modifier, is one of these genes. ISG15 is conjugated to a subset of target proteins. The functional consequence of this ISGylation is still unclear. ISGylated proteins are not degraded by the proteasome as ubiquitinylated proteins are (Malakhov *et al.* 2002; Ritchie & Zhang, 2004). Recently published data indicate that ISGylation negatively modulates interferon signaling (Chua *et al.* 2009; Broering *et al.* 2010), in addition ISGylation and ISG15 itself directly promote HCV replication (Chen *et al.* 2010; Broering *et al.* 2010). These observations may explain why elevated expression of ISGs, and ISG15 in particular, during HCV infection is beneficial for the hepatitis C virus (Figure 5).

4.3 Innate immunity against HDV

There are only few studies on the interaction of HDV with host innate responses. Like many other viruses, HDV seems to have developed anti-IFN-α strategies as it negatively affects the activation of IFN-α signaling by interfering the JAK-STAT signal transduction pathway. An early publication from McNair *et al.* demonstrated that neither IFN-α nor IFN-γ was able to inhibit HDV gene expression and formation of genomic and antigenomic RNA in cell

lines stably transfected HDV genomes (McNair *et al.* 1994). However, such cell lines showed no defect in upregulation of ISGs like PKR, 2'-5' OAS and IRF-1 or in induction of an antiviral status after IFN treatment. These cells were able to upregulate IFN-β after Poly I:C treatment. The presence of HDV RNA did not affect PKR function.

In contrast, Pugnale *et al*. showed in a transient tranfection system that hepatoma cells replicating HDV have an impaired response to IFN-α (Pugnale *et al.* 2009). By unknown mechanisms, the phosphorylation of both STAT-1 and STAT-2 was greatly impaired, consequently, both factors did not relocate into the nucleus. In addition, the IFN-α stimulated tyrosine phosphorylation of IFN receptor-associated JAK kinase Tyk2 was also inhibited by HDV, without affecting either the tyrosine phosphorylation of Jak1 or the expression of type I IFN receptor subunits. Both studies showed consistently that IFNs are not able to suppress HDV. Pugnale *et al.* could detect the inhibition of IFN signaling in HDV replicating cells, likely due to the higher levels of viral RNA and proteins in the transient transfection system (Pugnale *et al.* 2009). Despite of the dsRNA nature of HDV genomic and antigenomic RNAs, there was no apparent activation of IFN pathways in the stably transfected cell lines, indicating that HDV RNA may be sequestered during replication (McNair *et al.* 1994).

Another report demonstrated that large HDV antigen (L-HDAg) may enhance the ISG MxA more than 3-fold. However, the upregulation of MxA by IFN-α is generally very strong and may reach levels of more than 100-fold compared to unstimulated controls. Thus, the ability of L-HDAg to activate ISG expression is rather low (Williams *et al.* 2009). Thus, HDV is a weak inducer of cellular IFN responses and is likely able to inhibit IFN signaling. In addition, it has also been reported that IFN-α inducible protein ADAR1 modulates HDV gene expression and genome replication by editing the HDV genome (Hartwig *et al.* 2004).

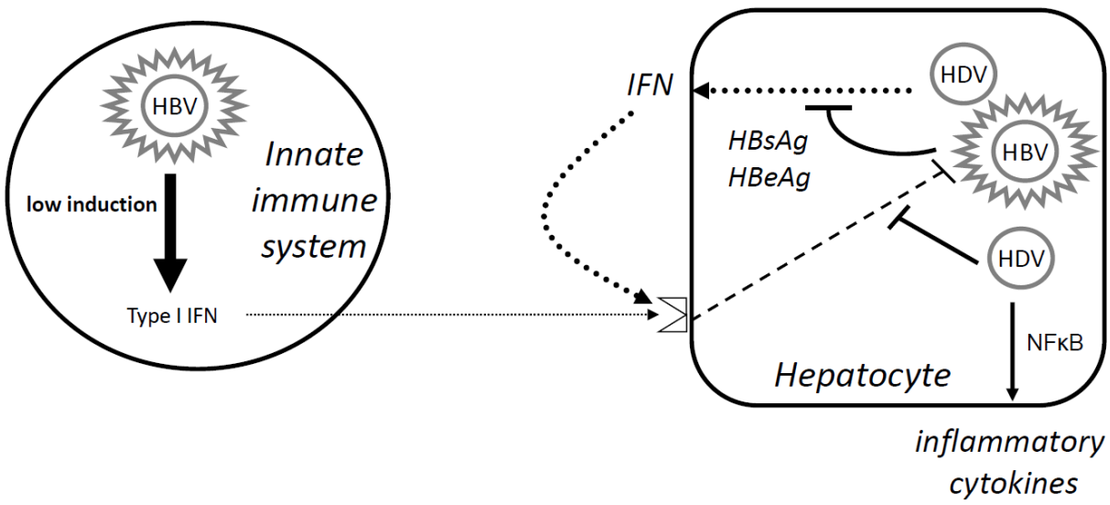


Fig. 6. Role of the innate immunity during pathogenesis of HBV HDV coinfection
HBV as well as HDV only induce a weak type IFN response. HBsAg or HBeAg are supposed to inhibit endogenous expression of IFNs. Activated cells of the innate immune system might still produce type I IFNs. HDV is able to block JAK/STAT signaling, thereby subverting the IFN response. HDV additionally promotes NFκB activation and secretion of inflammatory cytokines.

NFκB activation is involved in many inflammatory processes and in cancer. The L-HDAg has been shown to mediate TNF-α-induced NFκB signaling, probably through the direct association with TRAF2, a protein implicating the early signaling events (Park *et al.* 2009). Several studies revealed a relationship between L-HDAg, S-HDAg, genomic RNA or antigenomic RNA and the proteome of the cell (Mota *et al.* 2009; Mota *et al.* 2008). Modified expression profile of proteins involving regulation of nucleic acid and protein metabolism, energy pathways, signal transduction, transport, apoptosis and cell growth were found. Host factors involved in HDV replication have been determind using a small inhibitory RNA (siRNA) screening. Cells stably trasfected with the S-HDAg were treated with siRNA before HDV infection (Cao *et al.* 2009). It has been reported that a part of the genome, described as an RNA promoter, directy interacts with some cellular proteins (Beard *et al.* 1996) (Figure 6).

It could be demonstrated that two of these host factors, the eukaryotic translation elongation factor 1 alpha 1 (eEF1A1) and the glyceraldehyde-3-phosphate dehydrogenase (GAPDH), are involved in RNA processing and in the translation machinery. Of note, these genes are often considered and used as housekeeping genes (Sikora *et al.* 2009).

5. Coinfection of HBV and HCV

Clinical investigations on disease outcomes and progression in patients coinfected with HBV and HCV are diverse and contradictory. Viral interference or reciprocal replicative suppression of the two viruses probably occurs (Liaw *et al.* 1994; Zarski *et al.* 1998). Due to a missing model system for HBV/HCV coinfection in the past, virological and molecular aspects are poorly understood (Brass & Moradpour, 2009). Resent studies investigated the mechanisms of HBV and HCV coinfection by heterologous overexpression of viral proteins, leading to conflicting results. It has been demonstrated that the HCV core protein and NS5A negatively regulate HBV replication, whereas other studies could not confirm these findings (Pasquinelli *et al.* 1997; Chen *et al.* 2003; Schuttler *et al.* 2002).

It seems to be important to address the question whether direct interference occurs between the viruses in order to understand the disease progression. Recent studies have addressed this issue (Eyre *et al.* 2009; Bellecave *et al.* 2009). The human hepatoma cell line Huh-7 supports HBV replication and formation of HBV virions. Huh-7 cells also can be used to study the HCV life cycle, including viral entry, RNA replication and release of infectious particles. Using this cell culture system, these authors independently showed that HBV and HCV are able to replicate in the same cell, without showing interfering processes. HBV replicating cells can be infected with cell culture-derived HCV resulting in secretion of infectious HCV. In addition, the inhibition of one of these viruses did not influence the replication of the other. It is well known that HBV replication, for example, may be suppressed in the presence of replicative HCV infection while eradication of HCV may lead to replicative activity of HBV infection. This phenomenon may be explained by the fact that HCV may induce local IFN production by NPCs through activation of TLR3 which may lead to suppression of HBV replication (Broering *et al.* 2008; Wu *et al.* 2007) (Figure 7).

6. Conclusions

TLRs have been identified as key regulators of innate and adaptive immune responses in the liver as they play a critical role in the pathogenesis and progression of many liver diseases

as well as in the regulation of tissue injury and wound healing processes. The local innate immune system represented by hepatocytes, liver sinusoidal endothelial cells, Kupffer cells and stellate cells, for example, is involved in the induction of systemic tolerance or inflammation and additionally cross-talks to the adaptive immune system. It has been suggested that the local innate immune system is of importance in the progression of HBV or HCV infection. PRRs, especially TLRs play a pivotal role in the pathogenesis of viral hepatitis due to their rapid signal transduction. It has been clearly demonstrated that TLRs participate in antiviral immunity.

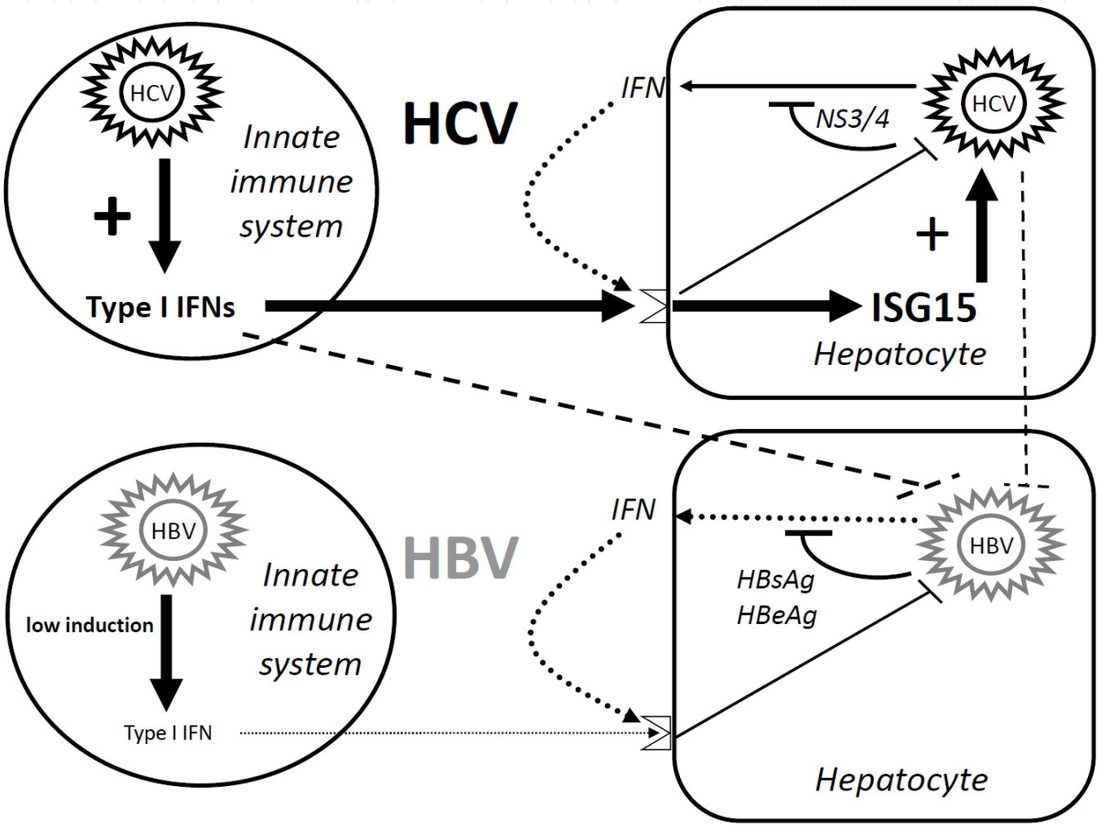


Fig. 7. Role of the innate immunity during pathogenesis of viral hepatitis
HCV infection directly induces type IFNs, later viral proteins like NS3/4 inhibits endogenous expression of IFNs. Activated cells of the innate immune system might still produce type I IFNs resulting in increased ISG15 expression in infected cells and therefore promoting HCV replication. HBV likewise seems to inhibit endogenous IFN expression, additionally inhibiting TLR activation in the local immune system. This may explain way HCV but not HBV induce an initial type I IFN response during acute infection. In case of HBV/HCV co-infection, HCV-activated NPC may inhibit HBV replication by the production of type I IFNs.

As a consequence, various evading strategies have been evolved by hepatitis viruses (HBV, HCV and HDV) to counteract these antiviral activities:
The hepatic innate immune system is able to sense PAMP structures of these hepatotropic viruses, resulting in secretion of antiviral cytokines, in particular interferons, and therefore

limits viral replication. Conversely, the hepatitis viruses may counteract and subvert the innate immunity by evolutionary adaptation.

The Hepatitis B virus for example developed a mechanism to block the expression of interferon sensitive genes, especially MyD88, an adaptor molecule involved in mostly all of the TLR signaling parthways. In addition HBV evades the TLR2 signaling, which results in limitation of viral replication, by directly decreasing its expression. These evasion strategies may explain the absence of an antiviral response during infection and the description as a 'stealth virus'. Coinfection with Hepatitis D virus is additionally accompanied by further evasion of the IFN response.

In contrast to this Hepatitis C virus initially induces a strong type I IFN response. However, the virus is able to control this antiviral signaling by evasion strategies directly targeting the TLR3 or RIG-I pathway, which initiate IFN-β expression. In addition, HCV developed different mechanisms to block the JAK-STAT signaling, resulting in abrogation of the IFN response, in particular the expression of ISGs with antiviral functions. HCV paradoxically needs one of these response genes, ISG15, which promotes HCV replication and negatively regulates the IFN response.

These evolutionary developed adaptations of HBC, HCV and HDV to their host invert the benefits of the antiviral response, induced by the local innate immune system. The inadequate but consistent activation of the hepatic innate immunity results in tolerance induction and permits progression of viral persistence and chronic infections. Therefore, therapeutic manipulations of the hepatic TLR pathways are of high interest for the development of novel treatment strategies.

7. References

Aggarwal, R., Naik, S. 2009, Epidemiology of hepatitis E: current status, J. Gastroenterol. Hepatol., 24(9), pp. 1484-1493.

Akira, S., Takeda, K. 2004, Toll-like receptor signalling, Nat.Rev.Immunol., 4(7), pp. 499-511.

Akira, S., Uematsu, S., Takeuchi, O. 2006, Pathogen recognition and innate immunity, Cell, 124(4), pp. 783-801.

Alexopoulou, L., Holt, A. C., Medzhitov, R., Flavell, R. A. 2001, Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3, Nature, 413(6857), pp. 732-738.

Alter, M. J. 2007, Epidemiology of hepatitis C virus infection, World J.Gastroenterol., 13(17), pp. 2436-2441.

Asselah, T., Bieche, I., Narguet, S., Sabbagh, A., Laurendeau, I., Ripault, M. P., Boyer, N., Martinot-Peignoux, M., Valla, D., Vidaud, M., Marcellin, P. 2008, Liver gene expression signature to predict response to pegylated interferon plus ribavirin combination therapy in patients with chronic hepatitis C, Gut, 57(4), pp. 516-524.

Bacon, B. R., Gordon, S. C., Lawitz, E., Marcellin, P., Vierling, J. M., Zeuzem, S., Poordad, F., Goodman, Z. D., Sings, H. L., Boparai, N., Burroughs, M., Brass, C. A., Albrecht, J. K., Esteban, R. 2011, Boceprevir for previously treated chronic HCV genotype 1 infection, N.Engl.J.Med., 364(13), pp. 1207-1217.

Beard, M. R., MacNaughton, T. B., Gowans, E. J. 1996, Identification and characterization of a hepatitis delta virus RNA transcriptional promoter, J.Virol., 70(8), pp. 4986-4995.

Bellecave, P., Gouttenoire, J., Gajer, M., Brass, V., Koutsoudakis, G., Blum, H. E., Bartenschlager, R., Nassal, M., Moradpour, D. 2009, Hepatitis B and C virus

coinfection: a novel model system reveals the absence of direct viral interference, Hepatology, 50(1), pp. 46-55.

Bertoletti, A., Gehring, A. J. 2006, The immune response during hepatitis B virus infection, J.Gen.Virol., 87(Pt 6), pp. 1439-1449.

Bigger, C. B., Brasky, K. M., Lanford, R. E. 2001, DNA microarray analysis of chimpanzee liver during acute resolving hepatitis C virus infection, J.Virol., 75(15), pp. 7059-7066.

Bigger, C. B., Guerra, B., Brasky, K. M., Hubbard, G., Beard, M. R., Luxon, B. A., Lemon, S. M., Lanford, R. E. 2004, Intrahepatic gene expression during chronic hepatitis C virus infection in chimpanzees, J.Virol., 78(24), pp. 13779-13792.

Biron, C. A. 1998, Role of early cytokines, including alpha and beta interferons (IFN-alpha/beta), in innate and adaptive immune responses to viral infections, Semin.Immunol., 10(5), pp. 383-390.

Blindenbacher, A., Duong, F. H., Hunziker, L., Stutvoet, S. T., Wang, X., Terracciano, L., Moradpour, D., Blum, H. E., Alonzi, T., Tripodi, M., La, M. N., Heim, M. H. 2003, Expression of hepatitis c virus proteins inhibits interferon alpha signaling in the liver of transgenic mice, Gastroenterology, 124(5), pp. 1465-1475.

Bode, J. G., Ludwig, S., Ehrhardt, C., Albrecht, U., Erhardt, A., Schaper, F., Heinrich, P. C., Haussinger, D. 2003, IFN-alpha antagonistic activity of HCV core protein involves induction of suppressor of cytokine signaling-3, FASEB J., 17(3), pp. 488-490.

Brass, V., Moradpour, D. 2009, New insights into hepatitis B and C virus co-infection, J.Hepatol., 51(3), pp. 423-425.

Breiman, A., Grandvaux, N., Lin, R., Ottone, C., Akira, S., Yoneyama, M., Fujita, T., Hiscott, J., Meurs, E. F. 2005, Inhibition of RIG-I-dependent signaling to the interferon pathway during hepatitis C virus expression and restoration of signaling by IKKepsilon, J.Virol., 79(7), pp. 3969-3978.

Broering, R., Wu, J., Meng, Z., Hilgard, P., Lu, M., Trippler, M., Szczeponek, A., Gerken, G., Schlaak, J. F. 2008, Toll-like receptor-stimulated non-parenchymal liver cells can regulate hepatitis C virus replication, J.Hepatol., 48(6), pp. 914-922.

Broering, R., Zhang, X., Kottilil, S., Trippler, M., Jiang, M., Lu, M., Gerken, G., Schlaak, J. F. 2010, The interferon stimulated gene 15 functions as a proviral factor for the hepatitis C virus and as a regulator of the IFN response, Gut, 59(8), pp. 1111-1119.

Cao, D., Haussecker, D., Huang, Y., Kay, M. A. 2009, Combined proteomic-RNAi screen for host factors involved in human hepatitis delta virus replication, RNA., 15(11), pp. 1971-1979.

Chang, S., Kodys, K., Szabo, G. 2010a, Impaired expression and function of toll-like receptor 7 in hepatitis C virus infection in human hepatoma cells, Hepatology, 51(1), pp. 35-42.

Chen, L., Borozan, I., Feld, J., Sun, J., Tannis, L. L., Coltescu, C., Heathcote, J., Edwards, A. M., McGilvray, I. D. 2005, Hepatic gene expression discriminates responders and nonresponders in treatment of chronic hepatitis C viral infection, Gastroenterology, 128(5), pp. 1437-1444.

Chen, L., Sun, J., Meng, L., Heathcote, J., Edwards, A. M., McGilvray, I. D. 2010, ISG15, a ubiquitin-like interferon-stimulated gene, promotes hepatitis C virus production in vitro: implications for chronic infection and response to treatment, J.Gen.Virol., 91(Pt 2), pp. 382-388.

Chen, S. Y., Kao, C. F., Chen, C. M., Shih, C. M., Hsu, M. J., Chao, C. H., Wang, S. H., You, L. R., Lee, Y. H. 2003, Mechanisms for inhibition of hepatitis B virus gene expression and replication by hepatitis C virus core protein, J.Biol.Chem., 278(1), pp. 591-607.

Chua, P. K., McCown, M. F., Rajyaguru, S., Kular, S., Varma, R., Symons, J., Chiu, S. S., Cammack, N., Najera, I. 2009, Modulation of the Interferon {alpha} Anti-Hepatitis C Virus Activity by ISG15, J.Gen.Virol..

de Lucas S., Bartolome, J., Carreno, V. 2005, Hepatitis C virus core protein down-regulates transcription of interferon-induced antiviral genes, J.Infect.Dis., 191(1), pp. 93-99.

Di Bisceglie, A. M. 1997, Hepatitis C and hepatocellular carcinoma, Hepatology, 26(3 Suppl 1), pp. 34S-38S.

Di Bisceglie, A. M. 1998, Hepatitis C, Lancet, 351(9099), pp. 351-355.

Diebold, S. S., Kaisho, T., Hemmi, H., Akira, S., Reis e Sousa 2004, Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA, Science, 303(5663), pp. 1529-1531.

Dolganiuc, A., Norkina, O., Kodys, K., Catalano, D., Bakis, G., Marshall, C., Mandrekar, P., Szabo, G. 2007, Viral and host factors induce macrophage activation and loss of toll-like receptor tolerance in chronic HCV infection, Gastroenterology, 133(5), pp. 1627-1636.

Dolganiuc, A., Oak, S., Kodys, K., Golenbock, D. T., Finberg, R. W., Kurt-Jones, E., Szabo, G. 2004, Hepatitis C core and nonstructural 3 proteins trigger toll-like receptor 2-mediated pathways and inflammatory activation, Gastroenterology, 127(5), pp. 1513-1524.

Duesberg, U., von dem, B. A., Kirschning, C., Miyake, K., Sauerbruch, T., Spengler, U. 2002, Cell activation by synthetic lipopeptides of the hepatitis C virus (HCV)--core protein is mediated by toll like receptors (TLRs) 2 and 4, Immunol.Lett., 84(2), pp. 89-95.

Epstein, J., Eichbaum, Q., Sheriff, S., Ezekowitz, R. A. 1996, The collectins in innate immunity, Curr.Opin.Immunol., 8(1), pp. 29-35.

Eyre, N. S., Phillips, R. J., Bowden, S., Yip, E., Dewar, B., Locarnini, S. A., Beard, M. R. 2009, Hepatitis B virus and hepatitis C virus interaction in Huh-7 cells, J.Hepatol., 51(3), pp. 446-457.

Fearon, D. T., Locksley, R. M. 1996, The instructive role of innate immunity in the acquired immune response, Science, 272(5258), pp. 50-53.

Feldmann, G., Nischalke, H. D., Nattermann, J., Banas, B., Berg, T., Teschendorf, C., Schmiegel, W., Duhrsen, U., Halangk, J., Iwan, A., Sauerbruch, T., Caselmann, W. H., Spengler, U. 2006, Induction of interleukin-6 by hepatitis C virus core protein in hepatitis C-associated mixed cryoglobulinemia and B-cell non-Hodgkin's lymphoma, Clin.Cancer Res., 12(15), pp. 4491-4498.

Foy, E., Li, K., Sumpter, R., Jr., Loo, Y. M., Johnson, C. L., Wang, C., Fish, P. M., Yoneyama, M., Fujita, T., Lemon, S. M., Gale, M., Jr. 2005, Control of antiviral defenses through hepatitis C virus disruption of retinoic acid-inducible gene-I signaling, Proc.Natl.Acad.Sci.U.S.A, 102(8), pp. 2986-2991.

Foy, E., Li, K., Wang, C., Sumpter, R., Jr., Ikeda, M., Lemon, S. M., Gale, M., Jr. 2003, Regulation of interferon regulatory factor-3 by the hepatitis C virus serine protease, Science, 300(5622), pp. 1145-1148.

Frese, M., Pietschmann, T., Moradpour, D., Haller, O., Bartenschlager, R. 2001, Interferon-alpha inhibits hepatitis C virus subgenomic RNA replication by an MxA-independent pathway, J.Gen.Virol., 82(Pt 4), pp. 723-733.

Frese, M., Schwarzle, V., Barth, K., Krieger, N., Lohmann, V., Mihm, S., Haller, O., Bartenschlager, R. 2002, Interferon-gamma inhibits replication of subgenomic and genomic hepatitis C virus RNAs, Hepatology, 35(3), pp. 694-703.

Gale, M., Jr., Blakely, C. M., Kwieciszewski, B., Tan, S. L., Dossett, M., Tang, N. M., Korth, M. J., Polyak, S. J., Gretch, D. R., Katze, M. G. 1998, Control of PKR protein kinase by hepatitis C virus nonstructural 5A protein: molecular mechanisms of kinase regulation, Mol.Cell Biol., 18(9), pp. 5208-5218.

Gale, M., Jr., Kwieciszewski, B., Dossett, M., Nakao, H., Katze, M. G. 1999, Antiapoptotic and oncogenic potentials of hepatitis C virus are linked to interferon resistance by viral repression of the PKR protein kinase, J.Virol., 73(8), pp. 6506-6516.

Guidotti, L. G., Guilhot, S., Chisari, F. V. 1994, Interleukin-2 and alpha/beta interferon down-regulate hepatitis B virus gene expression in vivo by tumor necrosis factor-dependent and -independent pathways, J.Virol., 68(3), pp. 1265-1270.

Guidotti, L. G., Ishikawa, T., Hobbs, M. V., Matzke, B., Schreiber, R., Chisari, F. V. 1996, Intracellular inactivation of the hepatitis B virus by cytotoxic T lymphocytes, Immunity., 4(1), pp. 25-36.

Guo, H., Jiang, D., Ma, D., Chang, J., Dougherty, A. M., Cuconati, A., Block, T. M., Guo, J. T. 2009, Activation of pattern recognition receptor-mediated innate immunity inhibits the replication of hepatitis B virus in human hepatocyte-derived cells, J.Virol., 83(2), pp. 847-858.

Hadziyannis, S. J. 1997, Review: hepatitis delta, J.Gastroenterol.Hepatol., 12(4), pp. 289-298.

Hartwig, D., Schoeneich, L., Greeve, J., Schutte, C., Dorn, I., Kirchner, H., Hennig, H. 2004, Interferon-alpha stimulation of liver cells enhances hepatitis delta virus RNA editing in early infection, J.Hepatol., 41(4), pp. 667-672.

Hayashi, P. H., Zeldis, J. B. 1993, Molecular biology of viral hepatitis and hepatocellular carcinoma, Compr.Ther., 19(5), pp. 188-196.

Heim, M. H., Moradpour, D., Blum, H. E. 1999, Expression of hepatitis C virus proteins inhibits signal transduction through the Jak-STAT pathway, J.Virol., 73(10), pp. 8469-8475.

Helbig, K. J., Lau, D. T., Semendric, L., Harley, H. A., Beard, M. R. 2005, Analysis of ISG expression in chronic hepatitis C identifies viperin as a potential antiviral effector, Hepatology, 42(3), pp. 702-710.

Honda, K., Taniguchi, T. 2006, IRFs: master regulators of signalling by Toll-like receptors and cytosolic pattern-recognition receptors, Nat.Rev.Immunol., 6(9), pp. 644-658.

Hoesel, M., Quasdorff, M., Wiegmann, K., Webb, D., Zedler, U., Broxtermann, M., Tedjokusumo, R., Esser, K., Arzberger, S., Kirschning, C. J., Langenkamp, A., Falk, C., Buning, H., Rose-John, S., Protzer, U. 2009b, Not interferon, but interleukin-6 controls early gene expression in hepatitis B virus infection, Hepatology, 50(6), pp. 1773-1782.

Hui, D. J., Bhasker, C. R., Merrick, W. C., Sen, G. C. 2003, Viral stress-inducible protein p56 inhibits translation by blocking the interaction of eIF3 with the ternary complex eIF2.GTP.Met-tRNAi, J.Biol.Chem., 278(41), pp. 39477-39482.

Isogawa, M., Robek, M. D., Furuichi, Y., Chisari, F. V. 2005, Toll-like receptor signaling inhibits hepatitis B virus replication in vivo, J.Virol., 79(11), pp. 7269-7272.

Jacobson, I. M., McHutchison, J. G., Dusheiko, G., Di Bisceglie, A. M., Reddy, K. R., Bzowej, N. H., Marcellin, P., Muir, A. J., Ferenci, P., Flisiak, R., George, J., Rizzetto, M., Shouval, D., Sola, R., Terg, R. A., Yoshida, E. M., Adda, N., Bengtsson, L., Sankoh, A. J., Kieffer, T. L., George, S., Kauffman, R. S., Zeuzem, S. 2011, Telaprevir for previously untreated chronic hepatitis C virus infection, N.Engl.J.Med., 364(25), pp. 2405-2416.

Jurk, M., Heil, F., Vollmer, J., Schetter, C., Krieg, A. M., Wagner, H., Lipford, G., Bauer, S. 2002, Human TLR7 or TLR8 independently confer responsiveness to the antiviral compound R-848, Nat.Immunol., 3(6), p. 499.

Kimura, K., Kakimi, K., Wieland, S., Guidotti, L. G., Chisari, F. V. 2002, Activated intrahepatic antigen-presenting cells inhibit hepatitis B virus replication in the liver of transgenic mice, J.Immunol., 169(9), pp. 5188-5195.

Knolle, P. A., Gerken, G. 2000, Local control of the immune response in the liver, Immunol.Rev., 174, pp. 21-34.

Lee, J., Wu, C. C., Lee, K. J., Chuang, T. H., Katakura, K., Liu, Y. T., Chan, M., Tawatao, R., Chung, M., Shen, C., Cottam, H. B., Lai, M. M., Raz, E., Carson, D. A. 2006, Activation of anti-hepatitis C virus responses via Toll-like receptor 7, Proc.Natl.Acad.Sci.U.S.A, 103(6), pp. 1828-1833.

Li, K., Foy, E., Ferreon, J. C., Nakamura, M., Ferreon, A. C., Ikeda, M., Ray, S. C., Gale, M., Jr., Lemon, S. M. 2005, Immune evasion by hepatitis C virus NS3/4A protease-mediated cleavage of the Toll-like receptor 3 adaptor protein TRIF, Proc.Natl.Acad.Sci.U.S.A, 102(8), pp. 2992-2997.

Liaw, Y. F., Tsai, S. L., Chang, J. J., Sheen, I. S., Chien, R. N., Lin, D. Y., Chu, C. M. 1994, Displacement of hepatitis B virus by hepatitis C virus as the cause of continuing chronic hepatitis, Gastroenterology, 106(4), pp. 1048-1053.

Lin, W., Choe, W. H., Hiasa, Y., Kamegaya, Y., Blackard, J. T., Schmidt, E. V., Chung, R. T. 2005, Hepatitis C virus expression suppresses interferon signaling by degrading STAT1, Gastroenterology, 128(4), pp. 1034-1041.

Lin, W., Kim, S. S., Yeung, E., Kamegaya, Y., Blackard, J. T., Kim, K. A., Holtzman, M. J., Chung, R. T. 2006, Hepatitis C virus core protein blocks interferon signaling by interaction with the STAT1 SH2 domain, J.Virol., 80(18), pp. 9226-9235.

Lindenbach, B. D., Evans, M. J., Syder, A. J., Wolk, B., Tellinghuisen, T. L., Liu, C. C., Maruyama, T., Hynes, R. O., Burton, D. R., McKeating, J. A., Rice, C. M. 2005, Complete replication of hepatitis C virus in cell culture, Science, 309(5734), pp. 623-626.

Malakhov, M. P., Malakhova, O. A., Kim, K. I., Ritchie, K. J., Zhang, D. E. 2002, UBP43 (USP18) specifically removes ISG15 from conjugated proteins, J.Biol.Chem., 277(12), pp. 9976-9981.

Manns, M. P., McHutchison, J. G., Gordon, S. C., Rustgi, V. K., Shiffman, M., Reindollar, R., Goodman, Z. D., Koury, K., Ling, M., Albrecht, J. K. 2001, Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial, Lancet, 358(9286), pp. 958-965.

McClary, H., Koch, R., Chisari, F. V., Guidotti, L. G. 2000, Relative sensitivity of hepatitis B virus and other hepatotropic viruses to the antiviral effects of cytokines, J.Virol., 74(5), pp. 2255-2264.

McCormick, C. J., Challinor, L., Macdonald, A., Rowlands, D. J., Harris, M. 2004, Introduction of replication-competent hepatitis C virus transcripts using a

tetracycline-regulable baculovirus delivery system, J.Gen.Virol., 85(Pt 2), pp. 429-439.

McNair, A. N., Cheng, D., Monjardino, J., Thomas, H. C., Kerr, I. M. 1994, Hepatitis delta virus replication in vitro is not affected by interferon-alpha or -gamma despite intact cellular responses to interferon and dsRNA, J.Gen.Virol., 75 (Pt 6), pp. 1371-1378.

Medzhitov, R. 2001, Toll-like receptors and innate immunity, Nat.Rev.Immunol., 1(2), pp. 135-145.

Medzhitov, R., Janeway, C., Jr. 2000, Innate immune recognition: mechanisms and pathways, Immunol.Rev., 173, pp. 89-97.

Mota, S., Mendes, M., Freitas, N., Penque, D., Coelho, A. V., Cunha, C. 2009, Proteome analysis of a human liver carcinoma cell line stably expressing hepatitis delta virus ribonucleoproteins, J.Proteomics., 72(4), pp. 616-627.

Mota, S., Mendes, M., Penque, D., Coelho, A. V., Cunha, C. 2008, Changes in the proteome of Huh7 cells induced by transient expression of hepatitis D virus RNA and antigens, J.Proteomics., 71(1), pp. 71-79.

Nakano, T., Shapiro, C. N., Hadler, S. C., Casey, J. L., Mizokami, M., Orito, E., Robertson, B. H. 2001, Characterization of hepatitis D virus genotype III among Yucpa Indians in Venezuela, J.Gen.Virol., 82(Pt 9), pp. 2183-2189.

Park, C. Y., Oh, S. H., Kang, S. M., Lim, Y. S., Hwang, S. B. 2009, Hepatitis delta virus large antigen sensitizes to TNF-alpha-induced NF-kappaB signaling, Mol.Cells, 28(1), pp. 49-55.

Pasquetto, V., Wieland, S. F., Uprichard, S. L., Tripodi, M., Chisari, F. V. 2002, Cytokine-sensitive replication of hepatitis B virus in immortalized mouse hepatocyte cultures, J.Virol., 76(11), pp. 5646-5653.

Pasquinelli, C., Shoenberger, J. M., Chung, J., Chang, K. M., Guidotti, L. G., Selby, M., Berger, K., Lesniewski, R., Houghton, M., Chisari, F. V. 1997, Hepatitis C virus core and E2 protein expression in transgenic mice, Hepatology, 25(3), pp. 719-727.

Perrault, M., Pecheur, E. I. 2009, The hepatitis C virus and its hepatic environment: a toxic but finely tuned partnership, Biochem.J., 423(3), pp. 303-314.

Pflugheber, J., Fredericksen, B., Sumpter, R., Jr., Wang, C., Ware, F., Sodora, D. L., Gale, M., Jr. 2002, Regulation of PKR and IRF-1 during hepatitis C virus RNA replication, Proc.Natl.Acad.Sci.U.S.A, 99(7), pp. 4650-4655.

Poordad, F., McCone, J., Jr., Bacon, B. R., Bruno, S., Manns, M. P., Sulkowski, M. S., Jacobson, I. M., Reddy, K. R., Goodman, Z. D., Boparai, N., DiNubile, M. J., Sniukiene, V., Brass, C. A., Albrecht, J. K., Bronowicki, J. P. 2011, Boceprevir for untreated chronic HCV genotype 1 infection, N.Engl.J.Med., 364(13), pp. 1195-1206.

Preiss, S., Thompson, A., Chen, X., Rodgers, S., Markovska, V., Desmond, P., Visvanathan, K., Li, K., Locarnini, S., Revill, P. 2008, Characterization of the innate immune signalling pathways in hepatocyte cell lines, J.Viral Hepat., 15(12), pp. 888-900.

Pugnale, P., Pazienza, V., Guilloux, K., Negro, F. 2009, Hepatitis delta virus inhibits alpha interferon signaling, Hepatology, 49(2), pp. 398-406.

Racanelli, V., Rehermann, B. 2006, The liver as an immunological organ, Hepatology, 43(2 Suppl 1), p. S54-S62.

Ritchie, K. J., Zhang, D. E. 2004, ISG15: the immunological kin of ubiquitin, Semin.Cell Dev.Biol., 15(2), pp. 237-246.

Rizzetto, M., Canese, M. G., Arico, S., Crivelli, O., Trepo, C., Bonino, F., Verme, G. 1977, Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers, Gut, 18(12), pp. 997-1003.

Rizzetto, M., Hoyer, B., Canese, M. G., Shih, J. W., Purcell, R. H., Gerin, J. L. 1980, delta Agent: association of delta antigen with hepatitis B surface antigen and RNA in serum of delta-infected chimpanzees, Proc.Natl.Acad.Sci.U.S.A, 77(10), pp. 6124-6128.

Saito, T., Hirai, R., Loo, Y. M., Owen, D., Johnson, C. L., Sinha, S. C., Akira, S., Fujita, T., Gale, M., Jr. 2007, Regulation of innate antiviral defenses through a shared repressor domain in RIG-I and LGP2, Proc.Natl.Acad.Sci.U.S.A, 104(2), pp. 582-587.

Sato, K., Ishikawa, T., Okumura, A., Yamauchi, T., Sato, S., Ayada, M., Matsumoto, E., Hotta, N., Oohashi, T., Fukuzawa, Y., Kakumu, S. 2007, Expression of Toll-like receptors in chronic hepatitis C virus infection, J.Gastroenterol.Hepatol., 22(10), pp. 1627-1632.

Schott, E., Witt, H., Neumann, K., Taube, S., Oh, D. Y., Schreier, E., Vierich, S., Puhl, G., Bergk, A., Halangk, J., Weich, V., Wiedenmann, B., Berg, T. 2007, A Toll-like receptor 7 single nucleotide polymorphism protects from advanced inflammation and fibrosis in male patients with chronic HCV-infection, J.Hepatol., 47(2), pp. 203-211.

Schuttler, C. G., Fiedler, N., Schmidt, K., Repp, R., Gerlich, W. H., Schaefer, S. 2002, Suppression of hepatitis B virus enhancer 1 and 2 by hepatitis C virus core protein, J.Hepatol., 37(6), pp. 855-862.

Sikora, D., Greco-Stewart, V. S., Miron, P., Pelchat, M. 2009, The hepatitis delta virus RNA genome interacts with eEF1A1, p54(nrb), hnRNP-L, GAPDH and ASF/SF2, Virology, 390(1), pp. 71-78.

Silverman, R. H. 1994, Fascination with 2-5A-dependent RNase: a unique enzyme that functions in interferon action, J.Interferon Res., 14(3), pp. 101-104.

Su, A. I., Pezacki, J. P., Wodicka, L., Brideau, A. D., Supekova, L., Thimme, R., Wieland, S., Bukh, J., Purcell, R. H., Schultz, P. G., Chisari, F. V. 2002, Genomic analysis of the host response to hepatitis C virus infection, Proc.Natl.Acad.Sci.U.S.A, 99(24), pp. 15669-15674.

Sumpter, R., Jr., Loo, Y. M., Foy, E., Li, K., Yoneyama, M., Fujita, T., Lemon, S. M., Gale, M., Jr. 2005, Regulating intracellular antiviral defense and permissiveness to hepatitis C virus RNA replication through a cellular RNA helicase, RIG-I, J.Virol., 79(5), pp. 2689-2699.

Sun, Z., Wada, T., Maemura, K., Uchikura, K., Hoshino, S., Diehl, A. M., Klein, A. S. 2003, Hepatic allograft-derived Kupffer cells regulate T cell response in rats, Liver Transpl., 9(5), pp. 489-497.

Suzuki, F., Arase, Y., Suzuki, Y., Tsubota, A., Akuta, N., Hosaka, T., Someya, T., Kobayashi, M., Saitoh, S., Ikeda, K., Kobayashi, M., Matsuda, M., Takagi, K., Satoh, J., Kumada, H. 2004, Single nucleotide polymorphism of the MxA gene promoter influences the response to interferon monotherapy in patients with hepatitis C viral infection, J.Viral Hepat., 11(3), pp. 271-276.

Takeda, K., Akira, S. 2005, Toll-like receptors in innate immunity, Int.Immunol., 17(1), pp. 1-14.

Taylor, D. R., Puig, M., Darnell, M. E., Mihalik, K., Feinstone, S. M. 2005, New antiviral pathway that mediates hepatitis C virus replicon interferon sensitivity through ADAR1, J.Virol., 79(10), pp. 6291-6298.

Taylor, D. R., Shi, S. T., Romano, P. R., Barber, G. N., Lai, M. M. 1999, Inhibition of the interferon-inducible protein kinase PKR by HCV E2 protein, Science, 285(5424), pp. 107-110.

Terenzi, F., Pal, S., Sen, G. C. 2005, Induction and mode of action of the viral stress-inducible murine proteins, P56 and P54, Virology, 340(1), pp. 116-124.

Thompson, A. J., Colledge, D., Rodgers, S., Wilson, R., Revill, P., Desmond, P., Mansell, A., Visvanathan, K., Locarnini, S. 2009, Stimulation of the interleukin-1 receptor and Toll-like receptor 2 inhibits hepatitis B virus replication in hepatoma cell lines in vitro, Antivir.Ther., 14(6), pp. 797-808.

Vilasco, M., Larrea, E., Vitour, D., Dabo, S., Breiman, A., Regnault, B., Riezu, J. I., Eid, P., Prieto, J., Meurs, E. F. 2006, The protein kinase IKKepsilon can inhibit HCV expression independently of IFN and its own expression is downregulated in HCV-infected livers, Hepatology, 44(6), pp. 1635-1647.

Visvanathan, K., Skinner, N. A., Thompson, A. J., Riordan, S. M., Sozzi, V., Edwards, R., Rodgers, S., Kurtovic, J., Chang, J., Lewin, S., Desmond, P., Locarnini, S. 2007, Regulation of Toll-like receptor-2 expression in chronic hepatitis B by the precore protein, Hepatology, 45(1), pp. 102-110.

Wakita, T., Pietschmann, T., Kato, T., Date, T., Miyamoto, M., Zhao, Z., Murthy, K., Habermann, A., Krausslich, H. G., Mizokami, M., Bartenschlager, R., Liang, T. J. 2005, Production of infectious hepatitis C virus in tissue culture from a cloned viral genome, Nat.Med., 11(7), pp. 791-796.

Wang, B., Trippler, M., Pei, R., Lu, M., Broering, R., Gerken, G., Schlaak, J. F. 2009a, Toll-like receptor activated human and murine hepatic stellate cells are potent regulators of hepatitis C virus replication, J.Hepatol., 51(6), pp. 1037-1045.

Wang, C., Pflugheber, J., Sumpter, R., Jr., Sodora, D. L., Hui, D., Sen, G. C., Gale, M., Jr. 2003, Alpha interferon induces distinct translational control programs to suppress hepatitis C virus RNA replication, J.Virol., 77(7), pp. 3898-3912.

Wang, N., Liang, Y., Devaraj, S., Wang, J., Lemon, S. M., Li, K. 2009b, Toll-like receptor 3 mediates establishment of an antiviral state against hepatitis C virus in hepatoma cells, J.Virol., 83(19), pp. 9824-9834.

Wedemeyer, H., Manns, M. P. 2010, Epidemiology, pathogenesis and management of hepatitis D: update and challenges ahead, Nat.Rev.Gastroenterol.Hepatol., 7(1), pp. 31-40.

Wieland, S. F., Eustaquio, A., Whitten-Bauer, C., Boyd, B., Chisari, F. V. 2005, Interferon prevents formation of replication-competent hepatitis B virus RNA-containing nucleocapsids, Proc.Natl.Acad.Sci.U.S.A, 102(28), pp. 9913-9917.

Wieland, S. F., Spangenberg, H. C., Thimme, R., Purcell, R. H., Chisari, F. V. 2004a, Expansion and contraction of the hepatitis B virus transcriptional template in infected chimpanzees, Proc.Natl.Acad.Sci.U.S.A, 101(7), pp. 2129-2134.

Williams, V., Brichler, S., Radjef, N., Lebon, P., Goffard, A., Hober, D., Fagard, R., Kremsdorf, D., Deny, P., Gordien, E. 2009, Hepatitis delta virus proteins repress hepatitis B virus enhancers and activate the alpha/beta interferon-inducible MxA gene, J.Gen.Virol., 90(Pt 11), pp. 2759-2767.

Wu, J., Lu, M., Meng, Z., Trippler, M., Broering, R., Szczeponek, A., Krux, F., Dittmer, U., Roggendorf, M., Gerken, G., Schlaak, J. F. 2007a, Toll-like receptor-mediated control of HBV replication by nonparenchymal liver cells in mice, Hepatology, 46(6), pp. 1769-1778.

Wu, J., Meng, Z., Jiang, M., Pei, R., Trippler, M., Broering, R., Bucchi, A., Sowa, J. P., Dittmer, U., Yang, D., Roggendorf, M., Gerken, G., Lu, M., Schlaak, J. F. 2008, Hepatitis B virus suppresses toll-like receptor-mediated innate immune responses in murine parenchymal and nonparenchymal liver cells, Hepatology.

Wu, J., Meng, Z., Jiang, M., Zhang, E., Trippler, M., Broering, R., Bucchi, A., Krux, F., Dittmer, U., Yang, D., Roggendorf, M., Gerken, G., Lu, M., Schlaak, J. F. 2009, Toll-like receptor-induced innate immune responses in non-parenchymal liver cells are cell type-specific, Immunology.

Wu, M., Xu, Y., Lin, S., Zhang, X., Xiang, L., Yuan, Z. 2007b, Hepatitis B virus polymerase inhibits the interferon-inducible MyD88 promoter by blocking nuclear translocation of Stat1, J.Gen.Virol., 88(Pt 12), pp. 3260-3269.

Xia, C., Lu, M., Zhang, Z., Meng, Z., Zhang, Z., Shi, C. 2008, TLRs antiviral effect on hepatitis B virus in HepG2 cells, J.Appl.Microbiol., 105(5), pp. 1720-1727.

Xu, Y., Kock, J., Lu, Y., Yang, D., Lu, M., Zhao, X. 2011, Suppression of hepatitis B virus replication in Tupaia hepatocytes by tumor necrosis factor alpha of Tupaia belangeri, Comp Immunol.Microbiol.Infect.Dis..

Yoneyama, M., Kikuchi, M., Natsukawa, T., Shinobu, N., Imaizumi, T., Miyagishi, M., Taira, K., Akira, S., Fujita, T. 2004, The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses, Nat.Immunol., 5(7), pp. 730-737.

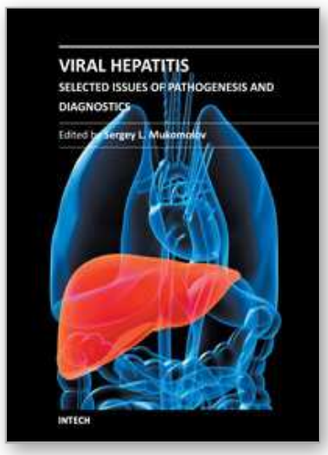
Zarski, J. P., Bohn, B., Bastie, A., Pawlotsky, J. M., Baud, M., Bost-Bezeaux, F., Tran van, N. J., Seigneurin, J. M., Buffet, C., Dhumeaux, D. 1998, Characteristics of patients with dual infection by hepatitis B and C viruses, J.Hepatol., 28(1), pp. 27-33.

Zeuzem, S., Andreone, P., Pol, S., Lawitz, E., Diago, M., Roberts, S., Focaccia, R., Younossi, Z., Foster, G. R., Horban, A., Ferenci, P., Nevens, F., Mullhaupt, B., Pockros, P., Terg, R., Shouval, D., van, H. B., Weiland, O., Van, H. R., De, M. S., Luo, D., Boogaerts, G., Polo, R., Picchio, G., Beumont, M. 2011, Telaprevir for retreatment of HCV infection, N.Engl.J.Med., 364(25), pp. 2417-2428.

Zhang, X., Meng, Z., Qiu, S., Xu, Y., Yang, D., Schlaak, J. F., Roggendorf, M., Lu, M. 2009, Lipopolysaccharide-induced innate immune responses in primary hepatocytes downregulates woodchuck hepatitis virus replication via interferon-independent pathways, Cell Microbiol., 11(11), pp. 1624-1637.

Zhong, J., Gastaminza, P., Cheng, G., Kapadia, S., Kato, T., Burton, D. R., Wieland, S. F., Uprichard, S. L., Wakita, T., Chisari, F. V. 2005, Robust hepatitis C virus infection in vitro, Proc.Natl.Acad.Sci.U.S.A, 102(26), pp. 9294-9299.

Zhou, A., Paranjape, J., Brown, T. L., Nie, H., Naik, S., Dong, B., Chang, A., Trapp, B., Fairchild, R., Colmenares, C., Silverman, R. H. 1997, Interferon action and apoptosis are defective in mice devoid of 2',5'-oligoadenylate-dependent RNase L, EMBO J., 16(21), pp. 6355-6363.



Viral Hepatitis - Selected Issues of Pathogenesis and Diagnostics
Edited by Dr. Sergey Mukomolov

ISBN 978-953-307-760-4
Hard cover, 152 pages
Publisher InTech
Published online 07, November, 2011
Published in print edition November, 2011

There are a lot of important issues related to viral hepatitis studies: molecular biology of viruses, laboratory diagnostics, epidemiology, treatment etc. However, there is a number of special textbooks and monographs on the subject. Considering this fact and rather fast progress in our understanding of the problem this book focuses on the important sections of the problem immune pathogenesis of parenterally transmitted viral hepatitis and some aspects of hepatitis diagnostics. Seven chapters were prepared by several groups of researchers to share information and results of studies with specialists working in the field and persons who are interested to learn about the viral hepatitis issue. The Nobel Prize Committee (the field of physiology and medicine, 2011) awarded Bruce A. Beutler and Jules A. Hoffmann for their discoveries concerning the activation of innate immunity whilst Ralph M. Steinman was awarded for his discovery of the dendritic cell and its role in adaptive immunity. We are proud to say that our book is in line with these discoveries, because 3 chapters cover the problems of innate and adaptive immune response in case of viral hepatitis.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Ruth Broering, Mengji Lu and Joerg F. Schlaak (2011). Toll Like Receptors in Chronic Viral Hepatitis – Friend and Foe, Viral Hepatitis - Selected Issues of Pathogenesis and Diagnostics, Dr. Sergey Mukomolov (Ed.), ISBN: 978-953-307-760-4, InTech, Available from: http://www.intechopen.com/books/viral-hepatitis-selected-issues-of-pathogenesis-and-diagnostics/toll-like-receptors-in-chronic-viral-hepatitis-friend-and-foe

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen