Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 4174 - 4184
Received 16 February 2021; Accepted 08 March 2021.

Polymorphism of Pro- And Anti-Inflammatory Cytokines in Chronic HBV and HCV Infection

Fayzullaev Khayrulla[1],Asilova Mukhaye[2], Kamalov Zaynitdin[3], Ziyadullaev Shukhrat[4]
[1,2,3] Institute of Immunology and Human Genomics of the Academy of Sciences of the Republic of Uzbekistan

[4] Samarkand State Medical Institute

Abstract.
To date, it has been established that in the formation of the immune response the most important place belongs to the polymorphic genes of the cytokines IL-1β, IL-6 and TNFα and the genes of their receptors. To date, convincing data on the association of single nucleotide substitutions with the features of the course of viral hepatitis have been obtained only for a small number of polymorphisms and there are no unambiguous data on the effect of polymorphism in the genes of the IL-1β, IL-6 and TNFα cytokines on the pathogenesis of chronic HBV and HCV infection, and the response to treatment and development of complications. Studies have established an association of polymorphic markers of the gene IL-10 (G1082A), IL-4 (C589T) and TNFα (G308A), which are located in the promoter regions, with the degree of liver fibrosis in CHC patients. In individuals of the Negroid race, the –863A allele of the TNF-α gene is associated with HCV clearance; in addition, the wild-type –863C / –308G haplotype correlates with the persistence of viral infection, although no such relationships were found among the Caucasians. Thus, given the presence of a pathogenetic relationship between the course of chronic HBV and HCV infection and the peculiarities of the functioning of the cytokines IL-1β, IL-6 and TNFα (regulation of inflammation and immune response and the stage of fibrotic changes in the liver), it is of particular interest to assess the role of gene polymorphism of these cytokines. in the development of chronic HBV and HCV infection, and its complications.

Ключевыеслова: polymorphisms, interleukin-4, interleukin-6, interleukin-10, tumor necrosis factor-alpha

Relevance.
Along with the outstanding successes of the international program "Human Genome", the problem of the diversity of the human genome is also attracting more and more attention. genetic polymorphism. In recent years, the association of candidate gene polymorphism with viral hepatitis, features of the course of this disease and its complications has been actively studied [54,57]. At the same time, particular importance is attached to the role of cytokine gene polymorphism - important participants in the immunopathogenesis of viral hepatitis, which determine the nature of the interaction of the pathogen and the macroorganism, affect the chronicity of HBV and HCV infections, and modify the rate of fibrogenesis in the liver. Thus, the functioning of the cytokine system is determined by several factors, primarily genetic factors, therefore, immunogenetic aspects determine the characteristics of the development and progression of viral hepatitis, including genetic ones. The molecular basis

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 4174 - 4184
Received 16 February 2021; Accepted 08 March 2021.

of hereditary factors is SNP in the genes of various cytokines and their receptors, which can be localized in the coding or promoter part of the gene. At the same time, SNP in the regulatory part of a gene can affect the level of its expression, which leads to a change in the amount of its product - protein [43, 45]. Based on the study of gene polymorphism, it became possible with a high degree of probability to predict the predisposition to the development of viral hepatitis C and the state of resistance. The phenotype of the host is of decisive importance. Unlike viral hepatitis C, the progression of fibrosis in viral hepatitis B is significantly more correlated with the genotype of the virus, but the polymorphism of the host cytokine genes can determine the development of hepatocellular carcinoma. However, data on studies of genetic factors for the progression of chronic hepatitis B and C are often contradictory and largely depend on the patients' belonging to a particular ethnic population [37].

When HCV and HBV infections interact with the immune system, both adaptive humoral reactions with the formation of virus-specific antibodies and T-cell reactions with the participation of cytokines are activated. In this case, the leading factor in the development of chronic viral hepatitis B and C is insufficient production of cytokines and / or a decrease in the sensitivity of viruses and body cells to them, which may be due to the influence of allelic variants of cytokine gene polymorphism [50]. Each gene of a cytokine and its receptor has up to 20 allelic variants, which differ mainly in their influence on the final level of cytokine production. Various combinations of allelic variants of cytokine genes can form both their balanced production, characteristic of two main groups of regulatory lymphocytes - Th1 and Th2, and unbalanced [49]. At the same time, an individual ensemble of allelic variants of cytokine genes can partly determine the nature of the inflammatory process, its course and outcomes [48,52].

To date, it has been established that in the formation of the immune response the most important place belongs to the polymorphic genes of the cytokines IL-1β, IL-6 and TNFα and the genes of their receptors. In this regard, studies continue to identify genetic markers that are associated with the individual reactivity of the body to the effects of hepatitis C and B viruses, and which allow predicting the rate of progression of fibrosis and the stability of the response to antiviral therapy [42,46,56]. It has been shown that the level of production of cytokines and their antagonists, the level of expression of receptors for a particular cytokine are determined by a set of allelic variants of cytokine genes and genes of their receptors inherited by humans [4,44].

IL-1β gene polymorphism and the risk of developing liver cirrhosis

The IL-1β gene is located on chromosome 2q14. The most studied polymorphism of the IL-1β gene is a single-nucleotide C-to-T substitution at position –511 of the gene promoter region, leading to an increase in IL-1β secretion [10]. The frequency of occurrence of –511C / T polymorphism does not differ in patients with Caucasian viral hepatitis C with different treatment outcomes [1,3]. Also, no correlation was found between the prevalence of IL-1B gene polymorphism (at positions –511 and +3954) and spontaneous elimination of HCV in England [25]. Studies have shown that the allele - 511T of the IL-1β gene is more often associated with a more severe degree of liver fibrosis in CHC patients [55]. In a study of patients with CHC in Japan, it was revealed that the genotype - 511TT of the IL-1β gene is an

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 4174 - 4184
Received 16 February 2021; Accepted 08 March 2021.

important risk factor for the development of HCC [33]. However, when comparing representatives of the Caucasian and Mongoloid races, the relationship between single nucleotide substitutions at the –511C / T position of the IL-1β gene and the incidence of HCC in the outcome of CHC was not established [39,40]. The effect of this polymorphism on the course of CHC and antiviral therapy in patients of East Slavic origin has not been fully studied [21].

The influence of IL-1β-31 T / C gene polymorphisms on the state of the immune response in HBV and HCV was established. The CC IL-1β-31 genotype was characterized by suppression of cellular immune responses, which was accompanied by overproduction of pro-inflammatory cytokines. In this study, differences in the occurrence of genotypes of genes IL-1β -31 T / C and IL-6 -174 G / C between patients with chronic viral hepatitis B and C and healthy people were identified. Patients with chronic viral hepatitis B and C were characterized by an increased frequency of the CC genotype of the IL-1β -31 T / C gene and the CC genotype of the IL-6 -174 G / C gene in comparison with the control group and, probably, more susceptible to the development of this disease in case of contact with pathogenic [29].

IL-6 gene polymorphism and the risk of developing liver cirrhosis

The IL-6 gene is located on chromosome 7p21. Since the late 1990s, several SNPs have been found in the promoter of this gene [32]. The presence of allelic variants in the promoter region of the IL-6 gene leads to different levels of transcription of this gene. It was found that polymorphism of the promoter part of the IL-6 gene (–174 G / C) affects the level of this cytokine in the blood [12]. People with allelic variants GG and GC have a higher serum content of this cytokine than people with the CC genotype [5]. The prevalence of the G allele differs in different ethnic groups: in representatives of the Caucasian race, this allele is found much less frequently than in representatives of other races [24]. So, in Europeans, the frequency of occurrence of the GG allele is 0.54 - 0.62; for Africans, Native Americans, Singaporeans - 0.87 - 1.00. Associations were found between the –174C / G polymorphism of the IL-6 gene and the stage of liver fibrosis in HCV in the indigenous inhabitants of Italy [8]. The G allele of the –174C / G polymorphism of the IL-6 gene was more often associated with the development of rapid liver fibrosis in CHC patients [4]. It is noteworthy that among the Italian population, the carriage of the –174G allele of the IL-6 gene and a high degree of fibrosis are more common in men [20]. The data of domestic studies are contradictory. In one study, it was shown that the genotypes of the IL-6 gene –174GC and –174CC are significantly more likely to be detected in a rapidly progressing than in a favorable course of the disease [41]. But in another study, conducted in the Tomsk region, among patients with a high degree of inflammatory activity, carriers of the 174GG genotype reliably prevailed. Carriage of genotypes -174CG and -174CC of the IL-6 gene was more common in patients with minimal and moderate inflammation. However, when assessing the value of the –174C / G polymorphism in the promoter region of the IL-6 gene in the development of fibrosis, insignificant differences in the frequencies of variant alleles and gene genotypes were obtained in patients with HCV infection with varying degrees of liver fibrosis [19]. Thus, there are no unambiguous data on the effect of polymorphism in the promoter region –174

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 4174 - 4184
Received 16 February 2021; Accepted 08 March 2021.

G> C of the IL-6 gene on the pathogenesis of chronic HCV infection and on the effectiveness of AVT.

Studies have revealed an increase in serum levels in patients with chronic HCV infection. The overproduction of IL-6 with an increase in its level in the blood serum was significantly more often associated with the carriage of the IL6 –174G gene allele than the IL6 –174C allele ($p < 0.05$). In addition, an association was found between the presence of cryoglobulinemia and associated systemic manifestations, including progression of fibrosis and kidney damage, among patients with elevated serum IL-6 levels compared with patients without an increase [51].

A study of patients with chronic viral hepatitis B and C showed an association of the level of IL-1β production in the blood with the IL-6 -174 G / C polymorphism. Carriers of wild-type GG were characterized by a higher synthesis of IL-1β in comparison with the group of heterozygous GC patients and abnormal CC homozygotes. Polymorphic variants IL-1β -31 TC and CC, as well as IL-6 -174 CC, are associated with a higher level of cytolysis, and the genotypes IL-1β -31 TT and IL-6 -174 GC and GG are associated with inactive hepatitis [11] ...

Studies of some authors have shown the effect of IL-6 polymorphisms (-597 and -174) on the severe course of chronic HCV infection [2] and chronic hepatitis B. In studies of another group of authors, no such relationships were found [18,26].

TNF-α gene polymorphism and the risk of developing liver cirrhosis

Tumor necrosis factor alpha (TNF-α) plays a special role in the formation of the antiviral immune response [18]. TNF-α is a multifunctional cytokine with pronounced pleiotropy, takes part in the formation of the body's defense reactions, stimulates the Th-1 cellular immune response, phagocytic and cytotoxic activity of cells, and regulates the processes of immune inflammation. All this contributes to the progression of liver fibrosis with an increase in the cytokine level TNF-α and IL-1βcontrol the balance between cell proliferation and apoptosis [25]. One of the important biological functions of TNF-α is its participation in the regulation of apoptosis, including in cells damaged by the virus [18]. TNF-α is secreted by various cells, for example, activated macrophages [45], cytotoxic T-lymphocytes in the liver [38].

There are numerous reports in the literature demonstrating changes in TNF-α production in viral infections. An increased level of TNF-α in blood plasma was found during exacerbation of such chronic infections as viral hepatitis, HIV, herpes type I, Epstein-Barr, influenza, poliomyelitis, tick-borne encephalitis, etc. [17]. With CHC, there is an increased level of TNF-α in the blood serum and in the liver parenchyma in patients [19]. HCV stimulates the secretion of TNF-α by human hepatocytes [29]. In particular, it is known that an increase in TNF-α production in chronic viral hepatitis C at an early stage of the infectious process can mediate increased apoptosis of hepatocytes, which leads to the destruction of the liver tissue, followed by a decrease in apoptotic cell death and, as a consequence, the possible development of malignant neoplasms [45] ... It is believed that the overproduction of this cytokine is one of the main mechanisms of activation of the infectious process during its transition from the latent state to the phase of clinical manifestations and indicates the progression of the disease.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 4174 - 4184
Received 16 February 2021; Accepted 08 March 2021.

The TNF-α gene is localized on chromosome 6 in the region where the molecules of the major histocompatibility complex of the first (HLA-A, B, C) and second (HLA-DP, DQ, DR) classes are encoded [46]. The TNFA gene promoter region includes 8 polymorphic regions with single nucleotide substitutions: - 1031T> C, - 863C> A, - 857C> T, - 575G> A, - 376G> A, - 308G> A, - 244G> A, –238G > A. However, the most significant are the single nucleotide substitutions of guanine for adenine at positions - 308 and - 238, which cause changes in the level of TNF-α production. It was shown that cells of donors homozygous for genotype A / A synthesize 3 times more cytokine than cells of individuals with genotype G / G [23]. Another polymorphic region of the TNFA gene that affects cytokine production is 238G> A. However, in this case, the replacement of guanine with adenine leads not to an increase but to a decrease in protein production. Stimulation of whole blood cells with lipopolysaccharide showed that cells with the G / A genotype synthesize 1.5 times less TNF-α than cells with the G / G genotype. Thus, single nucleotide substitutions at positions - 308G>A and 238G> A of the TNFA gene are associated with an increase and decrease in the expression level, respectively. Polymorphism - 308G> A of the TNFA gene also affects the transcriptional activity of the TNFB gene localized in the same cluster [14].

Several SNPs of this gene are known, localized in the main one in the promoter region [18], the most studied of which is the –308G / A polymorphism of the promoter region of the TNF-A gene. Polymorphism of the TNF-α gene at positions –308, –238, –863 of the promoter region affects the expression of TNF-α and is involved in the pathogenesis of many infectious diseases. For example, allele - 863A of TNF-α gene is associated with Crohn's disease [13] and human T-lymphotropic virus type I [25]. The results of studies of the involvement of the TNF-α polymorphic gene in the outcomes of acute hepatitis C are controversial, which may be due to different ethnicity of patients, as well as different sample sizes. There is a hypothesis that TNF-α can serve as a prognostic marker of HCV outcomes. It is known that the incidence of spontaneous HCV clearance is different among Caucasians and Africans. In individuals of the Negroid race, the –863A allele of the TNF-α gene is associated with HCV clearance; in addition, the wild-type –863C / –308G haplotype correlates with the persistence of viral infection, although such relationships were not found among the Caucasians [47]. The –863A allele of the TNF-A gene promoter is also associated with virus clearance in HCV patients among the Sicilian population [19]. The involvement of the –308 and –238 polymorphisms of the TNF-A gene in the elimination of HCV in individuals of the Caucasian race has not been established [7].

Thus, differences in the allele frequencies of the gene IL-4 (C589T), IL-10 (G1082A), TNFα (G308A) were revealed between patients with chronic hepatitis C and healthy individuals in an ethnically homogeneous group of residents of the Odessa region. In the same study, the association of polymorphic markers of the gene IL-10 (G1082A), IL-4 (C589T) and TNFα (G308A), which are located in the promoter regions, with the degree of liver fibrosis in CHC patients was established [33].

According to a meta-analysis by Chen Y. and Pei J. based on 12 studies from 2004-2007, no significant association was found between the –308G / A polymorphism of the TNF-α gene and the severity, viral load and frequency of spontaneous elimination of HCV among all individuals of different ethnic groups [6]. Although according to C.Y. Dai et al. TNF-a promoter polymorphism at position –308 correlates with the severity of fibrosis and viral load

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 4174 - 4184
Received 16 February 2021; Accepted 08 March 2021.

in CHC [9]. Among Caucasians, the –238A allele is more common in HCV patients than in uninfected people. Genotype-863CC of the TNF-α gene is more common in patients with CHC, while no such relationship was found for the –238G / A and –308G / A polymorphisms [38]. In indigenous people of Mexico, no differences were found in the prevalence of polymorphism - 238G / A and –308G / A of the TNF-A gene among sick and healthy people [35]. The –308A allele is more common among residents of Southeast Asia with cirrhosis of the liver as a result of CHC [38]. The frequency distribution of allelic variants of the –308 G / A polymorphism of the TNF-A gene is not associated with the risk of the development and chronicity of viral hepatitis C among the Eastern Slavs living in Western Siberia [53]. Analysis of polymorphic loci of the TNF-A gene in patients of the European population did not reveal associations with the effectiveness of antiviral therapy and with the rate of formation of liver fibrosis in CHC. [16]. The role of SNP –238 G> A of the TNF-α gene in patients of East Slavic origin has not been adequately studied [25].

Niro et al analyzed the effect of TNF-α polymorphism - T1031C, C863A, G308A, and G238A - on hepatitis B virus clearance. 184 patients with chronic hepatitis B and 96 controls with documented clearance were examined. It has been shown that in carriers of the _308 GG genotype and TCGG haplotype the prognosis is poor [27].

Genetic analysis revealed an association between polymorphisms in the TNF-α promoter region and HBV located at -308G / A [3,36], while another study suggested that TNF-α promoter polymorphisms (at position -238A, - 308A, -857T, -863A and -1031C) are important host genetic factors that can determine the clinical outcome of HBV infection [13,30]. These data may indicate a role for TNF-α in the pathogenesis of hepatitis B, as well as in the development of its complications.

Japanese scientists investigated the allele frequencies of the TNFα gene (polymorphisms _238 and _308) in patients with chronic HCV in inactive (n = 50) and active (n = 50) forms and in 40 healthy people. The allele frequencies of the promoter region of the gene did not differ in the groups, but at the same time, the influence of these two types of polymorphism, as well as polymorphism of the TNFα gene and the HLADRB1 haplotype, on the activity of chronic HCV was noted [34,51].

A number of studies have shown the contribution of polymorphisms –592A / C, –1082G / A, –819T / C to predisposition to hepatitis C, response to therapy and disease outcome in Caucasian and Mongoloid populations [15,17,20]. However, the results obtained are often contradictory. Thus, for TNFα and IL10 gene polymorphisms, a number of researchers have not established associations with hepatitis [22,28,30,31].

Studies of the genetic component of chronic viral hepatitis have shown that the IL4RA (Ile50Val) and TNFα (G-308A) genes are involved in the formation of the characteristics of the course of chronic viral hepatitis: the Ile / Val genotype of the IL4RA gene is associated with more pronounced stages of fibrosis, and the G / A genotype of the TNFα gene - with a low degree of fibrosis. Patients with chronic viral hepatitis who are carriers of the heterozygous genotype for the IL4RA gene (Ile50Val) will have an increased risk of developing liver fibrosis [21].

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 4174 - 4184
Received 16 February 2021; Accepted 08 March 2021.

CONCLUSION.

Thus, to date, convincing data on the association of single nucleotide substitutions with the features of the course of viral hepatitis have been obtained only for a small number of polymorphisms, and there are no unambiguous data on the effect of polymorphism in the genes of the IL-1β, IL-6 and TNFα cytokines on the pathogenesis of chronic HBV and HCV infection. , response to treatment and development of complications. Considering the presence of a pathogenetic relationship between the course of chronic HBV and HCV infection with the peculiarities of the functioning of the cytokines IL-1β, IL-6 and TNFα (regulation of inflammation and immune response and the stage of fibrotic changes in the liver), it is of particular interest to assess the role of gene polymorphism of these cytokines in the development of chronic HBV and HCV infection and its complications.

REFERENCES

[1] Abbas Z, Moatter T., Hussainy A., Jafri W. Effect of cytokine gene polymorphism on histological activity index, viral load and response to treatment in patients with chronic hepatitis C genotype 3. // World J. Gastroenterol. 2005. V. 11.No. 42. P.6656-6661.

[2] Barrett S., Collins M., Kenny C., Ryan E., Keane CO, Crowe J. Polymorphisms in tumor necrosis factor-alpha, transforming growth factor-beta, interleukin-10, interleukin-6, interferon-gamma, and outcome of hepatitis C virus infection. J. Med. Virol., 2003, vol. 71, no. 2, pp. 212-218.

[3] Basturk B, Karasu Z, Kilic M, Ulukaya S, Boyacioglu S, Oral B (2008) Association of TNF-alpha −308 polymorphism with the outcome of hepatitis B virus infection in Turkey. Infect Genet Evol 8: 20-25

[4] Bedossa P., Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group // Hepatology. 1996. V. 24. P. 289-293.

[5] Cecere A., Marotta F., Vangieri B. et al. Progressive liver in-jury in chronic hepatitis C infection is related to altered cel-lular immune response and to different citokine profile // Panminerva Med. 2004. No. 46. P. 171-187.

[6] Chen, Y. and J. Pei. An assessment of a TNF polymorphic marker for the risk of HCV infection: meta-analysis and a new clinical study design.// Infect. Genet. Evol. - 2009. No. 9 (6): P. 1356-1363.

[7] Constantini P. K., Wawrzynowicz-Syczewska, M; Clare, M; Boron-Kaczmarska, A; McFarlane, IG; Cramp, ME; Donaldson, PT Interleukin-1, interleukin-10 and tumor necrosis factor-alpha gene polymorphisms in hepatitis C virus infection: an investigation of the relationships with spontaneous viral clearance and response to alphainterferon therapy // Liver. 2002. V.22. No. 5. P.404-412.

[8] Cussigh, A., et al. Interleukin 6 promoter polymorphisms influence the outcome of chronic hepatitis C. // Immunogenetics. - 2011. No. 63 (1): P. 33-41.

[9] Dai, C. Y .; Chuang, W.L .; Lee, L. P .; Pan, W.C .; Huang, J. F .; Hsieh, M.Y .; Hou, N. J .; Lin, Z.Y .; Chen, S. C .; Hsieh, M.Y .; Wang, L.Y .; Chang, W.Y .; Yu, M.L. Association between transforming growth factor-beta polymorphism and virologic characteristics of chronic hepatitis C // Transl. Res. 2008, P. 151-156

[10] Di Giovine F.S., Takhsh E., Blakemore A.I., Duff G.W. Single base polymorphism at –511 in the human interleukin-1 beta gene (IL1 beta) // Hum. Mol. Genet. 1992. V. 1, No. 6. P. 450.

[11] Fabris C., Toniutto P., Bitetto D., Fattovich G., Falleti E., Fontanini E., Cussigh A., Minisini R., Occhino G., Pirisi M. Gene polymorphism at the interleukin 6 -174 G > C locus affects the outcome of chronic hepatitis BJ Infect., 2009, vol. 59, no. 2, pp. 144-145.

[12] Fishman D., Faulds G., Jeffery R., Mohamed-Ali V., Yudkin J. S., Humphries S., et al. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis // J. Clin Invest. 1998. V.102. P.1369-1376.

[13] Fletcher GJ, Samuel P, Christdas J et al (2011) Association of HLA and TNF polymorphisms with the outcome of HBVinfection in the South Indian population. Genes Immun 12: 552–558

[14] Karimi M., Goldie L. C., Cruickshank M. N., Moses E. K., Abraham L. J. A critical assessment of the factors affecting reporter gene assays for promoter SNP function: a reassessment of -308 TNF polymorphism function using a novel integrated reporter system. Eur. J. Hum. Genet. 2009. Vol. 17.P. 1454-1462.

[15] Knopp S., Hennig B.I., Frodsham A.I. et al. Interleukin-10 promoter polymorphisms and the outcome of hepatitis C virus infection // Immunogenetics. - 2003. - Vol. 53, No. 6. - P. 362-369.

[16] Larrea E., Garcia N., Qian C., Civeira M.P., Prieto J. Tumor necrosis factor alpha gene expression and the response to interferon in chronic hepatitis C // Hepatology. 1996. V.23. P.210-217

[17] Lee L.L., Tang J., Gibson A.W. et al. Interleukin-10 polymorphisms as predictors of sustained response in antiviral therapy for chronic hepatitis C infection // Hepatology.– 2001. - Vol. 33, No. 3. - P. 708-712.

[18] Liberek A., Jakbkiewicz-Banecka J., Kloska A., Swiderska J., Marek A., uczak G., Wierzbicki PM, Kmie Z., Szlagatys-Sidorkiewicz A., Marek K., Sznurkowska K., G ra-Gebka M., Liberek T., Zagierski M., Kami ska B., Wegrzyn G. Gene polymorphism of transforming growth factor beta1 (TGF-beta1) in the pathogenesis and clinical course of chronic hepatitis in children. Med. WiekuRozwoj., 2009, vol. 13, no. 3, pp. 171-179.

[19] Lio D, Caruso C, Di Stefano R et al. IL-10 and TNF-alpha polymorphisms and the recovery from HCV infection // Hum. Immunol. 2003. V. 64.P. 674-680.

[20] Lio D., Caruso C., Distefano R., Colonna Romano G. et al. IL-10 and TNF-alpha polymorphisms and the recovery from HCV infection // Hum. Immunol. - 2003. - Vol. 64.– P. 674–680.

[21] Macarthur, M., Hold, G. L., & El-Omar, E. M. (2004). Inflammation and Cancer II. Role of chronic inflammation and cytokine gene polymorphisms in the pathogenesis of gastrointestinal malignancy. American Journal of Physiology-Gastrointestinal and Liver Physiology, 286 (4), G515-G520.

[22] Mangia A., Santoro R., Piattelli M. et al. Interleukin-10 promoter polymorphisms and the out come of hepatitis C virus infection // Immunogenetics. - 2003. - Vol. 55, No. 6. - P. 362-369.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 4174 - 4184
Received 16 February 2021; Accepted 08 March 2021.

[23] Marinos G., Naoumov N. V., Rossol S., Torre F., Wong P. Y., Gallati H., Portmann B., Williams R. Tumor necrosis factor receptors in patients with chronic hepatitis B virus infection. Gastroenterol. 1995. Vol. 108. P. 1453-1463.

[24] Meenagh A., Williams F., Ross OA, Patterson C., Gorodezky C., Hammond M., Leheny WA, Middleton D. Frequency of cytokine polymorphisms in populations from western Europe, Africa, Asia, the Middle East and South America // Hum Immunol. 2002. V. 63. P. 1055-1061.

[25] Minton E.J., Smillie D., Smith P., Shipley S., McKendrick M.W., Gleeson D.C., Underwood J.C., Cannings C., Wilson A.G. Clearance of hepatitis C virus is not associated with single nucleotide polymorphisms in the IL-1, -6, or -10 genes // Hum Immunol. 2005. V.66. P.127-132.

[26] Minton E.J., Smillie D., Smith P., Shipley S., McKendrick M.W., Gleeson D.C., Underwood J.C., Cannings C., Wilson A.G. Clearance of hepatitis C virus is not associated with single nucleotide polymorphisms in the IL-1, -6, -10 genes. Hum. Immunol., 2005, vol. 66, no. 2, pp. 127-132.

[27] Niro G. A., Fontana R., Gioffreda D. et al. Tumor necrosis factor gene polymorphisms and clearance or progression of hepatitis B virus infection // Liver Int. - 2005. - Vol. 25, No. 6. — P. 1175-1181.

[28] Powell E.E., Edawards-Smith C.J. et al. Host genetic factor influence disease progressions in chronic hepatitis C // Hepatology. - 2000. - Vol. 31, No. 4. - P. 828-833.

[29] Romanova S.V., Vidmanova T.A., Zhukova E.A., Ermolina E.V., Tolkacheva N.I., Mayanskaya I.V., Timchenko I.A. The role of genetic polymorphisms of gene IL-1β (-31 T / C) and IL-6 (-174 G / C) in the course of chronic hepatitis B and C in children // Medical Immunology 2013, Vol. 15, 6, pp. 535-542

[30] Romero-Gomez M., Montes-Cano M. A., Otero-Fernandez et al. CLCIIA1 promoter gene polymorphisms and fibrosis progression in chronic hepatitis C // Gut. - 2004. - N 53. - P. 446-450.

[31] Rosen H.R., McHutchison J.G., Contad A.I. et al. Tumor necrosis factor genetic polymorphisms and response to antiviral therapy in patients with chronic hepatitis C // Am. J. Gastroenterol. - 2002. - Vol. 97, No. 3. - P. 714-720.

[32] Taga T., Kishimoto T. Gp130 and the interleukin-6 family of cytokines // Annu Rev Immunol. 1997. V.15. P.797-819.

[33] Tanaka Y., Nishida N., Sugiyama M., Kurosaki M., Matsuura K., Sakamoto N., Nakagawa M., Korenaga M., Hino K., Hige S., Ito Y., Mita E., Tanaka E., Mochida S., Murawaki Y., Honda M., Sakai A., Hiasa Y., Nishiguchi S., Koike A., Sakaida I., Imamura M., Ito K., Yano K., Masaki N ., Sugauchi F., Izumi N., Tokunaga K., Mizokami M. Genome-wide association of IL28B with response to pegylatedinterferonalpha and ribavirin therapy for chronic hepatitis C // Nat Genet. 2009. V.41. No. 10. P.1105-1109.

[34] Tokushige K, Tsuchiya N, Hasegawa K et al. Influence of TNF gene polymorphism and HLA_DRB1 haplotype in Japanese patients with chronic liver disease caused by HCV // Am. J. Gastroenterol. 2003 Vol. 98, No. 1. — P. 160-166.

[35] Trujillo-Murillo K., Perez-Ibave D., Munoz-Mejia C., Cordero-Perez P., Munoz-Espinosa L., Martinez-Rodriguez H., Bosques-Padilla F., Rivas-Estilla A.M. Prevalence

of the -308 and -238 tumor necrosis factor alpha (TNF-α) promoter polymorphisms in mexican chronic hepatitis C patients // Rev Gastroenterol Mex. 2010. V. 75, no. 1.P. 312-318.

[36] Wang B, Wang J, Zheng Yet al (2010) A study of TNF-alpha-238 and −308 polymorphisms with different outcomes of persistent hepatitis B virus infection in China. Pathology 42: 674-680.

[37] Wieland, S., Thimme, R., Purcell, R.H., and Chisari, F.V. (2004). Genomic analysis of the host response to hepatitis B virus infection. Proc. Natl. Acad. Sci. USA 101, 6669-6674

[38] Yee L. J., Tang J., Herrera J., Kaslow R. A., van Leeuwen D. J. Tumor necrosis factor gene polymorphisms in patients with cirrhosis from chronic hepatitis C virus infection // Genes Immun. 2000. V. 1. P. 386-390.

[39] Yu S. et al. Response to therapy with pegylated interferon and ribavirin for chronic hepatitis C in hispanics compared to non-Hispanic whites. // Am. J. Gastroenterol. - 2009. No. 104 (7): P. 1686-1692

[40] Yu Y., Chao L., R. F., Sheng B. The TNF-α, IL-1B and IL-10 polymorphisms and risk for hepatocellular carcinoma: a meta-analysis // Journal of Cancer Research and Clinical Oncology. 2011. V. 137, no. 6.P. 947-952.

[41] Abdullaev S.M., TselischevaYu.I., Samokhodskaya L.M. et al. Genetic factors of the aggressive course of chronic hepatitis C // Vestn. RAMS. 2007. No. 1. –p. 8-13.

[42] Analysis of the influence of genetic factors of the hepatitis C virus and polymorphism of genes of infected people on the development of liver fibrosis / L. I. Nikolaeva [et al.] // Epidemiology and infectious diseases. disease. - 2012. - No. 5. - p. 7-13 .;

[43] 43 D. D. Abramov, I.A. Kofnadi, K.V. Utkin [et al.] / Polymorphism of single nucleotides in the genes of cytokines and their receptors: biological effect and identification methods // Immunology. - 2011. - No. 5. - P. 275-278

[44] IV Sergeev [et al.] // Development of methods for large-scale studies of gene polymorphism that regulate various components of the immune response / Physiology and pathology of immunity. systems. - 2009. - T. 13, No. 4. - P. 21–26.

[45] Ivashkin V.T. Liver fibrosis / V.T. Ivashkin, Ch.S. Pavlov. - M .: GEOTAR Media, 2011. - 168 p .;

[46] Immunogenetic predictors of a rapid virological response to antiviral therapy in patients with chronic hepatitis C / ND Yushchuk [et al.] // Therapist. archive. - 2012. - T. 84, No. 11. - P. 11-16.

[47] S. A. Ketlinsky, A. S. Simbirtsev. Cytokines / - St. Petersburg. : Folio, 2008. - 552 p .;

[48] Ketlinsky, S.A. The role of T-helper types 1 and 2 in the regulation of cellular and humoral immunity // Immunology. - 2002. - No. 2. - p. 77-79.,

[49] V.K. Kozlov. Cytokine therapy: pathogenetic orientation in infectious diseases and clinical efficacy. A guide for doctors. - SPb .: Alter Ego, 2010 .-- 148 p.

[50] KuramshinD.Kh., Tolokonskaya N.P., Kozhevnikov V.S. et al. Subpopulations of lymphocytes and the level of proinflammatory cytokines in the blood of patients with viral hepatitis C and combined variant C + B // Zhurn. microbiol. - 2002. - No. 1. - S. 42-48., Hunter C.A., Reiner S.L. Cytokines and T cells in host defense // Curr. Opin. Immunol. - 2000. –N 12. - P. 413-418.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 4174 - 4184
Received 16 February 2021; Accepted 08 March 2021.

[51] Milovanova S., Tagay S., Korotchaeva Yu., Kozlovskaya L. Kidney damage associated with infection with hepatitis B and C viruses // Doctor. 2007. No. 6. P. 70-74.
[52] Nasllednikova I.O., Urazova O.I., Voronkova O.V. et al. Immunopathogenesis of bacterial and viral infections: the role of cytokine gene polymorphism // Allergology and immunology. - 2008. - T. 9, No. 3. - P. 294.
[53] Piguzova EA The system of tumor necrosis factor alpha and its receptors in the immunopathogenesis of persistent viral infections. // dis. Cand. biol. sciences. Tomsk, 2006.
[54] Ryazantseva N.V., Novitsky V.V., Belokon V.V. and other Cytokines and antiviral immunity // Advances in physiological sciences. 2006. T. 37, No. 4. p. 1-11.
[55] Samokhodskaya L.M., Ignatova T.M., Abdullaev S.M., Krasnova T.N., Nekrasova T.P., Mukhin N.A., Tkachuk V.A. Prognostic value of a combination of allelic variants of cytokine and hemochromatosis genes in patients with chronic hepatitis C. // Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2007. No. 2. P.50-56
[56] Tikhonova, N. Yu. The value of allelic variants of the interleukin-28B gene in chronic viral hepatitis C / N. Yu. Tikhonova, EZ Burnevich, TN Krasnova // Therapist. archive. - 2013. - T. 85, No. 12. - P.106-113 .;
[57] Freidin M.B., Goncharova I.A., Rudko A.A. et al. Genomic bases of susceptibility to infectious diseases // Molecular. the medicine. 2006. No. 3. P. 39-46