REVIEW

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Host immune response in chronic hepatitis C infection: involvement of cytokines and inflammasomes

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Abstract

Chronic liver disease is a major health issue worldwide and chronic hepatitis C (CHC) is associated with an increased risk of cirrhosis and hepatocellular carcinoma (HCC). There is evidence that the hepatitis C virus (HCV) infection is correlated with immune senescence by way of immune activation and chronic inflammation, which lead to increased metabolic and cardiovascular risk, as well as progressive liver damage. Both the innate and adaptive immunity are firmly tied to the prognosis of an infection with HCV and its response to antiviral therapy. HCV is therefore associated with increased pro-inflammatory status, heightened production of cytokines, prolonged systemic inflammation, as well as increased morbidity and mortality, mainly due to the progression of hepatic fibrosis and HCC, but also secondary to cardiovascular diseases. Viral hepatic pathology is increasingly considered a disease that is no longer merely limited to the liver, but one with multiple metabolic consequences. Numerous *in vitro* studies, using experimental models of acute or chronic inflammation of the liver, has brought new information on immunopathological mechanisms resulting from viral infections and have highlighted the importance of involving complex structures, inflammasomes complex, in these mechanisms, in addition to the involvement of numerous proinflammatory cytokines. Beyond obtaining a sustained viral response and halting the aforementioned hepatic fibrosis, the current therapeutic "treat-to-target" strategies are presently focused on immune-mediated and metabolic disorders, to improve the quality of life and long-term prognosis of CHC patients.

Keywords: chronic hepatitis C, cytokines, inflammasomes, inflammasome nucleotide-binding domain, leucine-rich repeat protein 3.

Introduction

Chronic liver disease is a significant global health issue and the most prevalent etiologies are represented by non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, chronic hepatitis B (CHB) and chronic hepatitis C (CHC) [1]. CHC, caused by the hepatitis C virus (HCV), affects over 71 million people globally and is correlated with an increased risk of cirrhosis, as well as hepatocellular carcinoma (HCC), ultimately causing 399 000 deaths annually [2].

In Romania, the overall prevalence of viral hepatic C pathology was estimated to be 4.9%, but recent studies have reported a percentage of 3.2 [3]. It can be assumed that more than one million people have anti-HCV antibodies, and if roughly 70% have active disease, this will be regarded as a public health problem [4].

Furthermore, the presence of the 1b genotype is notable (the prevalence in Romania is 92.6%; this prevalence is also recorded in the countries of Central and Eastern Europe, some countries in North Africa, Central and South America) [4], for it implies a lower response to antiviral therapy, making the need for both a higher dose and an extended therapeutic regimen, a particularly costly endeavor [5].

There is evidence that an HCV infection is associated with immune senescence, immune activation and chronic inflammation, which bring about an increased metabolic and cardiovascular risk, as well as progressive liver damage. Both innate and adaptive immunity is significantly tied to the prognosis of an HCV infection, as well as its response to antiviral therapy [6].

Research conducted in recent decades has focused on the study of the involvement of multiprotein complexes (inflammasomes) in the mechanisms involved in innate immunity. Inflammasomes are considered as caspase-activating complexes, but roles in intracellular signaling have also been reported, through mediation or even

involvement in the transmission of intracellular signaling. They also appear to have the ability to be involved in the recognition of pathogens, including liver viruses, in the mechanisms involved in oxidative stress and in insulin resistance respectively [7].

Since 2002, Martinon *et al.* showed that after the formation of these complexes between cysteine-dependent aspartate-directed protease-1 (caspase-1) and inflammasomes, pro-inflammatory mediators are released, such as interleukin-1beta (IL-1β) and IL-18. In the formation of these complexes, participate in most cases nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) molecules [8]. It was also observed that in addition to caspase-1, other elements can also participate in the formation of these complexes: cysteine-dependent aspartate-directed protease-5 (caspase-5), a pyrin and C-terminal caspase-recruitment domain (PYCARD), also known as apoptosis-associated speck-like protein containing a CARD (ASC) [9, 10].

Studies have highlighted that there is a close relationship between a chronic HCV infection and the promotion of inflammation and liver disease, as well as between IL-1β release and formation followed by activation of the inflammasome nucleotide-binding domain and leucine-rich repeat protein 3 (NLRP3) [11].

CHC infection and immune response

The liver, through the diversity of liver cells, is the key site involved in inflammatory processes. Also, important cells, such as myeloid cells [dendritic cells (DCs), neutrophils and macrophages (cells in which the virus does not have the ability to reproduce quickly)] are responsible for the synthesis of many effectors involved in triggering, mediating and regulating immune responses, both from innate and adaptive immunity: cytokines, adipokines, chemokines, reactive oxygen species (ROS) [12].

The innate immunity defense is the first to react *via* pattern recognition receptors (PRRs), which have the ability to recognize microbial pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). The receptors from the PRRs category are represented by: Toll-like receptors (TLRs), NLRs, retinoic-acid inducible gene I (RIG)-I-like receptors (RLRs) and lastly C-type lectin receptors (CLRs) [8].

Among the cells of innate immunity, natural killer cells (NK) and natural killer T (NKT) cells are the first cells that trigger the immune response [13]. Their activation is done through type I interferons (IFNs), a category that includes interferon-alpha (IFN-α), interferon-beta (IFN-β) and interferon-omega (IFN-ω), but also by type III IFNs [subtype with three members, IL-29 or interferon-lambda 1 (IFN-λ1), IL-28A or interferon-lambda 2 (IFN-λ2) and IL-28B or interferon-lambda 3 (IFN-λ3)] [14]. Activated NK and NKT cells will secrete type II IFNs, interferon-gamma (IFN-γ), also known as immune IFN, which together with tumor necrosis factor-alpha (TNF-α) are important effectors actively involved in innate immune response [15–18].

During an infection, activated macrophages and DCs produce a range of cytokines (IL-1β, TNF-α, IL-6), chemokines [C-X-C motif chemokine ligand 8 (CXCL8) or IL-8) and certain adhesion molecules (αXβ2, αDβ2) and cluster of differentiation 11c/cluster of differentiation 18 (CD11c/CD18)] [19]. Also, DCs have the property of presenting viral antigens to naïve T- and B-cells, *via* molecules of the major histocompatibility complexes (MHC) class I and class II [20]. Following said interaction, complexes form between the viral epitopes and the MHC, on the one hand, and T-cell receptors (TCR) on the other, bringing about the activation of T-cells within the systemic cellular immune response. Activated T-cells proliferate as well as differentiate into effector or memory T-cells [21].

It is worth pointing out that cytotoxic T-lymphocytes (CTLs), CD8+ T-cell subpopulations, become activated and subsequently begin exerting their cytolytic function, killing virus-infected cells (through apoptosis-mediated cytolysis) and secreting cytokines, such as IFN-β, IL-12, IL-1, and IL-18. Besides, cytotoxic CD8+ T-cells can produce IFN-γ and TNF-α [22]. IFN-β is important for directly inhibiting viral replication and increasing MHC class I up-regulation [23].

After activation, other CD4+ T-cell subsets become engaged in mediating the adaptive immune response by producing T-helper type 1 (Th1) cytokines, pro-inflammatory cytokines, such as IL-2, IFN-γ and TNF-α, implicated in the cell-mediated immune response [24]. The CD4+ T-cells also secrete T-helper type 2 (Th2) cytokines and anti-inflammatory cytokines (IL-4, IL-10, IL-13), which modulate the humoral immune response [25]. It has previously been established that T-cells can self-regulate their activity by way of synthesizing IL-10 and tumor growth factor-beta (TGF-β), which inhibit T-cell proliferation and cytokine synthesis either directly or *via* other cytokines [26, 27].

An important role in inducing/modulating the activity of cells involved in immune responses is also attributed to the HCV core proteins. Following the encoding and post-translational process, the HCV genome consists of three structural proteins [core protein (nucleocapsid protein) C; the envelope glycoproteins, E1 along with E2], as well as seven non-structural proteins [p7, NS2, NS3 (helicase/protease), NS4A, NS4B, NS5A and NS5B [ribonucleic acid (RNA) polymerase] [28]. Thus, studies have shown that the HCV core protein can selectively suppress IL-12 synthesis by DCs, or inhibit T-cells proliferation by direct or indirect action [29, 30]. It has also been observed that HCV NS3 and NS4 proteins stimulate the formation of IL-10 producing monocytes, with the cytokine having an immunosuppressive effect on the production of IFN-γ by CD4+ T-cells [31].

Soluble mediators found in patients with an HCV infection attract pro-inflammatory cells, metabolically activating them and increasing vascular permeability. Depending on their time of release, they are classified as the line I mediators [complement system, histamine and contact activation system (kinin system and coagulation system)], line II mediators (biologically active lipids) and line III mediators (cytokines) [32].

CHC infection and cytokines

Cytokines

Cytokines are small protein molecules that regulate the

cellular function of several immune cells. Their role has been evident in the defense against infectious agents, tumor cells and they are similarly involved in trauma, sepsis, and other immune responses. Particularly important is their involvement in the differentiation of T-cells and careful modulation of immune functions. Depending upon their target of action, function or which cell they are secreted from, they can be further classified into lymphokines, interleukins (ILs), monokines, IFNs, colony-stimulating factors, or chemokines [33]. Based on the response they exhibit from the immune cells they interact with, cytokines are regarded as pro-inflammatory or anti-inflammatory. Proper cell function is dependent on the balance between pro-inflammatory and anti-inflammatory cytokines. Cellular processes form an essential system that involves complicated signaling pathways and cascades of biochemical reactions. Such processes need to be tightly controlled, as disruption of established feedback mechanisms can lead to tissue damage. For instance, cytokine storms are known to occur in cases of overproduction, which, depending on their severity, can become life-threatening [34].

TNF-α

One particular cytokine involved in HCV infections is TNF-α, which activates fibroblasts and attracts them to the inflammatory site. Additionally, TNF-α plays a role in mediating the process of apoptosis and is capable of impeding tumor growth, inducing fever and even cachexia. It is produced mainly by activated macrophages and has a chemotactic effect on hepatocytes. It can facilitate leukocyte adhesion to targeted sites by way of engaging the expression of intracellular adhesion molecules (ICAMs), as well as integrins and selectins [35].

Hosomura *et al.* have shown that non-structural HCV proteins (NS3, NS4, NS5) play an important role in stimulating Kupffer cells (KCs) that will manufacture inflammatory cytokines like IL-1β and TNF-α [36]. Other studies have highlighted the correlation between elevated TNF-α concentrations with hepatic inflammation evaluated immunohistopathologically [histological activity index (HAI)] [37, 38], the association of increased TNF-α synthesis but accompanied by a decrease in IL-10 with severe liver damage and in patients with HCC [39], studies in which the role of the association between TNF-α and IL-6 with auto-antibodies [rheumatoid factor immunoglobulin M isotype (IgM-RF); antinuclear auto-antibodies (ANA); anti-cardiolipin immunoglobulin G isotype (IgG anti-aCL); anti-cyclic citrullinated peptide (CCP) antibodies immunoglobulin G isotype (IgG anti-CCP)] was studied, as to distinguish between patients having true early rheumatoid arthritis and HCV-related arthropathy [40–43], or in HCV patients, steatosis and obesity, which are associated with elevated serum concentrations of TNF-α and IL-6 [44].

IFN-γ

In contrast, activated NK cells and T-lymphocytes produce IFN-γ, a cytokine which is an important regulator of both innate and adaptive immunity in HCV infection. In response to virus-infected cells, NK cells interact with plasmacytoid dendritic cells (pDCs) and monocytes to produce IFN-γ [45].

However, when it comes to the treatment of patients with chronic HCV, the initial pan-genotypic therapeutic option was IFN-α, which demonstrated a sustained virological response rate of 8% up to 21% [46]. A significantly elevated level of IFN-γ, along with an increase in monocyte chemoattractant protein-1 (MCP-1) and IL-18, were highlighted in plasma harvested from humanized mouse model (HIL) infected with an HCV dose of 10^7 focus-forming units (FFU)/mL at 27±8 weeks after infection [47]. Similar findings to those reported in mice were also found in other studies in HCV infected individuals, the authors also mentioning that these three soluble proteins are involved in mediating the functions of macrophages and T-cells during HCV infection [48–51]. In other studies, blocking of IL-10 or TGF-β synthesis was attempted and it was observed that this inhibition is followed by activation and proliferation of T-cells involved in HCV pathophysiology and increased IFN-γ synthesis [32, 52–55].

Interleukins

The human genome encodes for roughly 50 ILs and analogous proteins, of which there are fifteen commonly known but distinctive types designated numerically. While a small subset is synthesized by macrophages, monocytes and endothelial cells, most ILs are generated by Th CD4+ lymphocyte subpopulations and they are not stored within cells. They are secreted swiftly, and briefly in response to triggers such as infectious agents. Post-synthesis they travel to each target cell and bind to specific receptors located on the surface, modulating cellular behavior as a result. ILs bolster the differentiation and growth of B-lymphocytes, T-lymphocytes, as well as hematopoietic cells [56].

IL-1α and IL-1β

IL-1 is an acute-phase protein and potent inflammatory cytokine produced locally by activated macrophages in response to various infections. B-lymphocytes, endothelium cells, fibroblasts, and astrocytes may also secrete IL-1, leading to a broad spectrum of biological functions in different tissues. IL-1 regulates diverse cellular processes during both acute and chronic infections, causing lymphocyte activation of CD4+ T-cells, B-cells and NK cells, neutrophil recruitment and subsequently enhancing phagocytosis. It can bring about an increased leukocyte/endothelial adhesion to the inflammatory focus [selectins, integrins, and intercellular adhesion molecules (ICAMs)] along with acute-phase proteins released by the liver. IL-1 stimulates the hypothalamic center of thermoregulation, thereby inducing a fever [12].

Additionally, it can exhibit chemotactic and activating effects on pro-inflammatory cells; it encourages the production of platelet aggregating factors, synthesis of von Willebrand factor, as well as attracting and increasing the activity of fibroblasts [56]. Furthermore, IL-1 contributes to myeloid cell differentiation through an increase in the expression of growth factors, specifically: granulocyte colony-stimulating factor (G-CSF), as well as granulocyte/macrophage colony-stimulating factor (GM-CSF). Beyond these, worth mentioning is its involvement in DC maturation and differentiation of T-helper type 17 (Th17) [57].

Defined as having two isoforms, IL-1α and IL-1β, both forms of IL-1 share the same IL-1 receptor type 1 (IL-1R1), which is expressed on specific cell types [58, 59]. IL-1α and IL-33 are cytokines that perform two functions, they bind to each's specific cell surface receptor and their intracellular precursor forms ultimately end up translocating to the nucleus in order to modulate the transcription of pro-inflammatory genes [60]. However, in order for IL-1β to reach its mature form, its precursor (pro-IL-1β) needs to be cleaved by cytosolic caspase-1. One study suggests that inhibition of inflammasome complex assembly using small interfering RNA (siRNA) against NLRP3, ASC or caspase-1 may lead to a reduction in the secretion of IL-1β by HCV-infected cells [9].

IL-6

In the liver, IL-6 is produced chiefly by KCs, subsequently enhancing the production of several acute-phase proteins, such as C-reactive protein, fibrinogen, haptoglobin, serum amyloid A, as well as others. One study suggests that the IL-6/signal transducer and activator of the transcription 3 (IL-6/STAT3) signaling pathway has a noteworthy inducible effect on micro-RNA-125b (*miR-125b*) gene expression and that STAT3 and siRNA or inhibitor may diminish the replication of HCV. Previously, *miR-125b* had been shown to regulate inflammation, as well as act as an oncogene pertaining to several cancer types [61]. Furthermore, increased production of IL-6 through the stimulation of TLR2 by HCV core protein may have a key role in the pathogenesis of B-cell non-Hodgkin's lymphoma (B-NHL) and hepatitis C-associated mixed cryoglobulinemia (MC). When viral antigens stimulate the host's inflammatory response through extracellular PRRs, they likely promote the development of MC and B-NHL in patients with chronic HCV [62].

As both a pro-inflammatory cytokine, as well as an anti-inflammatory myokine, IL-6 is synthesized by T- and B-lymphocytes, fibroblasts, endothelial cells, keratinocytes, synoviocytes, chondrocytes and epithelial cells in response to bacterial and viral infections, inflammation or trauma, with swift detectable plasma levels. Not only is it involved in the growth and differentiation of B-cells but it also stimulates Ig production, as well as hematopoiesis by acting synergistically with IL-3. Last but not least, it can induce adrenocorticotropic hormone (ACTH) secretion and other pituitary hormones, such as growth hormone, luteinizing hormone and prolactin [63].

Its role as an anti-inflammatory myokine is brought about through its inhibitory effects on IL-1 and TNF-α, along with the activation of IL-10 and IL-1 receptor antagonists (IL-1ra). IL-6 is a pleiotropic cytokine consisting of 184 amino acids, with a molecular weight of about 21 kDa, depending on the degree of glycosylation, playing a vital role in priming T-cell growth, influencing their differentiation and inhibiting the apoptosis of lymphocytes. It is recognized as a marker of the host inflammatory response and a mediator of both innate and cell-mediated immunity. Moreover, it acts as a promoter for the differentiation of Th17-cells, which secrete IL-17 [64].

Albumin and transferrin synthesis in the liver are both decreased following exposure to IL-6, hepatocyte regeneration processes being opted for instead [65]. Nevertheless, following HCV infection, patients who show compellingly higher than average levels of IL-6, appear to respond poorly to antiviral therapy [48, 66, 67]. The use of IL-6 and IL-10 as biomarkers may be appropriate for early CHC detection. While being involved in our body's immune response, IL-6 has a further protective role through the enhancement of lymphocyte effector functions, hence being of use along with other factors in T-cell immunotherapy for those suffering from chronic HCV infection [68].

IL-28

Synthesized by regulatory T-cells (also known as "Tregs"), IL-28 stimulates cell presentation of viral antigens to CD8+-type T-lymphocytes, as well as upregulating TLR-2 and TLR-3 expression. TLRs are known to be involved in innate immunity and they interact with different antigens according to their subtype [69]. Of note, TLR-3 can recognize double-stranded RNA (dsRNA) and subsequently initiate the production of type 1 IFN. It has been recently shown that a specific polymorphism (*rs12979860*) near the *IL-28B* gene has been correlated with a heightened response to treatment with IFN and Ribavirin in HCV-infected patients. This specific polymorphism has also been associated with interferon-lambda 4 (IFN-λ4) protein, which may have a role in clearing HCV [70, 71].

It is known that IL-28A or IFN-λ2 and IFN-λ3, formerly known as IL-28B, along with IL-29 or IFN-λ1 are three cytokines that are part of type III IFNs, IFN-λ [72, 73].

Dolganiuc *et al.* have obtained elevated serum concentrations of IL-28A and IL-29 in patients with chronic HCV, but also in the liver [elevated messenger RNA (mRNA) levels of IL-28 and IL-29, but also receptors expression], which may indicate that chronic inflammation of the liver would be produced by a double pathophysiological mechanism, by the action of the virus and by the immune response to the virus. In the experiments performed, it has been shown that DCs exposure to IFN-λ is followed by inhibition of IL-12 synthesis but not IL-2 production, suggesting an immunomodulatory effect of IFN-λ on DC and T-cells [74]. These results are in line with other studies previously published but it also denies the results of other studies [75–79].

IL-22

IL-22, a cytokine belonging to the IL-10 family, is comprised of eight other soluble proteins (IL-28A, IL-28B, IL-29, IL-10, IL-19, IL-20, as well as IL-24) [80]. There is evidence to suggest that the IL-22 specific receptor cannot be highlighted in immune cells with immune mediation functions, but it can only be expressed on liver cells, epithelial cells that paste the gastrointestinal tract, in the skin and lung (territories where IL-22 implicitly exerts its effects, namely regulating inflammation of the local tissue) [81, 82].

Th17 lymphocyte has been found to synthesize IL-22, in addition to the IL-17A and IL-17F cytokines [83], but it was found that IL-22 is synthesized by gamma/delta T (γ/λ T) cell lymphocytes subpopulations [84] and innate lymphoid cells (ILCs, lymphoid cells of innate immunity considered to be the newest members of the lymphoid line; three groups were described, such as group 1/ILC1s, repre-

sented by NK cells, group 2/ILC2s, which synthesizes IL-5 and IL-13, playing an essential role in the immune response to helminth infections, group 3/ILC3s, originally described as intestinal lymphoid cells with a role in activating NK cells) [85, 86].

Sabat *et al.* observed that increased IL-22 concentrations and its inhibitor IL-22 binding protein (IL-22BP) in cultures highlights a significant correspondence with protection from hepatic fibrosis along with portal hypertension in patients with chronic HCV infection, thus having a key role in hepatic regeneration through the proliferation of hepatocytes and their migration [87].

Eyerich *et al.* have described a novel set of Th lymphocytes other than Th1, Th2, Th17 or other T-lymphocytes known to date, in the studies performed to the patients with inflammatory skin diseases (atopic dermatitis, contact dermatitis, epithelial hyperplasia of psoriasis), a subset named Th22, a unique subset that can mediate skin inflammatory processes, a new set that may be a target in the future for therapeutic intervention [88, 89].

IL-27

IL-27 is regarded as a pro-inflammatory cytokine and being part of the IL-6/IL-12 family, it mediates the activity of T-cells and implicitly participates to coordinate the activity of the cells involved in the innate immune response. Studies performed *in vitro*, have shown that IL-27 has biological effects, for example, the stimulation of CD4+ Th-lymphocytes and IL-12 stimulates the activation of mouse native cells, initiation of Th1 differentiation and proliferation, the activation of innate immune cells and release of IFN-γ [90].

It has been found that the IL-27 specific receptor, consisting of two signal molecules (IL-27Rα and gp130) is found in the immune cells involved in both the innate immune response and those involved in the adaptive response [91]. Also, there are studies, that have highlighted as IL-27 acts like IFN, having antiviral activity inhibiting HCV replication [92, 93].

IL-10 and IL-12

IL-10 is released by several immune cells, as they are Th2-lymphocytes, B-cells and macrophages [94]. IL-12 is a potent cytokine with pro-inflammatory action, synthesized especially by antigen-presenting cells after they are stimulated by IFN-γ [10]. It is an important factor involved in differentiating naïve T-cells into Th1- and Th2-cells, a potent modulator of both immune, innate and adaptive responses [95, 96]. In several studies, elevated serum concentrations of IL-10 and IL-12 were obtained in patients with chronic HCV with statistical significance, values associated with the degree of an inflammatory process or have statistically positive correlations with HCV progression [97–102].

IL-35

IL-35 has recently emerged as a novel immunosuppressive and anti-inflammatory cytokine secreted by regulatory T-cells, regulatory B-cells, DC and to a lesser extent by monocytes, endothelial cells and smooth muscle cells [103]. A recent study demonstrated how serum IL-35 levels can be elevated in patients with CHC and how IL-35 stimulation may reduce inflammatory cytokine production by the liver through STAT1/3 inhibitions. Moreover, the overall level of "Tregs" became elevated due to IL-35 stimulation, and this stimulation likewise inhibited cellular proliferation and increased the making of anti-inflammatory cytokines, such as IL-10 [104].

IL-17

Several types of Th-cells have crucial functions following activation; the subtype Th17-cells, a subset of CD4+ T-cells, are notably increased in HCV infection, being involved in its progression to chronicity. Th17-cells increase the inflammation of the liver and release pro-inflammatory cytokines, such as IL-17A, IL-17F, IL-21, and IL-22, because of stimulating the differentiation and expansion of Th17-cells by IL-1, IL-6, IL-23 or TNF-α [57, 64, 83]. On the other hand, IL-23, which is part of the IL-12 family, is essential for the survival as well as the extension of the Th17 population along with their inflammatory consequences [105, 106].

More recently, it was demonstrated that IL-23 and IL-17 (IL-23/Th17 axis) are the pivotal cytokines implicated in the immune as well as the inflammatory reaction pertaining to chronic liver diseases [107]. It was also observed that an imbalance between "Tregs" and Th17-cells regulates the immune response during antiviral treatment [108, 109]. Regarding IL-21, a recent report, published in 2018, reported that higher levels are predictors of sustained virological response in patients with HCV [6].

CHC infection and inflammasomes

Cysteine-dependent aspartate-directed protease-1 (caspase-1)

The caspase-1, also known as IL-1-converting enzyme (ICE), is an enzyme initially synthesized as an inactive zymogen (pro-caspase-1). This enzyme becomes the active form when it is assembled within inflammasomes complex, when it has the role of mediating the transformation of cytokine precursors for IL-1β, as well as IL-18 (pro-IL-1β and pro-IL-18), into intensely involved active forms in initiating immune mechanisms [9].

Activation of IL-1β and IL-18 will lead to differentiation of Th-lymphocytes in Th1 and Th17 populations, intensely involved in adaptive immune defense mechanisms. Compared to other cytokines, in which the regulation is done at transcriptional level, in the case of these two cytokines (IL-1β and IL-18) the synthesis takes place by stimulating the TLR or RLR receptors, with the synthesis of inactive forms. The final step of the synthesis is post-activation of inflammasomes mediated by NLR receptors [110–112].

Inflammasomes

Inflammasomes are considered protein complexes, at the cytosolic level, activated in various situations to which the host organism is subjected, *e.g.*, metabolic disorders following stress or infectious processes [113, 114].

Studies have shown that several viruses, as they are hepatitis viruses (hepatitis B virus, HCV) [9, 115], respiratory tropism viruses (influenza A virus, respiratory syncytial virus) [116–118], deoxyribonucleic acid (DNA) viruses (herpes viruses, such as *Herpes simplex* virus 1; varicella–

zoster virus) [119, 120], *Vaccinia* virus [121], human papillomavirus [122], have an important role in activation the inflammasomes, launching the aforementioned signaling cascade [123].

Regarding the structure of these complexes, a ring disposition was observed composed of three binding elements: NLR proteins [actively involved in inflammatory processes being the isotypes NLRP1, NLRP3, NLRP6 and NLR containing CARD domain, proteins 4 and 5 (NLRC4 and NLRC5)], ASC and caspase-1 (in some cases caspase-5 may be included) [124]. Depending on the NLRs or RLRs receptors that are included in the annular structure of the complex, four types of inflammasomes are known: NLRP3 inflammasome, inflammasome absent in melanoma 2 (AIM2), RIG-I inflammasome and γ-IFN-inducible protein 16 (IFI16) inflammasome. Of these types, it has been observed that the first three forms, NLRP3, AIM2 and RIG-I, are mainly involved in viral infections [125].

The HCV RNA-induced IL-1β secretion is thought to be dependent upon the participation of inflammasome units like NLRP3, ASC, as well as caspase-1. Production and activation of IL-1β and IL-18 as pro-inflammatory cytokines swiftly follows [125, 126].

Nucleotide-binding domain and NLRP3 inflammasome

The NLRP3 inflammasome complex has recently received the attention of researchers. The most important agonists of this complex that induce its formation have been identified as viruses, both liver viruses and viruses with respiratory tropism, but bacterial or fungal causes should not be excluded. Ulland *et al.* have shown that the NLRP3 inflammasome can be activated by various bacterial pathogens, such as lipopolysaccharides, bacterial endotoxins, but also bacterial RNA [111, 112]. Due to the role that these inflammasomes have in sustaining our immunity, several viruses encode for proteins which can assist in blocking their specific pathway, therefore preventing IL-1β production or halting the activation of caspase-1 [125].

The structure of NLRP3 respects the ring, tripartite, typical arrangement of inflammasomes: a pyrin and PYCARD, NOD domain and a C-terminal-leucine-rich repeats (LRRs) domain [126]. This structure will form the basis of the formation of inflammatory complexes. During inflammatory processes, after these complexes of inflammasomes are formed, they become active and able to enzymatically activate caspase-1 and the cascade of reactions culminates with the release of mature and active cytokines, IL-1β and IL-18, respectively [113, 126–128].

Burdette *et al.* have been highlighted the novel induction, as well as the assembly of the NALP3 inflammasome complex, in human hepatoma cells that had been infected with HCV (using mock-infected and HCV-infected Huh7.5 cells) followed by IL-1β synthesis, as a result of a proteolytic process of activating pro-caspase-1 and turning it into mature caspase-1 [9]. Also, authors have noticed an inhibition (using ROS inhibitor Diphenyleneiodonium) of only 60% of IL-1β secretion in HCV-infected cells incubated with Pyrrolidine Dithiocarbamate (PDTC), thus demonstrating the involvement of ROS in the induction of inflammasome complex assembly and stimulate IL-1β secretion, respectively [9, 10, 129].

In another study, it was intended to evaluate the involvement of various inflammasomes in liver cells, using experimental models of acute and chronic inflammation of the liver. It was observed that inflammasomes, such as NLRP-1, NLRP-3, and AIM2, were predominantly revealed at the level of KCs and in epithelial cells from the sinusoids, less expressed in peripheral myofibroblasts and hepatic stellate cells (HSCs) and very important these inflammasomes have not been highlighted in hepatocyte cultures. It has also been demonstrated *in vitro* that the stimulation with lipopolysaccharide (LPS) of cell cultures containing HSCs was followed after a while of a strong NLRP3 expression in hepatocytes [130].

Two different studies were published and have reported that hepatocytes are activated and express inflammasome complex but do not stimulate the sufficient synthesis of IL-1β and IL-18 [131, 132]. Other studies support the production of ROS as a result of HCV stimulation induced by NLRP3 inflammasome complex assembly, along with the activation of a specific pathway, named the nuclear factor-*kappa* B (NF-κB) pathway and production of IL-1β and IL-18 cytokines [51, 133]. Additionally, Guarda *et al.* have shown that treatment with type I IFN (IFN-α and IFN-β) inhibits the activity of NLRP1b and NLRP3 inflammasomes, which will not trigger the activation of the caspase-1 enzyme and thus IL-1β maturation does not occur [134].

All these results obtained in many studies, over the past two decades, show that NLRP3 inflammasome complex or IL-1β may constitute new therapeutic targets, in an attempt to get better management of chronic HCV infections.

Conclusions

In this brief review, we have attempted to highlight the fact that the inflammatory process triggered by HCV infection is the result of several mechanisms, such as the recognition of HCV RNA and viral protein components by immune cells belonging to both innate and acquired immunity, a second mechanism being the excessive synthesis of numerous pro-inflammatory and anti-inflammatory cytokines, chemokines, adipocytokines, activating the assembly of inflammasomes complex, mechanisms to which are added the action of ROS, as finally on a global basis to influence both the local inflammatory response (at the level of the hepatocyte, where viral replication occurs), as well as systemic inflammation. Also, these structures, immune cells or inflammasomes, involved in these mechanisms may constitute new therapeutic targets, to ameliorate the damage to the liver micromedium and prevent the occurrence of irreversible liver tissue injuries.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Anca Marilena Ungureanu and Mihail Virgil Boldeanu equally contributed to the manuscript.

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