IMMUNOGENETIC ASPECTS OF PATHOGENESIS OF CHRONIC HCV-INFECTION (REVIEW)

KHAMID KARIMOV, SEVARA AZIMOVA, BAKHTIYOR IRISKULOV

Tashkent Medical Academy, Research Institute of Hematology and Blood Transfusion, Uzbekistan

ABSTRACT

Viral hepatitis B and C is a relevant issue because of high prevalence and degree of chronicity, late diagnosis and poor prognosis. Today, protein products of numerous genes are involved in the pathogenesis of viral pathology of the liver. In this review, the authors analysed 42 literature sources on genetic basis of susceptibility to various infectious diseases. Study of the role of immunogenetic factors is of great practical importance to develop methods for predicting outcomes of viral hepatitis.

UDC CLASSIFICATION & KEYWORDS

■ 616-022.6 ■ 616-056.7 ■ 577.158.83 ■ Chronic Hepatitis ■ Hcv-infection ■ Pathogenesis ■ Immunogenetic Factors ■ CTLA-4 Gene ■

INTRODUCTION

Infectious diseases are a convenient model for studying genophenotypic features in the determination of complex multifactorial signs of a human, because of possibility to allocate an underlying factor that determines the development of disease [1,2,3,4,5]. Viral hepatitis as a model of such pathologies are characterized by high prevalence, high degree of chronicity, late diagnosis and poor prognosis. The study of hepatitis B and C viruses dictates the need to identify the peculiarities of the human genome.

The relevance of this infection is associated with the fact that viral hepatitis B and C are widespread diseases. According to the WHO, hepatitis B infects more than 5% of population in the world and hepatitis C approximately 1%. Due to high degree of chronicity, severity of complications, lack of effective therapies this problem is a field of studies of specialists of various profiles. Hepatitis B and C are the most common etiologic factors for hepatocellular carcinoma. Co-infection develops in 3% of European population and causes 5% of cases of acute viral hepatitis [6,7]. 200 million people in the world are infected with hepatitis C virus. Even in civilized countries like the UK, hepatitis C virus infects 600 thousand people. However, cause for concern that a large number of carriers of the virus have been not identified [8].

The beginning of this century marked the beginning of active study the genetic basis of susceptibility to various infectious diseases. Heredity is important in the realization of increased individual human sensitivity to the appearance, course and outcome of various diseases. Because of the close relationship between structure and function of HLA, as well as its role in the immune response, HLA-genes are regarded to be markers with pathogenetic significance in many diseases.

A number of studies show that the genes have the controlling role in the implementation processes of immune responsiveness, resistance to certain infections, co-operation of immune cells, immune suppression, etc. [9,10,11,12,13,14].

New insight into pathogenesis of chronic viral hepatitis (immunogenetic factors)

Today, there are numerous genes which protein products are involved in the pathogenesis of hepatitis [15,16]. Of them, the family of genes that determine the functioning of detoxification of xenobiotics and regulation of the immune system has the special significance. Until recently, the study of genes of HLA traditionally is poor. However, of course, other immune system genes directly involved in the antiviral response in HCV-infection have significant value.

There is enough information showing the importance of dysfunction of enzymes of biotransformation of xenobiotics and anti-inflammatory cytokines (TNF-a, TGF-b) and cytotoxic T-lymphocytes (CTLA-4) in the pathogenesis of viral diseases of the liver. Immune status is conditioned primarily by genetic factors. In this context, immunogenetic aspects define the features of the development and progression of viral hepatitis.

In particular, CTLA-4 (antigen of four cytotoxic T-lymphocytes) is a receptor expressing on the membranes of T-cells, mediates inhibition of the immune response of T-cells [17,18].

The simultaneous interaction of the MHC 11 molecule, bearing an antigenic peptide, and B7 ligand, located on the cell membrane, with T-cell and SD28 receptors of T-lymphocytes, respectively, is important for efficient antigen presentation. Subsequent termination of lymphocytic response is connected with activation of T-helpers and cytotoxic T-lymphocytes, which begin to express CTLA-4 receptors [19,20,21,22]. Maintaining homeostasis after active immune response to antigen is largely ensured by inhibitory effect of CTLA-4, due to reduced transcription of IL-2, cessation of proliferation of T-lymphocytes with the subsequent development of functional indifference [23]. Suppressive effect of CTLA-4 on the activation of T-cells is confirmed by laboratory and clinical studies [24,25].

Now, there are two mechanisms of release of the inhibitory effect of CTLA-4. The first specific signal is sent at the time of the binding of complex "antigen+MHC" of antigen-presenting cells with T-cell receptor. The second, non-specific, signal is

sent after the connection of another T-cell receptor (SD28) with its ligands on the surface of cells presenting antigen [26]. T-cell response in the initial phase is characterized by limited expression of B7 and CTLA-4. Then, at the late stage of immune response is mediating inhibition of proliferation of T-lymphocytes, which are mainly connected with B7 sequestration [27], delaying B7-SD28 signal, and with decreased IL-2 production. Dariavach et al. [28] found that CTLA-4 gene is localized on chromosome 2q33 and consists of four exons. CTLA-4 gene consists of 149 amino acids and is expressed by activated CD4 and CD8 T-lymphocytes. The researchers found that CTLA-4 gene has three polymorphic markers: -318S/T in the promoter region, +49 A/G in the first exon, and AT dinucleotide repeat sequences, whose number varies from 7 to 30, located in the 3'-untranslated region. Population studies suggest linkage of alleles -318T and +49A [29], alleles -318S and +49G [30] and alleles (AT)7 and +49G [31]. Of these three polymorphisms, only that at position +49A/G (Thr17Ala) has functional significance and is associated with the development of immunopathological processes [32], so, determination of this polymorphism has the important diagnostic value.

Alleles of CTLA-4 gene, carrying the A or G at position 49 of first exon, correspond to threonine or alanine in the leader peptide of CTLA-4 molecule. G allele is characterized by reduced control over the proliferation of T-cells and is associated with the development of immunopathological diseases. Experiments *in vitro* have demonstrated that in cells with +49 GG genotype proliferative response to stimulation by B-lymphocytes and dendritic cells was more significant, in comparison with cells that have genotype AA 49 [31,33]. This reflects accumulation of 3H thymidine mRNA expression of interleukin-2 and IL-2 secretion.

Currently, the influence of CTLA-4 on various diseases has been actively investigating. For example, Yee et al. [34] analyzed the polymorphism of +49 A/G of CTLA-4 gene in patients with chronic hepatitis C: 79 patients with sustained virological response after combined therapy with interferon and ribavirin and 79 patients with persistent viremia who although received etiological treatment. These data demonstrated the relationship of allele G with sustained virologic response. However, the study of influence of the polymorphic locus of CTLA-4 in viral hepatitis B conducted by Alizadeh et al. [35] showed that the genotype 318C/T influences the susceptibility to the development of this pathology.

Comparative analysis of polymorphism of the immune system in patients with chronic hepatitis B and C in the experimental and control groups revealed that the frequency of the identified genes in all groups was within the values characteristic for European populations of the world [36]. In this case, CTLA-4 gene had the highest level of polymorphism in chronic hepatitis C in the Russian population.

Despite of available literature, the effect of genotype by certain polymorphic variants of genes on variability of parameters that important for the development and progression of chronic viral hepatitis is poor understood.

Along with that, several researchers have evidence of association of polymorphism 49 A/G of CTLA-4 gene with diabetes mellitus type 1 – an autoimmune disease, in the development of which hereditary predisposition has the significant role. For example, Abramov et al. [37] showed the presence of association of polymorphism 49 A/G of CTLA-4 gene with diabetes mellitus type 1 in the Russian population. Studies by Skorodok et al. [38] revealed that genotype AA of polymorphism 49 A/G of CTLA-4 gene increases the risk of autoimmune thyroiditis in the preschool age period, and the absence of genotype GG may lead to more severe disease with impaired thyroid function.

Valuiskyh et al. [39] noted that the frequency of polymorphism of CTLA-4 gene in patients with bowel inflammatory diseases did not differ significantly, depending on the nature of the course, severity and form of the disease, as well as presence of complications.

Studies carried out by Alieva et al. [42] in 44 patients with allergic rhinitis and 70 apparently healthy donors of the Uzbek population found that the incidence of "adverse allele" of polymorphism 49A/G of CTLA4 gene in the experimental and control groups did not differ significantly, amounting for 73.3 and 72.9 %, respectively.

We should note that researches conducted in most cases include studies of one or more of the polymorphisms in isolation.

Conclusion

The information on the combined analysis, including the determination of connection of genotype as a combination of several alleles of polymorphisms, is still incompletely understood. The contribution of unfavorable alleles of genetic markers in the development and chronicity of viral hepatitis is yet unknown. In addition, there is no clear understanding of the role of each gene in the pathogenesis of hepatitis. Taking into account that the progression of disease is associated not with virological factors, but with the peculiarities of microorganism [40, 41], study of the role of immunogenetic factors, such as CTLA-4, is of great practical importance to develop methods for predicting outcomes of viral pathology of the liver.

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