The impact of Toll-like receptors on the immune system functioning and on the immunopathogenesis of chronic hepatitis C: a modern view (literature review)

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Materials and methods. The method of reviewing and systematizing as well as the method of content analysis were used to overview the scientific literature as for the role of Toll-like receptors. For this purpose, we employ survey data collected from the world professional literature and analyzed the results of current researches.

Conclusions. The innate immune system plays a prominent role in the primary protection of the body against pathogens which recognition depends on the Toll-like receptors family whereas the genetic analysis is considered as a promising method of preventive and personalized medicine. The advantage of genetic markers regardless of age and other factors contain information about susceptibility to multifactorial diseases which can be used to create a «genetic passport» of a person. Perceptions about the impact of the Asp299Gly polymorphism of the Toll-like receptor 4 gene and Gln11Leu of the Toll-like receptor 7 gene on the immunopathogenesis of chronic hepatitis C are ambiguous and this research provides a good starting point for discussion and further study which will allow optimizing the therapeutic and diagnostic tactics for this disease based on the complex evaluation of immunity which are defined by the determined polymorphisms.

_key words:_ Toll-like receptors, polymorphism, chronic hepatitis C.

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Key words: Toll-like receptors, polymorphism, chronic hepatitis C.
Despite the great advances in the study of immunopathogenesis of chronic hepatitis C a number of questions regarding diagnosis, prognosis and effectiveness of treatment of this infection remain to be addressed. We present an overview of literature that relates to work presented here. In recent years there has been renewed interest in mechanisms of the damaging effect of hepatotropic viruses on the liver and the role of the immune system in the progression of pathology. This issue provokes a number of gaps and shortcomings. A thorough understanding of the immunopathogenetic features of chronic hepatitis C and the role of individual immune system receptors in this process will significantly improve chronic hepatitis C therapy and advance an individual treatment approach, minimizing the financial costs and harm of side effects of medicines. Future advancements of gene polymorphism investigations as a factor in genetic susceptibility to infectious diseases and their peculiarities are expected to provide new opportunities for identifying at-risk groups and selecting personalized therapy for each patient. The study of chronic hepatitis C, the Toll-like receptors (TLRs) is a topic under intense research and pivotal importance.

Aim

The aim of the research is to analyze the data of modern professional literature regarding the role of individual TLRs in the immunopathogenesis of chronic hepatitis C.

Materials and methods

In the course of the expertiment methods of review, system and content analysis allowed us to explore and delve into the study of TLRs. We present an overview of the world professional literature that relates to study presented here.

A recent study on the role of TLRs in the functioning of the immune system.

TLRs were first detected in Drosophila melanogaster in 1985 by C. Nüsslein-Volhard (German) and E. Wieschaus (USA), the discovery of TLRs was an important event for the research in immunology and was highly estimated, thus Hoffmann (Luxembourg) and B. Beutler (USA) were awarded the Nobel Prize in Physiology or Medicine in 2011 [1]. TLR4 was the first element to be discovered, then other TLRs in mammals and humans came [2]. Currently 13 TLRs are known, and 10 TLRs of which have been studied in humans [3–4]. Most TLRs are located on the cell surface – TLR1, TLR2, TLR5, TLR6, TLR10; an example of an intracellular arrangement is TLR3, TLR7, TLR8, TLR9, some TLRs can be expressed both intracellularly and extracellularly (TLR4, TLR11, TLR12, TLR13) [2–3,5].

Receptors of the TLRs family recognize pathogens and, upon activation, increase the local synthesis of proinflammatory cytokines, prostaglandins, chemokines that trigger the mechanism of implementation of the inflammatory response – a cascade of adapter and signaling molecules that leads to the induction of innate and adaptive immunity [5–8]. TLRs interact with adapter molecules and transmit an immunogenic signal to effectors, transcription factors, and target genes that together form a TLR-dependent signaling pathway. This pathway functions as a complex, consistent system of functionally interacting molecules. The most conservative role of TLR-activation of antimicrobial immunity in the skin, mucous membranes of the respiratory, gastrointestinal and urogenital tracts [8–11].

The analysis of the functions of different TLRs revealed that cells of the innate immune system activate different signaling pathways depending on the infectious pathogen. The genes which encode elements of the signaling pathway are coherently regulated in concert. Genetic variability not only of TLRs but also of molecules of TLR-dependent signaling pathways can play an important role in recognizing PAMPs (pathogen-associated molecular structures) and altering the immune response to infection [3,8,12]. It is reasonable to claim that clarifying the role of TLR in infectious pathology will let on conducting diagnostics timely and predicting the nature of the disease in advance. Moreover, this allows to study the pathogenetic aspects of its development, as well as to justify the choice of adequate therapy [12–13].

TLR participation in innate immunity is ensured by:

– initiating of secretion of proinflammatory cytokines which are required for physiological immunological response under various influences, among which various infections occupy the central place [6];
transcription factors are known today. However, the nucleotide of TLR activation is complex and multicomponent, but it is mediated by protein kinases (MAPKs). The entire signaling pathway involves adapter proteins (MyD88 and Toll-interacting protein – TOLLIP), protein kinases (IL-1R-associated kinase – IRAK) and TNF-receptor associated factor 6 (TRAF-6). IRAK-M is sequentially activated, which leads to the production of cytokines, antiviral peptides and interference with intracellular signaling in two ways [23]. Typically, TLR, with the exception of TLR3, use the MyD88-dependent pathway in which IRAK is sequentially activated, which includes 4 subunits – 2 active kinases (IRAK-1 and IRAK-4) and 2 non-catalytic subunits (IRAK-2 and IRAK-M). Then IRAK-4 phosphorylates IRAK-1. Phosphorylated IRAK-1 binds to TRAF-6 and simultaneously activates NF-κB, mitogen-activated protein kinases (MAPKs). The case of NF-κB, the protein remains in the cytoplasm, binding to the NF-κB (IκB) inhibitor. Phosphorylation of the inhibitor, which makes it possible to move NF-κB to the nucleus. Simultaneous activation of NF-κB and MAPKs induces transcription of various inflammatory genes, including tumor necrosis factor (TNF), interleukins (IL) 1, 6, 8 and 12. In addition, TLR4 can trigger an immune response via the MyD88-independent pathway. It is carried out by an adapter protein capable of inducing interferon (IFN), which leads to phosphorylation of transcription factors: interferon-regulating factor-3 (IRF-3) and NF-κB. These two transcription factors potentiate the action of each other, stimulate the production of type I interferons (IFN-α, IFN-β, IFN-γ) and activation of interferon-inducible genes [8,23–24]. The TLR7, TLR8, TLR9 genes are also capable of initiating type I interferon synthesis through the MyD88-dependent signaling pathway upon activation of IRF-3 and IRF-7 [5,24]. In addition, signals from TLR7, activating IRF-7, stimulate the production of antiviral cytokines, including type I and II interferons, which turn would activate the processes of destruction of intracellular pathogens, while activation of NF-κB induces a pro-inflammatory effect through cytokine secretion, such as TNF-α, IL-6 and IL-12 [25–26]. General scheme of TLRs signaling pathways by J. Howell et al. (2013) is depicted in the Fig. 1 [26].

The wide range of TLRs ligands and their presence on most cells of the body contributes to the involvement of TLR in the pathogenesis of many diseases [5–6,8,12]. Defects in the TLRs gene system: impaired ligand recognition, TLR expression, signal transduction, production of...
effector molecules, and their polymorphism can lead to the development of infectious, autoimmune and oncological diseases, allergopatology [2,5,8,27–30].

The point mutations at the DNA level that encode the structure of the receptor can disrupt its normal functioning and underlie the individual variability of the human genome [30]. The most common cause of differences in gene structure is so-called single nucleotide polymorphism (SNP), which occurs after about 290 base pairs, resulting in the formation of specific alleles of genes, which affects the development of protective reactions and susceptibility to particular diseases [5,8,11,28–30]. Nowadays, the conceptual basis of predictive genomic medicine is the very idea of genetic polymorphism [31].

The gene polymorphism implies that several variants can be copied from the same gene, structurally different from the copy of the same protein, some of them copied or not active at all, or may have the opposite function. When localized in exons, SNPs change the codons of the genetic code, which can lead to replacement of amino acids in peptides, sometimes their presence is associated with an increase or decrease in the concentration/activity of the gene product, thus genetic polymorphism is a source of individual differences, in particular in susceptibility and their course [28,32]. The presence of predisposition genes does not mean that a person can necessarily develop certain pathological conditions, gene polymorphism does not allow determining the time of the disease occurrence, but allows us to identify the characteristics of metabolism, drug metabolism and individual risk of susceptibility to a particular disease.

Thus, our findings indicate that in infectious pathology TLRs gene polymorphism affects the individual features of immunity and leads to immunological disorders caused by activating and inactivating genetic damage to the receptors of innate recognition or signaling molecules [5,8]. According to S. Mukherjee et al. (2019) a common feature of TLRs functional polymorphism is a decrease in the ability to recognize the corresponding ligands, which results in less pronounced cell activation after encountering pathogens [32]. It is reported that in infectious diseases, «mutations» of genes can lead to impaired recognition of infectious agents and imbalance of the functioning of the system of innate immunity, which will eventually be manifested by increased susceptibility to infections and susceptibility to the development of chronic inflammatory processes [5,8,13,28,30].

Thus, over the past several decades there has been a sustained research activity in TLRs genes area not only in terms of basic knowledge but also in the practicalities of predictive and personalized medicine [31]. Along there are some studies in the issue discussed but still the research about the role of TLRs genes polymorphism in chronic hepatitis C remains limited which makes the relevance of our study.

Impact of Asp299Gly polymorphism of TLR4 gene and Gin11Leu of TLR7 gene on chronic hepatitis C immunopathogenesis.

Nowadays, the rapid accumulation of knowledge about the genetic basis of pathological processes enriches the idea of immunopathogenesis of common human diseases, which, of course, belongs to chronic hepatitis C. In terms of studying both the immunopathogenesis of the disease the gene TLR4, which interacts with the protein envelope of viruses, structural and non-structural proteins of hepatitis C virus (HCV), and the TLR7 gene, a ligand of which is single-stranded are of particular interest [3,5,6,25,26].

The TLR4 gene is located in the 9th chromosome (9q32–33), its exogenous ligands are lipopolysaccharides of gram-negative bacteria, lipoteichoic acid, taxol, flavolinin, F-protein of respiratory syncytial virus, type 1 fimbriae, and fimbriae, mycobacterium tuberculosis ligands, viral glycoproteins, and endogenous — fibronectin, low density lipoproteins, heat shock proteins, β-defensins, HMGB-1 hyaluronan [9,33]. The polymorphic marker Asp299Gly (rs4986790) of the TLR4 gene is a single nucleotide replacement of adenine (A) by guanine (G) at the +896 position of exon 3, which leads to amino acid replacement of aspartic acid (Asp) by glycine (Gly) chain 29. This nonsense mutation, altering the structure of the extracellular domain of TLR4, leads to the loss of negative charge of the site at position 299, which disrupts the process of recognition of bacterial lipopolysaccharide [4,10].

According to the results of research studies, the frequency of point mutations of the TLR4 gene is very low (<1 %), with the exception of the genetic polymorphism Asp299Gly, the frequency of which is >5 % [8,28,34]; Asp299Gly is virtually undetectable in Asian populations [33]. The practical significance of this polymorphism is associated with inhibition of phosphorylation after lipopolysaccharide stimulation, which in turn leads to a decrease in the translocation of NF-κB into the nucleus and affects the inhibition of the synthesis of proinflammatory cytokines IL-6 and TNF-α and production of IL-10 [33].

The TLR7 gene is located on Xp22.2, chromosomes and is a component of the body’s antiviral defense system. It consists of a single exon and encodes a transmembrane protein of 1049 amino acids, it is localized in intracellular membrane compartments – endosomes, which in turn isolates it from a possible contact with endogenous nucleic
acids. The receptor is able to activate the transcription factors NF-κB and IRF-7 [25]. The signal is transmitted through the adapter proteins MyD88, TRAF-6, IRAK-4 [35–36]. Exogenous ligands for TLR7 are small synthetic through the adapter proteins MyD88, TRAF-6, IRAK-4 factors NF-κB and IRF-7 [25]. The signal is transmitted in infection with HCV [44].

consider its carrier as a risk factor for chronic hepatitis C population control data 4.5 times, which gives reason to it reaches 40.0 % [41–43]. In L. Sizovа et al. (2016) it is whereas according to C. Guarner-Argente et al. (2010) Asp299Gly polymorphism among chronic hepatitis C patients is studied. Thus, in the works of O. D. S. Pires-Neto et al. (2015) and A. A. Al-Qahtani et al. (2014) it is indicated that the Asp299Gly polymorphism of the TLR4 gene was detected in 6.9–9.1 % of patients with chronic hepatitis C, whereas according to C. Guamer-Argete et al. (2010) it reaches 40.0 % [41–43]. In L. Sizova et al. (2016) it is claimed that the prevalence of Asp299Gly polymorphism among chronic hepatitis C patients is 15.2 % and exceeds population control data 4.5 times, which gives reason to consider its carrier as a risk factor for chronic hepatitis C infection with HCV [44].

A large number of existing studies show that carriers of the polymorphic genotype Asp299Gly of the TLR4 gene have a more severe course of chronic hepatitis C which means that the viral load registered is higher and susceptibility to bacterial infections is increased, which is associated with decreased production of IL-6 and IL-10 or with the development of encephalopathy and also the inflammation as a reaction which can block the translocation of bacterial antigens in cirrhosis [43,45–47]. However, in other papers, there is no significant influence of this polymorphism on the clinical and laboratory characteristics of chronic hepatitis C [48–50].

The scientific data on the effect of the TLR4 gene Asp299Gly polymorphism on the process of fibrosis in the liver and its rate in chronic hepatitis C are extremely controversial. Thus, a number of studies claim that it has a connection to a higher rate of progression of liver fibrosis and the risk of cirrhosis [43,51] as well, other studies, by contrast, claim that the ability of Asp299Gly can slow down the clinical progression of chronic hepatitis C and act as a protective factor for the development of cirrhosis and hepatocellular carcinoma [52,53], whereas A.A. Al-Qahtani et al. (2014), O. D. S. Pires-Neto et al. (2015), and G. Dubinskaya et al. (2016), independently of one another, concluded that there is no influence on this process [41–43,54].

The results of studies by M. Peris et al. (2015), G. M. Dubynska et al. (2016) and M. S. Iqbal et al. (2017) point to the association of the TLR4 gene Asp299Gly polymorphism with the low efficacy of interferon antiviral chronic hepatitis C therapy [46,55–56], but no similar effect was found in M. Emonts (2008) [49].

Scientific reports regarding the involvement of the TLR7 gene and its peculiarities in the pathogenesis of HCV infection are ambiguous. It is reported that through this gene the induction of innate immunity in HCV-infected is induced, the blocking of HCV RNA, the stimulation of production of antiviral cytokine IFN-α by dendritic cells [57–58], and in the presence of Gln11Leu polymorphism, TLR7 expression is reduced by hepatocytes and epithelial cells of the biliary tract, a positive correlation of this phenomenon with liver damage in inflammation, activation of myofibroblasts and the development of liver fibrosis in chronic hepatitis C indicate the results of studies by S. Y. Mohamed et al. (2017) [40].

In some studies, the prevalence of the TLR4 gene Asp299Gly polymorphism among chronic hepatitis C patients is studied. Thus, in the works of O. D. S. Pires-Neto et al. (2015) and A. A. Al-Qahtani et al. (2014) it is indicated that the Asp299Gly polymorphism of the TLR4 gene was detected in 6.9–9.1 % of patients with chronic hepatitis C, whereas according to C. Guamer-Argete et al. (2010) it reaches 40.0 % [41–43]. In L. Sizova et al. (2016) it is claimed that the prevalence of Asp299Gly polymorphism among chronic hepatitis C patients is 15.2 % and exceeds population control data 4.5 times, which gives reason to consider its carrier as a risk factor for chronic hepatitis C infection with HCV [44].
sence of associations between its presence and the progression of liver fibrosis in chronic hepatitis C [36–37,62], others to the protective role of polymorphism in this process in chronic hepatitis C [54], whereas in the study of F. Z. Fahhir (2018), this polymorphism is described as a profibrogenic factor [63].

E. Schott et al. (2008), M. El-Bendary et al. (2018) and S. I. Malov et al. (2018) report a correlation of the presence of the Gln11Leu polymorphism of the TLR7 gene with increased susceptibility to HCV and adverse response to interferon antiviral therapy in chronic hepatitis C patients [64–66], as confirmed by a study by S. A. Taghavi et al. (2009), but without the gender dependence of this fact [34], but it is denied in the works of Y. M. Mosaad et al. (2019) and S. S. Sleptsova et al. (2019) [62,67].

Thus, the analysis of scientific works of domestic and foreign authors shows that the susceptibility to HCV, as well as the formation of complications in humans are genetically determined and genes of the immune response and inflammation play an important role in this. In this regard, the creation of differential diagnostic and prognostic criteria for the course and consequences of chronic hepatitis C, developed on the basis of the study and analysis of the genetic material of each patient, is of particular importance.

Conclusions

1. The innate immune system plays a prominent role in the primary protection of the body against pathogens whose recognition depends on the TLRs family, and genetic analysis is a promising method of preventive and personalized medicine.

2. The advantage of genetic markers is that, regardless of age and other factors, they carry information about the susceptibility to multifactorial diseases, which can be used to create a «genetic passport».

3. Perceptions about the impact of the Asp299Gly polymorphism of the TLR4 gene and Gln11Leu of the TLR7 gene on chronic hepatitis C immunopathogenesis are ambiguous and require further study, which will allow optimizing the therapeutic and diagnostic tactics for this disease based on a comprehensive evaluation of the features of immunoreactivity.

Prospects for further research. Future studies could fruitfully explore this issue further by studying the immunopathogenetic mechanisms of TLR4 impact as well as TLR7 genes impact on the course of chronic hepatitis C and other infectious pathologies.

Conflicts of interest: authors have no conflict of interest to declare.

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and gender-related features.


