Chronic Viral Hepatitis: Etiology, Pathogenesis of Liver Damage and Mechanisms of Persistence

Irwan Setiabudi

Department of Clinical Pathology, Faculty of Medicine,
University of Hang Tuah/dr. Ramelan Navy Hospital, Surabaya

ABSTRACT

Chronic hepatotropic viruses commonly evade the antiviral defence systems of the body and cause a long - lasting persistent infection. The prolonged nature of the infection ensures that every infected person has ample opportunity to transmit the virus to others, allowing many millions of people world-wide to become infected. Three viruses commonly cause chronic hepatitis B virus, hepatitis C virus and hepatitis Delta virus.

Virus specific CD8 T cells of the host, represent the main effector cells against viral infection. Where as the antiviral cytokines have a major role in the control of viral replication (non-cytolytic inhibition).

To cause persistent infection, a virus must avoid the host defences and that hepatotropic viruses have developed elaborate strategies to achieve this. In the case of hepatitis B virus, two proteins are involved in the inhibition of the host defences; those are the core protein that has been shown to inhibit the production of interferon and the polymerase protein has been shown to inhibit its effect. Where as in the case of hepatitis C virus, the NS5A and E2 protein reduce the effect of interferon by inhibiting the antiviral kinase.

In order to survive and persistent in the liver, the hepatotropic viruses must be able to avoid both arms of the immune system, either by mutation of viral proteins or by preventing activation of the immune system.

Keywords: *Hepatotropic viruses, core proteins, interferon.*

INTRODUCTION

Viral hepatitis is a systemic disease primarily involving the liver and necroinflammatory is basically responsible for the majority of its clinical and laboratory features.[1] In viral hepatitis, depending on its etiology, there is a variable incidence of clinically significant hepatic and extrahepatic manifestations, complications and progression to chronicity.

Chronic hepatitis is defined as a chronic inflammatory reaction of the liver of more than six months duration, as demonstrated by persistently abnormal serum aminotransaminase levels and characteristic histologic findings.[2] The ultimate goal therapy to chronic hepatitis is to heal hepatic inflammation and necrosis, thereby halting progression to cirrhosis and hepatocellular carcinoma.[3]

ETIOLOGY

Three viruses commonly cause chronic viral hepatitis: hepatitis B virus (HBV), hepatitis delta virus (HDV) and hepatitis C virus (HCV).Virulogically these three pathogens are remarkably different (HBV is a DNA virus, while HDV and HCV are RNA viruses), but all have developed mechanisms that allow persistent infection and overall they infect over 500 millions people world-wide.[4] Hepatitis B virus (HBV) is a non-cytopathic, hepatotrophic DNA virus that cause acute and chronic necroinflammatory liver disease.

The vast majority of adults acutely infected, recover from the disease, controlling virus replication and developing a long lasting immunity, only in about 5% progress to chronic state. In contrast, neonatal infections are rarely cleared and most (± 90%) of these children become chronically infected.[5]

Chronic hepatitis B is characterized by a state of HBV–specific T cell hyporenponsiveness. HBV-specific cytotoxic T cells mediate protection but can also be the principle effectors of liver damage. An efficient HBV-specific CD8 response can promote viral control without persistent liver pathology, whereas an inadequate CTL response, may contribute to liver pathology not only directly, but also via the recruitment of non-antigen-specific T cells into the infected liver.[5]

Hepatitis D virus is a unique hepatitis RNA virus. It is replication defective, though, in that it is incapable of making its own envelope protein, rather its envelope consists of the hepatitis B surface antigen (HbsAg), therefore envelope production require HBV and HVD transmission and entry into hepatocyte, require HBV though super infection or co-infection.[6]

Acute co-infection with HBV, the infection usually in 80% to 95% of cases, with elimination of HBV though humoral and cellular resolves immune mechanism. In contrast, super infection may result in chronic HDV-HBV in more than 70% to 80% of cases. Similar to acute co-infection, acute HDV super infection may result in fulminate hepatitis in 2% to 20% of cases.[6]

Chronic HDV does progress to cirrhosis frequently and the development of cirrhosis is also more rapid than chronic HBV or chronic HCV and there is predominance of co infected patients with cirrhosis who are young. Slowly progressive mild disease is more common in endemic areas. On the other hand, HDV disease appear to be more severe in non-endemic areas where injection drug use is the main form of transmission.[6]

Hepatitis C virus (HCV) was first identified in 1989 as a member of flaviviridae. Now, an estimate of 170 millions people worldwide are infected with hepatitis C virus. Nowadays, the majority of patients with acute HCV infection are intravenous drug users and the risk of vertical transmission from HCV infected mothers to their children is only 1% to 5%. Recent studies on acute infection demonstrated that sexual contact with an HCV positive partner was the only risk factor to be identified in 20% to 30% of patients. Other potential exposure (occupational, hemodialysis, household) account for about 10% of new infextions.[7] Although it is widely accepted that hepatitis C virus infection is a major cause of an end-state liver disease and hepatocelluler carcinoma, the natural history and hence the prognosis of the infection are still controversial.

Since HCV is a non-cytopathic virus in most circumstances, the immune response almost certainly plays a central role, not only for the control of the infection, but also for the pathogenesis of liver disease and the progression of acute HCV infections to chronic cases, occur in approximately 75% to 85%[8] and it always implies the presence of some degree of liver damage in chronic viral hepatitis.[9]

PATHOGENESIS OF LIVER DAMAGE

Virus-specific CD8 T cells represent the main effector cells against a viral infection, where as the antiviral cytokines has a major role in the control of viral replication (non-cytolytic inhibition).

The appearance of CD8+ human leukocyte antigen-restricted cytotoxic T cells is important in the pathogenesis of liver cells damage and that cell necrosis in several viral infections in humans, can be mediated by cytotoxic T lymphocytes (CTLS) that recognize viral antigens on the surface of infected cells in the context of HLA class.[10]

T lymphocytes can be cytotoxic and destroy infected cells by inducing apoptosis through the release of perforin, granzyme and secrete cytokines such as TNF-alpha and interferon gamma.[7] Three distinct mechanisms, namely Fas, TNF alpha and/or perforin-based cell lysis have been implicated in hepatocyt death during inflammatory liver disease.[11] Fas-mediated death is a rapid process, requires neither RNA nor protein synthesis. Expression of Fas (CD 95), a mediator of apoptosis is required the induce the death of the hepatocyts.

TNF-mediated apoptosis can be induced by membrane–bound and soluble TNF alpha, whereas the perforin–mediated mechanism may contribute to the lysis of antigen presenting, Fas and TNF alpha resistant cells.[11]

The presence of a CTL response that unable to control viral infection, could then cause chronic recruitment of inflammatory cells that will sustain necro–inflammatory activity, promoting the long-term complication of viral infection such as fibrosis, cirrhosis and hepatocellular carcinoma.[5] How do hepatotropic viruses cause chronic infection in the liver ?

MECHANISMS OF LIVER PERSISTENCE

Chronic infection with persisting hepatitis viruses B or C (HBV or HCV) reflex an initially ineffective immune response to hepatocyt that express viral antigens, resulting in an unstable balance between tolerance and immunity to infected hepatocyt, with multiple host and viral determinants in play.

To cause persistent infection in the liver, a virus must

avoid host defences and the hepatotropic viruses have developed elaborate strategies to achieve this.[4] The innate immune system is the first line of defence against pathogens and the most important innate antiviral defence system is the type I interferons. These interferons are rapidly produced by virally infected cells and once released, they bind to cell surface receptors and induce the production of a large number of proteins that inhibit viral replication.

The functions of some of the proteins that are induced by type I interferons are well characterized, but no function has been identified for many of them. Some of the interferon-inducible proteins are produced in an inactive form and are activated by viral products. For example, type I interferon induce the production of a protein kinase known as PKR. In the presence of a replicating RNA virus, this protein is activated by double stranded RNA and the activated kinase, inhibits cellular protein production, thereby leading to suppression of viral replication, whereas other interferon-inducible proteins inhibit the replication of other viruses.[4]

It is assumed that many hundreds or so interferon-induced proteins identified to date, inhibits the replication of specific viruses, although not all of the targets have been identified.

In addition to activating an antiviral state in cells exposed to viruses, the type I interferon's have immunomodulatory effects. They facilitate immune recognition of virally infected cells by increasing the cell surface expression of human leucocyte antigen (HLA) class I antigen. This presentation of viral antigens to T cells is enhanced by type I interferon, which up-regulate HLA class I antigens.

Viruses that lead to prolonged infection must have developed mechanisms to overcome the effect of these interferon and many viruses encode proteins that inhibit interferon system in some way.[4]

In the case hepatitis B virus; two proteins are involved in this inhibition:

1. The core protein which inhibits the production of interferon
2. The polymerase protein which inhibits the effect of interferon

In the case of hepatitis C virus, the NS5A and E2 proteins reduce the effect of interferon, by inhibiting the viral kinase, PKR.[4] The NS5A region has been associated with sensitivity to interferon in genotype 1b isolate in Japan.[12]

So, persistent viral infection is associated with avoidance of both arms of the immune system and the exact mechanisms of persistent viral infection are not completely understood, possibly through:

1. Mutation of viral proteins
2. By preventing activation of the immune system.[4]
3. Inhibit the generation of an appropriate immune response, e.g. The infection of dendritic cells as one mechanism which may be used by hepatitis C virus.

In vertical transmission, hepatitis B virus produces a small protein (HBeAg), which crosses the placenta and induces tolerance to itself and related hepatitis B proteins. Since the immune system has come to contact with the protein in early life, the immune system then believes the protein to be self and is therefore unable to mount an effective immune system.[4]

CONCLUSIONS

1. Chronic viral hepatitis commonly cause by three hepatotropic viruses, hepatitis B virus (HBV), hepatitis delta virus (HDV), hepatitis C virus (HCV).
2. Virus specific CD8 T cells represent the major effector cells againt a viral infection, where as the antiviral cytokines has major role in the control of viral replication (non-cytolytic inhibition).
3. Persistent viral infection is associated with avoidance of both arms of the immune system by the hepatotropic viruses, either by producing proteins that inhibit the action of interferon, by mutation of viral proteins or inhibit the generation of an appropriate immune response, so that the antibody or T cell can no longer recognize the viral protein and hence the virus can evade the antiviral defence of the body.

REFERENCES

1. Brooks GF, Butel JS, Morse SA. Hepatitis Viruses. In Jawetz, Melnick & Adelberg's. Medical Microbiology 27th ed. Mc Graw Hill, Boston 2001.p.403-17
2. Tierney M, McPhee SJ, Papadakis MA. Viral hepatitis. In current medical diagnosis & treatment 2002. 41st ed. Lange Medical Books/McGraw Hill: Med Publ Div; New York 2002.p.678-86
3. Maillard M, Golland JL. Suppressing hepatitis B without resistance-so far, so good. N Engl J Med 2003;34:8-9
4. Foster GR, Goldin RD. Management of chronic viral hepatitis. 1st ed. Martin Dunitz Ltd, London 2002.p.1-9
5. Webster, Bertolett. Immunopathogenesis and treatment of hepatitis B virus infection. In: Gershwin, Vierling, Manns. Liver immunology. 1st ed. Hanley & Belfus Inc. Philadelphia 2003.p.203
6. Fox RK, Wright TL. Viral Hepatitis. In: Friedman, McQuaid,

Grendell. Current diagnosis & treatment in gastroenterology. 2nd ed. Lange Med Books Graw-Hill, New York 2003.p.546-62
7. Wedemeyer, Cornberg, Manns. Immunopathogenesis and therapy of hepatitis. In: Gershwin, Vierling, Manns. Liver immunology, 1st ed. Hanley & Belfus Inc. Philadelphia 2003.p.223-49
8. Setiawan BP. Perkembangan mutakhir tatalaksana infeksi virus hepatitis C Fokus terapi dengan interferon. Naskah Lengkap Pendidikan Kedokteran Berkelanjutan XVII, Ilmu Penyakit Dalam FK UNAIR/RS dr Soetomo, Surabaya 2002.p.158-63.
9. Hadziyannis SJ. Viral hepatitis-clinical feature. In: Liver disease, diagnosis and management. 1st ed. Bacon & Di Bisceglie, Churchil Livingstone, USA 2000.p.79-97
10. Hadem J. Immunopathogenesis and treatment of hepatitis A. In: Gershwiin, Vierling, Manns. Liver Immunology. 1st ed. Hanley & Belfus Inc. Philadelphia 2003.p.185-201
11. Rehermann B. Intrahepatic T cell. In Gershwin, Vierling, Manns. Liver immunology. 1st ed. Hanley & Belfus Inc. Philadelphia 2003.p.47-57
12. Mc Hutchison JG, Manns MP, Poynard T, Wong, JB. Hepatitis C infection. 1st ed. Science Press Ltd. London 2002.p.1-61