Genes Determining the Course of Virus Persistence in the Liver: Lessons from Murine Infection with Lymphocytic Choriomeningitis Virus

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Key Words

Immunopathology • Viral infection • Hepatitis • Liver

Abstract

More than 500 million people worldwide are persistently infected with either hepatitis B virus (HBV) or hepatitis C virus (HCV). Although both viruses are poorly cytopathic, persistent infection causes severe immunopathologic damage to liver tissue; histologically, such damage is characterized by fatty liver disease, liver fibrosis, and a higher likelihood of hepatocellular carcinoma. Virus-specific CD8⁺ T cells play a crucial role during infection with hepatitis viruses. On the one hand, rapid activation of CD8⁺ T cells can control the virus and therefore inhibit its persistence. On the other hand, once the virus persists in the liver, the chronic activation of virus-specific T cells leads to continued liver cell damage. This double-edged role of CD8⁺ T cells determines the final outcome of infection. In half of cases of human HCV infection, the virus persists; in the other half, the virus is controlled. Additional insights into the molecular mechanisms that determine the course of the disease may be gained from

the study of appropriate murine models. This review discusses the similarities and differences between infection with lymphocytic choriomeningitis virus (LCMV) in mice and chronic infection with hepatitis virus in humans.

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Introduction

Persistent infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is a widely distributed disease [1]. Both viruses are poorly cytopathic; nevertheless, infection can lead to severe, life-threatening liver disease. CD8⁺ T cells are crucial to this process [2-5]. By lysing virus-infected hepatocytes, CD8⁺ T cells can inhibit the rapid propagation and distribution of the virus, thereby protecting the host from persistent viral infection. Once the virus persists, however, continued activation of CD8⁺ T cells can lead to constant immunopathologic damage, which may lead to the complete destruction

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1015-8987/10/0263-0263\$26.00/0

Accessible online at:
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of liver tissue [1, 3, 6, 7]. The antiviral defense involves a variety of additional mechanisms, including the innate immune system [8] and the induction of neutralizing antibodies [9]. Studying the concerted action of the innate and adaptive immune systems during viral infection requires an appropriate *in vivo* model in which the mechanisms involved in the control of viral infection and the mechanisms of immunopathology can be elucidated.

Lymphocytic choriomeningitis virus (LCMV) is a single-stranded RNA virus that belongs to the Arenaviridae [10]. LCMV is well adapted to rodents and replicates well in mice [10]. In murine cells it is not cytopathic but instead causes an infection that is prone to persistence [11]. CD8⁺ T cells are essential for the control of the virus [11]. The infection of C57BL/6 mice with 200 plaque-forming units (PFUs) of LCMV does not lead to marked hepatitis because the virus is eliminated by CD8⁺ T cells more rapidly than it propagates in the liver tissue. Infection with 2×10⁶ PFUs, however, leads to more widely distributed replication of the virus in hepatocytes [12].

In some aspects LCMV infection in mice is similar to HCV infection in humans. In both diseases, CD8⁺ T cells are essential for the control of virus [13]. As is true in HCV infection [14], the liver damage that occurs after LCMV infection is not induced by the virus itself but rather by the immune response to the virus [14]. Two strains of LCMV are commonly used in animal models. The Armstrong strain, which is called neurotropic [15, 16], can also replicate well in various organs. In contrast, the WE strain of LCMV replicates primarily in macrophages [10, 12, 17] and in various epithelial and parenchymal cells [18]. Four days after mice are infected with 2×10⁶ PFUs of LCMV-WE, the virus has spread from macrophages to hepatocytes [17]. When cytotoxic CD8⁺ T cells are primed, they infiltrate the liver and recognize the virus-infected hepatocytes. Therefore, the degree of damage caused by the immune response is positively correlated with the number of virus-infected hepatocytes. The more time that is required for the immune system to be activated and for the virus-specific T cells to infiltrate the liver, the more hepatocytes will be infected by virus. Finally, a delayed immune response leads to enhanced immunopathology (Fig. 1) [12].

As a consequence of the virus-specific CD8⁺ T-cell response, C57BL/6 mice infected with LCMV-WE develop a transient case of hepatitis that lasts for approximately 7 days. During that time, several

Fig. 1. Relationship between virus and T cells. If the T-cell response at the beginning of infection is weak, the virus replicates strongly, and this replication leads to T-cell exhaustion (extreme left; low immunopathology). An early T-cell response at the beginning of infection leads to rapid control of virus and the formation of T-cell memory (extreme right; low immunopathology). However, if the virus has enough time to replicate in the liver and T cells still expand, virus-infected cells will be attacked by CD8⁺ T cells, and this attack will lead to strong immunopathology (middle).

genes determine the outcome of liver cell damage. Among these are genes that influence the innate immune response and genes that influence T-cell and B-cell stimulation. In addition, genes that are directly activated in the target organ can influence the outcome of disease. In murine studies, the role of certain genes can be analyzed by using gene-targeted mice; in humans, the linkage of gene polymorphisms with disease outcome can provide insights into the role of certain genes. Several genes important in human hepatitis have been found to play an important role in LCMV-induced hepatitis (Table 1).

Molecules influencing innate virus control

For the rapid elimination of a liver-tropic virus, activation of the innate, first-line, nonadaptive immune system is important [78, 79]. The innate immune system recognizes pathogens by using pattern-recognition receptors (PRRs) that lead to activation. PRRs recognize specific patterns on pathogens, such as double-stranded RNA and bacterial wall components [80, 81]. In virus

Function	Gene	Control of LCMV	Control of HCV
<i>Genes involved in innate immune response</i>			
Pattern-Recognition Receptor	RIG-I, MDA5, TLRs	[19]	[20, 21]
Innate Signalling	MyD88	[19, 22, 23]	???
Antiviral Activity	Interferon type I	[24-27]	[28, 29]
Antiviral Activity	Interferon type III		[30, 31]
Inflammatory Response	TNF- α	[26, 32]	[33-35]
<i>Genes involved in T-cell stimulation</i>			
T-cell Priming/Antigen Recognition	MHC I, Tap, TCR, CD8	[13, 36-38]	[39-43]
T-cell Priming	IL-2	[44, 45]	[46]
T-cell priming	IL-7	[47-49]	[50-52]
T-cell exhaustion	PD-1	[53, 54]	[7, 51, 55]
T-cell priming	IFN-I	[56, 57]	
T-cell exhaustion	IL10	[58, 59]	[34, 60-63]
T-cell function	IFN- γ , Type II IFN	[27, 64]	[65]
T-cell function	Perforins	[66]	
<i>Genes influencing the B-cell response</i>			
Neutralizing antibodies		[18, 67-71]	[9, 72-74]
Neutralizing antibodies	CD40	[75]	
<i>Genes activated in the target organ</i>			
Blood Flow	Serotonin	[76]	
Chemokine Production	???	[26]	
Blood Flow/T-cell Function	iNOS	[77]	

Table 1. Comparison of genes that are involved in LCMV-induced hepatitis and in human hepatitis. Genes are classified according to their involvement in the innate immune system, in adaptive immunity, or in the target organ. LCMV, lymphocytic choriomeningitis virus. HCV, hepatitis C virus. RIG-I, retinoic acid inducible gene I. MDA5, melanoma differentiation-associated gene. TLRs, Toll-like receptors. MyD88, myeloid differentiation primary response gene. TNF- α , tumor necrosis factor alpha. MHC I, major histocompatibility complex class I. TAP, transporters associated with antigen processing. TCR, T-cell receptor. IL, interleukin. PD, programmed death. IFN, interferon. AID, activation-induced deaminase. iNOS, inducible nitric oxide synthase.

infection, the most important PRRs are Toll-like receptors (TLRs) 3, 4, 7, 8, and 9; RNA helicase; retinoic acid inducible gene I (*RIG-I*); and melanoma differentiation-associated gene 5 (*MDA5*) [21, 82]. The production of IFN- α after LCMV infection depends on IPS-1, the central adaptor protein to RIG-I-like receptor, and MyD88 [19]. TLR2 was discussed to be involved in innate recognition [23]. Nevertheless the exact mechanism for MyD88 dependence as well as the mechanism of Interferon- β production are under debate [19, 22, 23]. HCV can be recognized by RIG-I and MDA5 [21]; however, HCV can interfere with RIG-I signalling by cleaving the adaptor protein Cardif [83].

One of the most effective effector cytokines of the innate immune system is the antiviral action of interferon type I (IFN-I) [24]. LCMV replication cannot be

controlled without this IFN-I response [24]. In humans, a polymorphism of *STAT1* has been found to be associated with chronic HCV infection; this finding suggests that signalling by IFN-I, IFN- γ (type II), or both is essential for control of the virus [84]. In humans, a polymorphism in the IFN receptor can influence the outcome of IFN therapy [28, 29]. Researchers recently described a *STAT1* gene mutation that leads to an almost complete absence of IFN signalling. Infants with this gene mutation are prone to several infections with viruses and bacteria. This gene mutation was not found to be associated with HCV infection [85, 86], but the ability to detect such an association may have been hampered by the fact that the study group was rather small.

Like IFN-I, IFN-III induces an antiviral state [87, 88]. The receptor for IFN-III is expressed on

hepatocytes, and IFN-III efficiently reduces the rate of HCV replication [30, 31]. A recent study showed that a polymorphism in the IFN-III receptor is associated with enhanced natural control of HCV [89, 90]. In addition, patients who were carriers of this polymorphism responded better to IFN therapy than did patients who were not carriers. In the LCMV system, IFN-III is less potent than type I IFN [91].

Molecules influencing CD8⁺ T-cell dependent virus

CD8⁺ T cells play an essential role in LCMV infection in mice and also in HCV and HBV infection in humans. Several genes that are involved in antigen processing, antigen recognition, and T-cell activation are essential for the control of LCMV infection in mice. Similar polymorphisms in such genes correlate with HCV carrier status in humans (Table 1) [40-43].

The role of the T cell-stimulating cytokine IL-2 is still controversial. Inhibition of IL-2 signalling by the immunosuppressant drug cyclosporin can delay the control of LCMV infection [45], although the genetically caused absence of IL-2 does not dramatically influence the control of LCMV [92]. At any rate, the early (pharmacological) presence of IL-2 in the LCMV model is beneficial for the control of virus [44]. In humans, loss-of-function polymorphisms of the *IL-2* gene lead to reduced control of HCV [46]. Whether early administration of IL-2 to humans is beneficial remains to be analyzed.

IL-7 is an important survival factor for CD4⁺ and CD8⁺ T cells [93]. The results of some studies have shown that reduced control of the virus is associated with reduced IL-7 signalling in CD8⁺ T cells [47, 48]. This reduced signalling is explained by the reduced expression of IL-7R α chains on T cells during chronic infection. As is the case with IL-2, therapeutic administration of recombinant IL-7 positively influences virus control [49]. The enhanced expression of this IL-7R α chain is associated with a strong CD8⁺ T-cell response during HBV infection [94]. Although clinical trials have evaluated the therapeutic application of IL-7 during HIV infection, the role of this cytokine in human virus-induced hepatitis remains to be analyzed.

The activity status of dendritic cells is essential for the priming and function of CD8⁺ T cells [95]. Dendritic cells expressing programmed death ligand (PD-L1) inhibit the expansion of CD8⁺ T cells [96, 97]. Therefore,

the lack of expression of PD-L1, the ligand for PD-1 on CD8⁺ T cells, is associated with enhanced CD8⁺ T-cell function in the LCMV system [53]. In chronic HCV infection, the exhaustion of CD8⁺ T-cell function is positively correlated with the expression of PD-1, a finding suggesting that signals from this receptor are indeed involved in T-cell dysfunction during “chronification” of HCV infection [7, 51, 55]. It remains unclear whether the blockade of PD-1 can induce the control of virus in HCV or HBV infection. Alternatively, this blockade could instead worsen the immunopathology in the liver. In the LCMV mouse model, the blockade of PD-1 has been demonstrated to be beneficial for virus control [54].

Several polymorphisms of the *IL-10* gene exist, and many of those polymorphisms influence the outcome of HCV infection [34, 60-63]. Enhanced IL-10 signalling is associated with virus persistence in human livers. In line with this finding, the absence of IL-10 is associated with enhanced control of LCMV [58]. IL-10 weakens the expansion of CD8⁺ T cells [58, 59]; therefore, the therapeutic blockade of IL-10 in vivo leads to enhanced virus control [59].

Recently, the absence of CD8 T-cell function in chronic virus infection was linked to deficient expression of IL-21 [98-100]. Patients with chronic HCV infection have been found to have low levels of IL-21, but it is unknown whether this deficiency in IL-21 influences control of the virus [101].

Still under debate is the role of CD27 in chronic virus infection. In HIV patients, the expression of CD27 is associated with the survival of CD8⁺ T cells [102, 103]; this finding suggests that CD27 plays a beneficial role. In LCMV infection, the absence of CD27 prevents the establishment of virus persistence. Lack of CD27 leads to the reduced response of CD4⁺ and CD8⁺ T cells in LCMV infection [104]. Reduction of CD4⁺ T-cell help in the spleen prevents immunopathology and also prevents the CD4⁺ T cell-dependent activation of polyclonal B cells [105]. Therefore only deliberate activation of CD4⁺ and CD8⁺ T cells is beneficial for the production of LCMV-specific neutralizing antibodies [18, 70], and the production of these antibodies is overall the greatest benefit for virus control.

The main effector genes of CD8⁺ T cells are the perforins and IFN- γ . Both genes are essential for the control of LCMV [27, 64, 66], and IFN- γ seems to play a similar decisive role in HCV [65]. The role of perforins in human hepatitis is presently elusive.

Molecules influencing B cell-dependent virus control

B cells are essential for the long-term control of LCMV, and such control is associated with the production of neutralizing antibodies [18, 67-71], as is demonstrated by the infection of mice lacking the B-cell receptor immunoglobulin M (IgM) or the complete Ig heavy chain [67, 71]. In mice, the activation-induced deaminase (*AID*) gene is essential for class-switch recombination of B cells and, therefore, for induction of neutralizing antibodies [18]. The absence of *AID* in *Aida*^{-/-} mice leads to virus persistence [18]. Mice lacking the major histocompatibility complex class II (MHC II) molecule cannot control LCMV. The MHC II molecule is important for CD4⁺ T-cell antigen recognition and, therefore, for the interaction between T cells and B cells. This interaction is essential for the production of virus-specific IgG. One of the most important co-receptors of this interaction is CD40. In LCMV infection, this interaction strongly influences B-cell responses [75]. Both the complete absence of CD4⁺ T-cell help and the enhanced CD4⁺ T-cell response are associated with the reduced production of neutralizing antibodies [70, 105].

The strong induction of neutralizing antibodies is associated with enhanced virus control in human hepatitis [9, 72-74]. Why some humans generate such neutralizing antibodies and others do not remains largely unknown.

Nonimmunologic molecules that influence virus control

Liver cell damage induces the production of nitric oxide (NO) [106-108], which reacts with other reactive oxygen species (ROS) to form peroxynitrite [109-111]. This process can lead to inactivation of CD95 signalling [112]. Depending on the cell type, this process can influence apoptosis and is therefore likely to be involved in virus control [113-117]. In inflamed tissue, NO is produced primarily by inducible NO synthase (iNOS) [106-108]. NO can also influence the microcirculation and may thereby also influence virus control [52, 111, 118, 119].

During LCMV infection, serotonin is released in the liver [76]. The release of serotonin is associated with platelet activation and with induced microcirculatory dysfunction in the liver. Reduced

microcirculation aggravates virus control, which finally leads to enhanced liver cell damage [76]. Whether serotonin plays any role in human hepatitis and whether treatment with serotonin inhibitors favorably influences the course of human viral hepatitis remain to be determined.

Limitations of the LCMV infection model

Several immunologic genes that influence the control of LCMV are also important for the control of human hepatitis virus. Therefore, we conclude that genes that have been found to influence LCMV infection are worthy of study in human hepatitis. However, there are specific differences between LCMV-induced hepatitis and human hepatitis. A defective immune response in mice leads to LCMV persistence in several organs, such as the liver, spleen, lung, kidney, and blood, and the infection may also spread to the brain.

In human hepatitis, virus replication occurs primarily in the liver. HBV can also replicate in Kupffer cells and other macrophages, HCV replicates only in hepatocytes.

A second difference between LCMV infection and HCV infection is the long-term progression of the disease. In human hepatitis, virus persistence induces constant immune activation in the liver, and this activation leads to the destruction of liver cells. In contrast, during the short life span of mice, LCMV persistence does not dramatically affect the function of liver cells. This fact could be explained by differences in the distribution of virus antigen, which will obviously affect the immune response during long-term virus persistence. In addition, the collateral damage to other organs may be more severe during LCMV infection; thus, the death of mice with chronic virus infection is probably due to other pathologic processes.

Conclusions

Several genes that are important for the control of LCMV hepatitis in a mouse model are also important in chronic viral hepatitis in humans. Accordingly, newly discovered genes that influence the outcome of LCMV hepatitis may be good candidates for studies in human hepatitis. However, the murine model of LCMV has two important limitations. First, the genes that directly influence virus replication probably

differ between infections with LCMV, HBV, and HCV [120]. Second, chronic LCMV infection does not lead to severe liver fibrosis after acute infection. Therefore,

genes that account for the triggering of human liver fibrosis may exert little influence on the clinical course of LCMV infection.

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