WEB OF SCIENTIST: INTERNATIONAL SCIENTIFIC RESEARCH JOURNAL
ISSN: 2776-0979, Volume 3, Issue 6, June, 2022

RELATIONSHIP BETWEEN VIRAL HEPATITIS B AND IMMUNITY

Shokhista Rustamova
Namangan State University, Uzbekistan

Muazzam Bakiyeva
Namangan State University, Uzbekistan

Tokhir Rahmonov
Namangan State University, Uzbekistan

Ra'no Inatullayeva
Namangan State University, Uzbekistan

Nazifa Sharipova
Namangan State University, Uzbekistan

Xurshida Muhitdinova
Namangan State University, Uzbekistan

Abstract
The basis for this study was the scientific results in the field of the study of immune mechanisms in the pathogenesis of viral hepatitis B, the significance of various factors of immunity in the formation of a chronic process, definitions new immune cells and their functional activity in various clinical manifestations of the disease.

Keywords: infection, hepatit, virus, immunity, human cells.

Introduction

The mechanisms by which hepatitis B virus (HBV) establishes and maintains chronic infection are poorly understood. Although in adults the acquired virus is usually cleared by robust immunity, most people infected at birth or at a very early age develop a lifelong chronic infection as a result. In addition, acute infections are not cured in about 5% of people infected in adulthood. The host cell mechanisms that ensure the establishment and development of acute infection and persistent infection remain unclear [1, 10, 17, 23,24].

The hepatitis B virus is cleared and controlled by the host's immune response in about 95% of people infected during adulthood, but the virus is chronic in more than 325

million people and is most common in those infected at birth or in early childhood [3, 8]. However, the reasons why HBV becomes chronic, automatically at birth or in early childhood, and in a more complex form in adulthood, remain uncertain. Is it simply related to immature immune systems in infants and young children, or does HBV genotype and other viral factors play a role? It is also not clear how HBV counteracts the natural host immune response to establish a persistent infection in the 5% of people infected in adulthood. Again, is this due to host factors, viral factors, or a combination of the two?

There are currently two schools of thought that either HBV is an "invisible" virus that initially establishes infection by avoiding the host's innate immune responses, or HBV facilitates initial infection and progression by actively manipulating the host's immune response in its interests.

Although the adaptive immune response is important for effective control of HBV infection, its role is more difficult to analyze, in part because HBV-infected patients are almost universally diagnosed within ≥10–12 weeks of infection [4, 5]. Studies with acute HBV-infected chimpanzees have shown that HBV did not modify host gene transcription at an early age and did not induce innate antiviral responses in hepatocytes and liver. Indeed, HBV did not enter the logarithmic phase of amplification until 5 weeks after infection, and no host transcripts, including IFN-α/β stimulated genes, were uniform or repressed during this period. Although it is possible that gene expression was below the detection limit, this phenomenon could also be explained by the following scenarios: HBV in chimpanzees is an invisible virus that cannot be detected by the innate immune response at an early stage of infection or HBV effectively suppresses the innate immune response very early after infection. Because only 5% of human adults progress to a chronic condition after an acute infection, it is also possible that a study using more chimpanzees might have identified innate antiviral responses in additional animals. Although aspects of the HBV life cycle, such as viral replication occurring within nucleocapsids, can effectively "hide" the viral nucleic acid from the cell, HBV proteins are expressed in the cytoplasm. Numerous studies have shown a direct interaction between these HBV-encoded proteins and innate immune responses, indicating that HBV has developed many mechanisms to counteract cellular defenses [6,7,8,22].

The human liver is an organ formed by two types of cells, non-parenchymal cells (Kupffer cells and sinusoidal endothelial cells) and parenchymal cells 14 (hepatocytes and modified epithelial cells), each with unique immunological characteristics. The innate immune response to HBV infection is mediated by an early response to specific “pathogen-associated molecular structures” and stimulates a subsequent adaptive

immune response that is critical for viral clearance [9]. Although HBV almost exclusively infects hepatocytes, it is becoming increasingly clear that other cells in the liver and peripheral blood play an important regulatory role in the innate immune response, which in turn regulates the adaptive immune response to infection.

Recovery of an adult infected with hepatitis B virus is associated with the involvement of T cells in HBV-infected hepatocytes in approximately 95% of cases. However, it is becoming increasingly clear that innate immune responses also play an important role in this process. Natural killer (NK) and natural killer T (NKT) cells are critical to host antiviral innate immune responses, linking the host to innate and adaptive immune responses, and play a central role in HBV clearance.

HBV infection has been found to directly activate NK cells by inducing cytokines such as IFN-, IFN-β, and interleukin (IL)-12, or indirectly by activating dendritic cells (DCs) and macrophages to produce IL-12, IL -18 and CXCR3 and other chemokines [11]. Activated NK cells destroy virus-infected target cells through direct cytotoxic effects, and also inhibit HBV replication by producing IFN-γ, tumor necrosis factor (TNF)-α, transforming growth factor-β, granulocyte macrophage colony-stimulating factor, and IL 10 [12 , 13, 14]. The development of a NK and NKT cell response in two HBV seronegative blood donors who became HBsAg- and HBV-DNA positive, at a constant normal level of 15 alanine aminotransferase, indicates that the innate immune system is capable of sensing HBV infection at a very early age [15]. In fact, a study quantifying hepatitis B virus (HBV) cognate replication kinetics and gene activation (a model of acute hepatitis B infection) 1 hour post-inoculation revealed a significant extended intrahepatic transcription of IFN-γ and IL-12, 3-6 hours post-inoculation [16]. It has been shown that in the early stages of human HBV infection, NK and NKT cells improved the production of IFN-γ and TNF-α in line with the peak of HBV replication, when the HBV-specific response of T cells was still very weak [15]. Within 48-72 h, NK and NKT cells were activated, and virus replication was temporarily reduced, indicating a stable innate immune response. However, T cells were activated only after 4-5 weeks. These data suggest that an innate immune response was activated, but a timely adaptive T cell response did not occur [16]. These observations are consistent with studies showing the highest frequency of circulating NK cells, where the earliest incubation period of natural HBV infection occurred, with NK cell numbers decreasing in line with the decrease in HBV DNA [5]. However, the role of NK cells in acute infection remains unclear. Recent results have shown that NK cell activation and the ability to produce IFN-γ decreased during peak viremia, and cytokines, including IFN type I, IL 15 and IFN-λ, were not appropriately induced during acute HBV infection. Transient inhibition of the NK response was consistent

with high levels of IL-10, which is an anti-inflammatory cytokine that inhibits NK and T cell function [17,21].

Rapid innate immune responses leading to viral clearance are not limited to non-parenchymal cells such as NK cells. Indeed, in vitro studies using differentiated HepaRG cells transduced with recombinant baculovirus 16 encoding the entire HBV genome showed that HBV elicited a strong and specific innate antiviral response in this cell line, resulting in non-cytopathic clearance of HBV DNA with upregulation of IFN-β , as well as other IFN-stimulated genes [20].

Chronic hepatitis is not always preceded by a recognizable acute form of hepatitis B. However, sometimes immediately after an acute episode there is a chronic infection process. In other cases, despite a sudden onset similar to an acute illness, chronic hepatitis is already present. Approximately 10% of adult patients with acute hepatitis B, HBsAg does not disappear from the blood serum within 12 weeks, and they become chronic carriers of the pathogen. Newborns with hepatitis B become chronic carriers in 90% of cases. Progression depends on the ongoing replication of the virus in the liver and the condition of the patient (especially the immune system). The virus has no direct cytopathic effect, and the lysis of infected hepatocytes is determined by the host's immune response. The persistence of the virus may be associated with a specific defect in T cells that prevents the recognition of HBV antigens. Impaired humoral and cellular immunity thus determines the outcome of hepatitis B. When there is a defect against the background of continued viral replication, a chronic carrier state develops with or without chronic hepatitis.

The phenomenon of viral interference, i.e. The ability of viruses to induce resistance of their infected cells to infection by other viruses or to interfere with viral replication in previously uninfected tissue culture cells has been known for a long time. In 1957, Isaacs and Lindenman isolated and described a factor capable of inducing cell resistance to a wide range of viruses. They suggested that this factor plays a similar role in vivo, blocking the spread of the virus to uninfected cells. The discovery of interferon caused a boom in research and expectations associated with 17 prospects for its possible clinical use, so that at present the field of its clinical application has become almost comprehensive: it is used as an antiviral agent, and in severe chronic infections, and even in diseases with unclear etiology and sluggish current process, for example, in multiple sclerosis. In the last decade, interferon therapy has been widely used in the treatment of acute and chronic hepatitis, but the effect of its use is ambiguous and depends on taking into account a number of concomitant infection factors. As for the role of interferon in the pathogenesis of CH, the data available in the literature are few and contradictory [2,17,18].

The pathogenesis of hepatitis B has a number of fundamental differences from hepatitis of other etiologies. The parenteral route of transmission of the pathogen ensures its hematogenous drift into the liver. The virus does not have a direct damaging effect on hepatocytes. Their cytolysis is carried out immunomediated, mainly due to the reaction of the cellular link of immunity through cytotoxic T-lymphocytes [4].

It has been established that with HB, the production of gamma-interferon, which activates the HLA system, is enhanced. As a result, class 1 histocompatibility molecules are expressed in combination with peptide antigens on the hepatocyte membrane, which are recognized by native cytotoxic T-lymphocytes. The latter proliferate and form clones of antigen-specific killers that infect virus-infected hepatocytes. To a lesser extent, the expression of class 2 histocompatibility molecules occurs, followed by the proliferation of type 1 T-helpers, which activate the bactericidal and cytotoxicity of macrophages. The latter, in turn, absorb the remains of necrotic intralobular and periportal hepatocytes [6].

The reaction from the humoral link is less significant in immunopathogenesis and consists in the production of specific antibodies to HBV antigens, their binding with the formation of immune complexes and the termination of circulation in the blood in a free form. However, the significance of the humoral response increases with the development of autoimmune processes that are involved in the genesis of chronic hepatitis [3].

The immunopathogenesis of HBs can be schematically represented as follows. In adults, the disease proceeds both with clinical symptoms (30-40%) and latently (60-70%), but usually ends with recovery, which indicates an adequate immune response. Chronic hepatitis develops in only 10-20% of adults who have had an acute infection, either latently or in a mild form, which is associated with an inadequate immune response. Pediatricians are less likely to see acute hepatitis B, since there is a direct correlation between a person's age and the presence of clinical manifestations in the acute stage of the disease. In children, the immune system is still "not mature enough" to recognize HBV as "foreign" and does not show sufficient activity to rid the body of the pathogen. That is why acute hepatitis B in most children is usually asymptomatic (90-95%), but very often leads to the development of chronic "carriage" of HBV (70-90%), and, consequently, chronic hepatitis (30-50%).

Thus, an adequate immune response, which ensures the relief of the infectious process, corresponds to acute hepatitis B of a cyclic course with complete recovery. It should be noted that although the immune response plays a dominant role in the pathogenesis of hepatitis B, the final outcome of the infectious process is not always

determined by the state of the immune system of the macroorganism. It is also necessary to take into account the biological cycle of development of the pathogen itself, in particular, the activity of viral replication. For example, with high replicative activity and an adequate immune response, a typical clinically manifest acute hepatitis B develops. In turn, the low activity of viral replication causes a weak protective reaction of the body, which leads to mild or asymptomatic course of hepatitis B with rapid relief of the infectious process and recovery. At the same time, 19 relatively mild manifestations of T-cell cytotoxicity can be considered as adequate [7,8,19,22].

Most clinicians associate the occurrence of fulminant hepatitis with the development of an excessive humoral hyperimmune response, resulting in massive liver necrosis. In this case, the regeneration of the liver tissue does not occur or develops slowly. Excessive immune response can be determined immunogenetically. Some researchers admit that mutant strains of HBV (in particular, the HBVe strain), as well as accelerated apoptosis of hepatocytes induced by HBV, may play a certain role in the genesis of the fulminant course of hepatitis [1, 3].

Chronization of the infectious process in hepatitis B is facilitated by a decrease in the production of alpha-interferon, which limits the spread of the virus from infected cells and protects intact hepatocytes. The presence of HBV replication, in particular, in peripheral mononuclear cells, the circulation of immune complexes, the direct inhibitory effect of the pathogen on the function of some systems play an important role in the pathogenesis of chronic hepatitis, predisposing to damage to other organs with the development of extrahepatic manifestations.

The course and outcomes of HBV infection are influenced by immunogenetic factors. Thus, during HLA phenotyping of HB patients, a weakened and delayed immune response is recorded with predominant frequency in representatives of the B-18, B-35, B-7, DR-2, and DR-7 phenotypes. In addition, it has been found that men are infected with HBV more often than women, since men more often than women have a genetically determined weakened immune response [4,24].

Conclusion

Thus, although progress in this area has been hampered by the absence of a reliable infection model, the main body of evidence base taken from various studies using models animals, primary human cells, cell lines and humans, showed that the innate immune response is an important regulator of HBV infection, and that HBV has developed numerous mechanisms that undermine innate immune response of the body. It is quite likely that such “subversive activity” contributes to the establishment and maintenance of permanent infection. However, it is to be hoped that, thanks to

further understanding of the intricacies of the interaction between IGW and innate immune response, scientists will be able to develop effective treatments for CHB infection, thereby giving hope to 325 million people around the world living with hepatitis B.

Reference

1. Abdurakhmanov, D.T. Chronic hepatitis B and D / D.T. Abdurakhmanov. - M.: GEOTAR-Media, 2012. - 421 p.
2. Asabe S, Wieland SF, Chattopadhyay PK, et al. The size of the viral inoculum contributes to the outcome of hepatitis B virus infection. J Virol 2009; 83: 89 9652-9662.
3. Audsley J, Littlejohn M, Yuen L, et al. HBV mutations in untreated HIVHBV co-infection using genomic length sequencing. Virology 2010; 405: 539-547. Medline doi:10.1016/j.virol.2010.06.038
4. Bakiyeva M. Sh., Zaynobiddinov A. D., Usmanov P. B.,Esimbetov A. TVasorelaxant Effect of Heteratisine and 6-O-Benzoyl Heteratizine on Functional Activity of Aorta Smooth Muscle Cells//International journal of Current Microbiology and Applied SciencesAcademy of Sciences of Uzbekistan-Tashkent, 2007. - 16 p.
5. Barchet, W., Cella, M., and Colonna, M. Plasmacytoid dendritic cells—virus experts of innate immunity. Semin Immunol. 2005; 17: 253–261
6. Baron JL, Gardiner L, Nishimura S, Shinkai K, Locksley R, Ganem D. Activation of a nonclassical NKT cell subset in a transgenic mouse model of hepatitis B virus infection. Immunity 2002; 16: 583-594. Medline doi:10.1016/S1074-7613(02)00305-9
7. Basler CF, Mikulasova A, Martinez-Sobrido L, et al. The Ebola virus VP35 protein inhibits activation of interferon regulatory factor 3. J Virol 2003; 77: 7945- 7956. Medline doi:10.1128/JVI.77.14.7945-7956.2003
8. Beck J, Nassal M. Hepatitis B virus replication. World J Gastroenterol. 2007; 13: 48-64. Medline
9. Bell SJ, Lau A, Thompson A, et al. Chronic hepatitis B: recommendations for therapy based on the natural history of disease in Australian patients. J Clin Virol 2005; 32: 122-127. Medline doi:10.1016/j.jcv.2004.10.009
10. Bondarenko A.L. - Epidemiology and infectious diseases. - 2008.
11. Chen Y, Wei H, Gao B, Hu Z, Zheng S, Tian Z. Activation and function of hepatic NK cells in hepatitis B infection: an underinvestigated innate immune response. J Viral Hepat 2005; 12: 38-45. Medline doi:10.1111/j.1365- 2893.2005.00543.x
12. Khokhlova O.N., Reizis A.R. - Pathogenetic and clinical significance of plasmacytoid dendritic cells in viral hepatitis C in children and adults - 2013, p. 146

13. Khokhlova O.N., Reizis A.R., Serebrovskaya L.V. Plasmacytoid dendritic cells in chronic hepatitis C in adults and children (role in pathogenesis and response to interferon therapy). infectious diseases. 2013. V. 11. No. 1. P. 6-11.
14. Khokhlova O.N., Reizis A.R., Serebrovskaya L.V., Chizhov S.A. Normal quantitative and functional parameters of plasmacytoid dendritic cells in peripheral blood in healthy children and adults. In the collection: Collection of scientific papers for the 50th anniversary of the Central Research Institute of Epidemiology of Rospotrebnadzor Moscow, 2013. P. 311-314.
15. Muazzam Bakiyeva, Shokhista Rustamova, Yodgormirza Nurmatov. Hypotensive Effect Of The Plant Alkaloid Digitaalisen On The Functional Activity Of Mmc Aortic Chrysallida Of Dihydroemetine On The Functional Activity Of Smc In The Aorta Of The Rat / The American Journal of Agriculture and Boimedical Engineering (ISSN – 2689-1018) December 30, 2020 | Pages: 42-48 Doi: https://doi.org/10.37547/tajabe/Volume02Issue12-08 IMPACT FACTOR 2020: 5. 34
16. N. D. Yushchuk, E. A. Klimova et al. Viral hepatitis. Clinic, diagnosis, treatment - M. : GEOTAR-Media, 2012. - 150 p.
17. Podymova, S.D. Chronic hepatitis / S.D. Podymov.- M.: Medicine, 2016. – 280 p.
18. Rodina D.V. - Med. immunology. - 2002. - No. 2. - P.253-254
19. Rustamova Sh.O., AbdullayevA.A.,TurdikulovaSh.U.Determination of quantitation of the HER2/neu gene in tumors by a rt-PCR method // International Journal of Advanced Science and Technology. – 2020. –№29/5. – P. 1612- 1618.
20. Shakhgildyan I.V., Mikhailov M.I., Onishchenko G.G. - Parenteral viral hepatitis (epidemiology, diagnosis, prevention). 2003, p. 384.
21. Shokhista Rustamova, Yodgormirza Nurmatov , Muazzam Bakiyeva , Tokhirjon Rakhmanov. Comparative Analysis Of Rt-Pcr And Immunohistochemistry Methods For Determining Her2 Status In Breast Cancer Samples/ European Journal of Molecular & Clinical Medicine ISSN 2515-8260 Volume 07, Issue 03, 2020/ Pages: 3924-3929.
22. Sukriti S, Pati NT, Bose S, Hissar SS, Sarin SK. Impaired antigen processing and presentation machinery is associated with immunotolerant state in chronic hepatitis B virus infection. J Clin Immunol 2010; 30: 419-425. Medline doi:10.1007/s10875-010-9379-4
23. Yarilin A.A. Immunology. 2010 P. 71-74
24. Yushchuk N.D., Vengerov Yu.A.; ASMOK. Infectious diseases: nat. hands / Ch. ed. - Moscow: GEOTAR-Media, 2009. - 1056 p.: tab. - (National leader). - Bibliography. at the end of ch. - Item decree: p. 1031-1047