Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 4164 - 4173
Received 16 February 2021; Accepted 08 March 2021.

Immunological Aspects of the Pathogenesis of Chronic HCV Infection

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Abstract.
Today, it is known that cytokines secreted by immune cells are critical in cell-mediated and humoral immune responses, as well as in antiviral activity, viral clearance, apoptosis, and fibrogenesis. A review of the literature has shown that the level of production of many cytokines is associated with the severity of LC and viral etiology of LC. An in-depth study of immunopathogenesis will make it possible to clarify the mechanisms of inadequate immune response in HCV infection, which will contribute to the diagnosis, prognosis of the course of these diseases and the choice of adequate therapy.

Keywords: HCV - infection, immunopathogenesis, adaptive immunity, innate immunity

Relevance

It has now been established that a number of factors influence the progression and outcomes of HCV infection: an external factor (pathogen), the mechanism of phenotype development with a predominant influence of cytotoxic T cells, regulatory T cells or natural killer cells, as well as the genotypic characteristics of the patient [45 , 48, 46].

To date, many mechanisms have been disclosed for the immediate activation and functioning of CD8 + T cells upon infection with HBV or HCV. The concepts of "exhaustion", "regulation" and immune "escape" are considered [19]. By "depletion" is meant a phenomenon reflecting dysfunction of CD4 and CD8 T cells in HCV infection. The suppression of the functional activity of T cells and their subsequent death, observed at a high viral load, are due to the expression of the Programmed Death-1 (PD-1) molecule by activated and functionally defective T cells. The role of this molecule in HCV infection requires further study. The experiment established the specific expression of CD161 (NK receptor) on HCV-specific CD8 + T cells, which may be related to PD-1 [23].

One of the mechanisms of long-term persistence of viral infection is the ability of HCV to inhibit the innate (innant) immunity, which leads to functional failure of cells that play a major role in the elimination of viruses - dendritic cells, macrophages, natural killer cells, and others [22]. The functional insufficiency of the innant immunity of the dough is associated with the suppression of adaptive immunity cells - HCV-specific CD8 + T-lymphocytes.

In persistent viral infections, the cleavage of the CD8 + T-specific cell phenotype occurs. At the same time, the functions of cytotoxicity and degranulation are preserved at the cellular level, and the production of cytokines is significantly inhibited [52]. Obviously, a chronic infectious process develops as a result of violations not in one, but in several components of the immune system. It is known that among the factors of innant immunity, NK cells play a

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 4164 - 4173
Received 16 February 2021; Accepted 08 March 2021.

key role in the elimination of viruses. In addition, it was found that the most important function of NK cells is the ability to produce cytokines IL-1, IL-2, IL-3, IL-8, TNFα, IFNα, β, γ, which allows us to regard these cells as the most important regulator of congenital and adaptive immunity [27, 57].

One of the factors in the development of fibrosis is an intense T-killer response. A number of studies have shown a certain correspondence between changes in the blood content and functional state of EK and EKT cells and the stages of fibrotic changes in the liver [43, 49].

The studies carried out to study the characteristics of the immune response in patients with chronic hepatitis C (CHC) showed that the cellular immune response plays a leading role not only in the elimination of viruses, but also in the process of chronicity of HCV infection. At the same time, many authors note that the imbalance in the production of Th1 \ Th2 cytokines by cells occupies an important place in the immunogenesis of chronic hepatitis [56].

As the results show, the performed correlation analysis in patients with CVHC revealed a direct reliable relationship between the total number of lymphocytes expressing HLA-DR and the content of B-lymphocytes (CD19) [54]. It is known that an increase in the expression of the HLA-DR molecule by B-lymphocytes occurs at the stage of their presentation of the antigen to T-helpers for recognition. Presenting an antigen, B cells stimulate T helper cells to differentiate into Th2 cells, which produce cytokines necessary for the further development of B cells, which confirms the development of a Th2 response that is ineffective for eliminating the viral pathogen [58, 59].

HCV belongs to the Flaviviridae family, whose genome is represented by an enveloped single-stranded helical RNA. HCV is a hepatotropic virus with great persistence potential. Intervention of HCV in the innate immune response can lead to disorders in the maturation of cells that exercise adaptive immunity, which are closely related to the activity of innate immunity. The results of studies indicate that, despite the early onset of HCV replication, the induction of HCV-specific T cells occurs after a long time interval from the moment of infection [40]. HCV-specific CD8 cells from the moment of their detection are distinguished by a decrease in effector functions, which is manifested in insufficient production of IFN-γ and IL-2. Spontaneous clearance of viral infection is characterized by full maturation of memory CD8 cells and manifests itself in the form of the CD127 + / CCR7 + phenotype, as well as restoration of CD8 functions [37]. The cellular mechanisms of HCV that allow efficient RNA replication, viral assembly, and acquisition of infectivity require further research [4].

In most people who have had acute hepatitis C (HCV), the immune system is unable to eliminate the virus, which allows it to replicate for a long time in hepatocytes and a number of other cells, including cells of the immune system. It is known that its antigens are weakly immunogenic and do not induce, at least, pronounced immunological reactions. Moreover, patients often have a detectable humoral and cellular immune response, both to structural and non-structural proteins of the virus [44, 55].

The most important feature of HCV infection is the ability of the virus to persist for a long time in the human body. Until now, all the factors of the virus and the host that determine the inability of the immune response to control the infection have not been established. Data on the biological properties of HCV and the frequency of

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chronicity (up to 85%) indicate the decisive role of viral factors aimed at modulating the host's immune response [30]. Thus, in acute and self-resolving HCV infection (as opposed to chronic HCV infection), the T-cell response is pronounced and highly specific, and among the lymphocytes, Th1 cells with the CD4 + phenotype and CD8 + cytotoxic lymphocytes prevail. At the same time, high concentrations of cytokines TNFα, IFNγ, IL-2, and IL-12 are determined in blood serum and liver tissue [47]. In the early stages of infection, suppression of the induction of the immune response is fundamental. The virus is able to influence the activation of CD4 + Th, disrupting the interaction of antigen-presenting cells and T-lymphocytes. Most researchers agree that the predominant participation of cytokines produced by Th2 cells is associated with viral persistence and chronicity of the process. Insufficient production of Th-1 cytokines is associated with the ability of IL-4 and IL-10 to inhibit Th-1 functions and inhibit the production of IFNγ and IL-2, which is one of the mechanisms of impairment of an adequate immune response in CHC [50]. In the process of chronicity of HCV infection, great importance is attached to the mechanisms of suppression of the implementation of the immune response, among which the greatest role is played by the virus avoiding the humoral and cellular immune response by mutation. Mutation of HCV epitopes, which are targets of cytotoxic T-lymphocytes, leads to disturbances in antigen processing and epitope recognition, antagonistic relationships of CTLs. The lack of an effective T-cell immune response is due to a low level of HCV replication, observed in almost 100% of hepatocytes, which leads to a low expression of HLA and other immunoinflammatory molecules on the surface of infected cells [36]. In chronic hepatitis C, the main manifestation of secondary immune deficiency should be considered a decrease in the quantitative and functional parameters of cellular immunity: T-helper lymphocytes, NK cells and mononuclear phagocytes.

На исход и течение процесса большое влияние оказывает количество инфицировавшего материала. Темпы прогрессирования обусловлены генотипом хозяина и степенью гетерозиготности популяции HCV. Выявлена роль иммуногенетических факторов в развитии HCV-инфекции: генотип HLA II класса определяет исход острой HCV-инфекции; гетерозиготность по гену гемохроматоза коррелирует со степенью фиброза; гетерозиготность по фенотипу PiMZ дефицита α1-антитрипсина определяет предрасположенность к фиброзу [41].

Kupffer cells are the dominant macrophages in the liver sinusoid population, as they express protein IFN-β [20]. Plasmacytoid dendritic cells (pDCs) are the second most important cell population that may contribute to the intrahepatic IFN response. Although cultures of pDCs do not react directly with HCV [31], they have been shown to accept HCV RNA via exosomes from cells that contain HCV subgenomic replicons [34]. This process requires direct contact between cells and leads to the activation of TLR7 in endosomes and the production of IFN-α by plasmacytoid dendritic cells [10]. However, this mechanism still needs to be confirmed in an infected liver.

A unique feature of HCV infection is the late-onset of acquired immune responses, which are usually detected no earlier than 8-12 weeks after infection. The proportion of patients who eliminate HCV in the acute phase is very small, and they differ from patients who develop chronic infection by an adequate CD4 + T cell

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response, better proliferation of T cells and IL-2, IFN-γ and TNF-α [9, 26, 32, 38].

The acquired antiviral immunity can be represented in the form of three components: antibody secretion, cytotoxic reaction of CD8 + T-lymphocytes and proliferative response of CD4 + T-lymphocytes. Antibodies, binding to viral particles, can prevent their penetration into target cells and promote phagocytosis of viral particles by immunocompetent cells. CD4 + lymphocytes are responsible both for assisting B cells in the secretion of antibodies and for activating cytotoxic lymphocytes; cytokines produced by CD4 + cells play an important role in both cases [49]. T- and B-links of immunity make a significant contribution to the elimination of the virus and liver damage, but in most cases they are not able to stop the persistence and pathological action of the pathogen.

Unlike CD4 + T cells, HCV-specific CD8 + T cells are usually "stunned" in all patients in the acute phase of HCV infection, as evidenced by impaired proliferation, IFN-γ production and cytotoxicity [21, 35] and increased expression on cellular surface of the programmed death-1 (PD-1) molecule [18]. Failure to generate successful HCV-specific CD8 + T cells in patients with chronic hepatitis is believed to be associated with depletion and loss of IL-21-producing Th17 cells [17].

Investigating the role of cytotoxic cells in the pathogenesis of the disease, Chisari et al. [7] calculated that in the liver, in which almost all cells were infected with the virus, there was less than one cytotoxic T cell per thousand infected hepatocytes. This overwhelming predominance of potential target cells suggests that there is some additional mechanism of cytotoxic T-cell mediated viral clearance in addition to direct destruction of infected cells by activating apoptosis signals and necroinflammatory responses. It has been found that passive transfer of virus-specific cytotoxic T cells leads to viral clearance through cytokine mechanisms, predominantly with the participation of γ-IFN and TNFα. Subsequently, it was shown that mechanisms of viral clearance unaccompanied by a cytopathic effect take place during HBV infection in chimpanzees [15]. Further, it was also found that a similar intracellular inactivation in the liver occurs in other, unrelated viral infections (LCMV, adenovirus, cytomegalovirus). Cytokines, γ-IFN, TNF-α, and possibly IL-2 inhibit viral expression and replication processes at the level of post-transcriptional events by destabilizing and destroying RNA in the nucleus and preventing the assembly of the viral nucleocapsid in the cytoplasm. Recently Guidotti et al. [14] provided evidence that the antiviral activity of -IFN is mediated by nitric oxide (NO).

Inhibitory molecules such as the T-cell immunoglobulin domain and mucin domain 3 (TIM-3) [24] and additional factors such as an increased number of Treg cells and inhibitory cytokines (such as IL-10 and TGF-b) are thought to also contribute to disorders of T-cell reactions in chronic HCV infection [11, 12, 28].

Over the past decade, the importance of natural killer cells (NK) has been widely described in chronic viral hepatitis [29]. In viral infections, NK cells exhibit rapid innate reactions by cytotoxicity against infected target cells by releasing antiviral cytokines. During killing, immature dendritic cells, secreted proinflammatory cytokines and chemokines, NK cells support the priming of T cells and organize the recruitment of other immune cells to the site of infection [39]. These mechanisms enhance the adaptive arm of the immune response,

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which ultimately clears infection, provides immune memory, and protects against re-infection.

NK cell responses are controlled by a large number of activating and inhibiting cell surface receptors. Activations include, among many others, receptors for natural cytotoxicity (NKp30, NKp44 and NKp46), lectin-like receptors (NKG2C, NKG2D), which are expressed as dimers with CD94, and signaling lymphocyte family receptors (SLAM) (2B4, CRACC, NTB-A) [6]. Inhibitory receptors include killer-cell immunoglobulin-like receptors (KIRs) and NKG2A / CD94. The receptors are expressed combinatorially, which create an estimated 6,000 to 30,000 phenotypically distinct subpopulations of NK cells individually in the blood of each individual. In the absence of infection, inflammation, or other disease, NK cells generally receive inhibitory signals. The expression of inhibitory receptors is genetically determined [16]. KIRs ligands, human leukocyte antigens (HLA), are thought to mediate the maintenance of self-sufficiency. NK cells are activated when signals from inhibitory receptors are decreased, for example when KIRs-binding MHC molecules are expressed on virus-infected cells, for example, when coated with an antibody, viral antigens and / or stress-induced ligands on infected cells are recognized. NK cells also respond to inflammatory cytokines such as type I interferons (IFNa and IFNb), IL-2, IL-12, IL-15, and IL-18, which are usually released in response to viral infections [5]. NK cell activation increases with the level of expression of activating receptors, allowing NK cells to become more responsive in the context of infection and inflammation.

To date, it is known that cytokines secreted by immune cells are of decisive importance in cell-mediated and humoral immune responses, as well as in antiviral activity, viral clearance, apoptosis, and fibrogenesis [33, 8]. Cytokines and immune cells interact with each other and form a complex immune response network that determines the development and progression of hepatitis. Cytokines not only play a key role in clearance [3], but are also essential for NK cells and cytotoxic T cells to balance their function in the immune response [25].

Studies have shown that insufficient induction of Th1 cells and increased Th2 cell activity may be associated with viral persistence in chronic HCV infection. The relationship between Th1 / Th2 cytokines and clinical manifestations was also analyzed. IL-6 levels were directly proportional to serum ALT levels, while levels were inversely proportional to HCV RNA load. Severe patients showed high levels of IL-4 and IL-6 compared to mild cases. Patients with genotype 1 had higher serum IL-6 levels than those with genotype 2, while patients with genotype 2a had lower serum levels of IL-2 than patients with genotype 2b. These data suggest that Th2 cytokines may play an important role in liver inflammation in HCV infection. IL-6 has been associated not only with chronic HCV infection but also with active liver inflammation. However, it is still unknown whether this is also one of the factors contributing to the higher rate of complications in patients with HCV genotype 1 infection compared with genotype 2 [1].

Studies of all 4 functional groups of cytokines involved in the pathogenesis of the inflammatory process - pro / anti-inflammatory cytokines (IL-1β, TNFα, IL-1ra, IL-10), immunoregulatory cytokines (IL-2, IFNγ, IL-12, IL-4 , IL-5, IL-6, IL-9, IL-13, IL-15, IL-17), growth factors (G-CSF, IL-7, FGF-β, PDGF, VEGF) and chemokines (IL- 8, IP-10, MCP-1, MIP-1α, MIP-1β, RANTES, Eotoxin) showed that

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patients with CP are active producers of cytokines and are characterized by increased secretion of cytokines from all 4 functional groups. Increased production of many cytokines is associated with the severity of LC and viral etiology of LC. At the same time, an increase in both spontaneous and LPS-stimulated secretion of cytokines indicates a preserved reactivity of blood cells to endotoxin [53]. In the studies of A. Antonelli et al. the level of IL-6 in the blood serum in patients with chronic HCV infection was also recorded an increased level of this cytokine compared with the group of healthy donors [2]. The content of cytokines and immunological parameters of the blood of HCV-infected patients was studied. The patients had significantly increased levels of TNFα, IL-4, pathogenic circulating immune complexes (CICs) in the blood serum, significantly reduced the percentage of CD3, CD4 and CD25 lymphocytes, the level of induced IFNγ and the proliferative response of lymphocytes, there was a deficit in the function of neutrophil phagocytes. A direct reliable relationship was found between the serum TNFα level and the severity of cytolysis, the severity of the inflammatory process in the liver [54]. It was found that activated HCV-specific clones of cytotoxic T-lymphocytes secrete a number of cytokines that enhance the progression of fibrosis and portal inflammation in CHC patients [13].

Thus, HCV infection is characterized by peculiar changes in the activity of the mediators of the Th1 and Th2 responses of the immune system. An in-depth study of immunopathogenesis will make it possible to clarify the mechanisms of inadequate immune response in HCV infection, which will contribute to the diagnosis, prognosis of the course of these diseases and the choice of adequate therapy.

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