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Editorial board member of *World Journal of Gastroenterology*, Wan-Long Chuang, MD, PhD, Doctor, Professor, Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung 807, Taiwan

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Ze-Mao Gong, Director
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Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
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PUBLISHER
Baishideng Publishing Group Inc
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REVIEW

Mononuclear phagocyte system in hepatitis C virus infection

Yu Yang, Zheng-Kun Tu, Xing-Kai Liu, Ping Zhang

Yu Yang, Xing-Kai Liu, Ping Zhang, Department of Hepatobiliary and Pancreatic Surgery, The First Hospital of Jilin University, Changchun 130021, Jilin Province, China

Zheng-Kun Tu, Institute of Translational Medicine, The First Hospital of Jilin University, Changchun 130061, Jilin Province, China

ORCID number: Yu Yang (0000-0002-1513-4883); Zheng-Kun Tu (0000-0001-6803-2015); Xing-Kai Liu (0000-0001-7856-3899); Ping Zhang (0000-0003-4944-2937).

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Corresponding author to: Ping Zhang, MD, Chief Doctor, Professor, Surgeon, Department of Hepatobiliary and Pancreatic Surgery, The First Hospital of Jilin University, No. 71, Xinmin Street, Changchun 130021, Jilin Province, China. z_ping@jlu.edu.cn
Telephone: +86-431-81875168
Fax: +86-431-81875168

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Abstract

The mononuclear phagocyte system (MPS), which consists of monocytes, dendritic cells (DCs), and macrophages, plays a vital role in the innate immune defense against pathogens. Hepatitis C virus (HCV) is efficient in evading the host immunity, thereby facilitating its development into chronic infection. Chronic HCV infection is the leading cause of end-stage liver diseases, liver cirrhosis, and hepatocellular carcinoma. Acquired immune response was regarded as the key factor to eradicate HCV. However, innate immunity can regulate the acquired immune response. Innate immunity-derived cytokines shape the adaptive immunity by regulating T-cell differentiation, which determines the outcome of acute HCV infection. Inhibition of HCV-specific T-cell responses is one of the most important strategies for immune system evasion. It is meaningful to illustrate the role of innate immune response in HCV infection. With the MPS being the important factor in innate immunity, therefore, understanding the role of the MPS in HCV infection will shed light on the pathophysiology of chronic HCV infection. In this review, we outline the impact of HCV infection on the MPS and cytokine production. We discuss how HCV is detected by the MPS and describe the function and impairment of MPS components in HCV infection.

Key words: Mononuclear phagocyte system; Hepatitis C virus; Monocyte; Dendritic cell; Macrophage

Core tip: Hepatitis C virus (HCV) infection is efficient to develop into chronic infection. Innate immune system can shape the acquired immune response, which can eradicate HCV directly. As the main component of innate immunity, the mononuclear phagocyte system (MPS) plays a vital role in HCV infection. In this review, we discuss the interaction between the HCV and MPS. MPS can detect HCV to promote virus eradication, and HCV can

shape the MPS to facilitate HCV persistence. We hope that this review will enable us to better understand HCV infection.

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INTRODUCTION

Hepatitis C virus and hepatitis C virus infection

Hepatitis C virus (HCV) is a positive sense single-stranded RNA virus that belongs to the family *Flaviviridae*[1]. HCV infection affects more than 170 million people worldwide and is regarded as a leading cause of chronic liver disease[2]. The viral genome is approximately 9.6 kb, encoding a single 3011-amino acid-long polyprotein. The polyprotein is cleaved into three structural proteins (core, E1, and E2) and seven non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B)[3]. HCV is classified into seven genotypes as well as 67 subtypes, and it shows significant genetic diversity among different nations[4]. Even within the same patient, HCV usually exists in blood as a group of related quasispecies[5]. Acute HCV infections are anicteric and asymptomatic[6]. Nevertheless, 15%-20% of HCV-infected patients can recover from an acute infection, whereas the remaining 80%-85% of patients will progress to chronic infection[6-8]. Chronic HCV infection is a leading cause of end-stage liver diseases, liver failure, and hepatocellular carcinoma, resulting in approximately 350000 deaths per year[9,10]. HCV infection is usually diagnosed *via* the detection of both HCV antibody and HCV RNA. In the absence of viral RNA, the detection of HCV antibody indicates a spontaneously resolved or cured infection[10]. The combination of subcutaneous pegylated interferon (peginterferon) alpha and oral ribavirin was once the standard treatment for chronic HCV infection. However, this combination results in a sustained virological response (SVR) in only approximately 50% of patients[11]. In 2011, the United States Food and Drug Administration approved a novel HCV therapy including direct-acting antiviral drugs and protease inhibitor drugs. These drugs significantly increased the response rate, thereby revealing a new era of HCV treatment[12,13].

Mononuclear phagocyte system

The term mononuclear phagocyte system (MPS) was developed in the late 1960s and early 1970s by van Furth[14]. The MPS encompasses monocytes, dendritic cells (DCs), and macrophages, and altogether they play vital roles in tissue development, maintenance of homeostasis, inflammation, and the innate immune defense against pathogens.

Monocytes constitute 5%-10% of the peripheral blood leukocytes in humans and are generated in the bone marrow and spleen[14]. During inflammation, monocytes can differentiate into macrophages and DCs[15-19], and they play important roles in both innate and adaptive immunity[20-24]. Circulating monocytes can traffic through the sinusoids, and thus, it has been proposed that liver-resident monocytes and circulating monocytes should be distinguished[25]. However, blood monocytes pass through the liver numerous times, and therefore, we will consider circulating monocytes with liver-resident monocytes as one entity in this review.

Human blood DCs are major histocompatibility complex (MHC) class Ⅱ [human leukocyte antigen D-related (HLA-DR)] positive and can be divided into myeloid DCs (mDCs) and plasmacytoid DCs (pDCs)[26]. pDCs are CD11c negative and are distinguished from mDCs using positive markers such as CD123, CD303, and CD304[26]. Alternatively, mDCs can be subdivided according to CD1c and CD141 expression[26]. Accordingly, DCs exist in $CD303^+$ pDCs, $CD11c^+$ $CD1c^+$ mDCs, and $CD11c^+$ $CD141^+$ mDCs populations. It is worth mentioning that all these subsets are present in the liver[25], and the $CD1c^+$ mDC population is the most prevalent liver DC subset[27]. Compared to blood DCs, hepatic DCs present an immature phenotype and have a lower capacity to stimulate T cells[27-29]. Furthermore, hepatic DCs produce more interleukin (IL)-10 and less IL-12p70[30,31], highlighting the tolerogenic peculiarity of hepatic DCs.

Macrophages are large phagocytic cells with multifunctional roles in development, homeostasis, and diseases[32]. Kupffer cells (KCs) are tissue-resident macrophages of the liver that have important functions in both the innate and acquired immune responses[32-34]. However, owing to their stationary state, they are not as potent as DCs in stimulating T cells[35]. Additionally, KCs can also regulate the functions of other hepatic cells[36,37]. As early as the 1990s, the interaction between KCs with natural killer (NK) cells and liver stellate cells was identified by electron microscopy, implying that the functions of NK cells and stellate cells may be shaped by KCs[38]. In our lab, we previously identified Toll-like receptor (TLR)-dependent crosstalk between human KCs and NK cells[39].

HCV infection is notorious for its propensity to become chronic due to the lack of robust acquired immune responses. The immune response against HCV infection is primarily controlled by the adaptive immune system; however, a robust acquired immune response is determined by the innate immune response[40]. In other words, proper innate immunity is essential for the initiation of the acquired immune response. Mounting evidence confirms that the MPS is crucial for innate immunity and plays an important role in multiple infections, including parasitic infections[41], tuberculosis[42], human immunodeficiency virus (HIV) infection[43,44], and respiratory syncytial virus infection[45]. Therefore, it is necessary to clarify the interaction between HCV and the MPS. The immunophenotype of the MPS in normal liver has been previously reviewed[25]. However, the impact

of HCV infection on the MPS has not been reviewed yet. Therefore, in this review, we summarize recent findings regarding the role of the MPS in HCV infection, and we focus on the function and impairment of MPS components following HCV infection.

DETECTION OF HCV BY THE MPS

Pathogen-associated molecular patterns (PAMPs) on HCV can be detected by three classes of pattern recognition receptors (PRRs): RIG I-like receptors (RLRs), TLRs, and NOD-like receptors (NLRs)[46]. These PRRs function early after infection, thereby restricting HCV replication[46].

RIG-I, representative of RLRs, can sense HCV RNA as non-self through the 5′-triphosphate (5′-ppp) found on the viral RNA in addition to the 3′ poly-U/UC tract[47,48]. Blocking of the signaling pathway of melanoma differentiation-associated gene 5 (MDA5), another member of the RLRs, led to enhanced HCV replication[49]. Both RIG-I and MDA5 utilize the adaptor protein mitochondrial antiviral signaling (MAVS) to initiate immune signaling, and they recognize different PAMPs, indicating that they may function complementarily[50-52]. In West Nile virus infection, RIG-I was found to play an important role in the early immune response after infection, whereas MDA5 was more important in the later period of infection[53].

Endosomal TLRs are the main sensors that detect HCV. Among them, TLR3 can sense double-stranded (ds)RNA[54,55], whereas the GU-rich sequences in HCV RNA can be recognized by TLR7 and TLR8[56,57]. Additionally, TLR2 is specialized in HCV protein detection[58]. Wang *et al*[54] previously demonstrated that interferon (IFN)-stimulated genes (ISGs) are upregulated in primary human hepatocytes after polyinosinic: polycytidylic acid (polyI:C) stimulation, owing to the expression of TLR3. However, the authors observed that HCV infection weakened the ability of hepatocytes to induce ISG expression compared to the polyI:C stimulation[54], indicating that TLR3 signaling may be impaired by HCV. Consistently, it was previously established that TIR-domain-containing adapter-inducing interferon-β (TRIF), an adaptor protein of TLR3 signaling, can also be cleaved by the NS3/4A protease[59,60].

It is worth mentioning that the results described above were derived from primary human hepatocytes or hepatocyte cell lines infected by HCV. *In vivo,* uninfected hepatocytes were able to sense the adjacent infected cells by TLR3[55]. Extracellular dsRNA was detected by the uninfected hepatocytes in a macrophage scavenger receptor 1 (MSR1)-dependent manner[55]. MSR1 can bind to the viral dsRNA and transport it to the endosome, within which TLR3 is engaged[55]. This mechanism may be employed by the MPS to trigger an antiviral state in a TLR3-dependent manner. Furthermore, HCV-infected cells can induce the production of type Ⅰ IFN from pDCs[61]. Additionally, HCV RNA activates the MPS populations like mDCs and pDCs to produce proinflammatory cytokines and chemokines, including IL-1β, tumor necrosis factor (TNF)-α, IL-6, IL-12, IL-10, CXCL9, and CXCL10[57]. Particularly, the GU-rich sequences induce type I IFN from monocytes and pDCs[57]. In contrast, the polyU/UC sequences of HCV RNA activate IL-1β production from the nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome of macrophages, resulting in persistent liver inflammation[62,63].

In addition, HCV proteins can also activate the MPS. It was identified that HCV core protein (HCVc) and NS3 activate monocytes[64] and macrophages[58], thereby triggering inflammatory pathways in a TLR2-dependent manner[58]. Additionally, HCVc and NS3 inhibit DC differentiation[64]. Furthermore, TLR1 and TLR6, co-receptors of TLR2, are also involved in HCVc and NS3-induced macrophage activation[65].

Compared to the HCV RNA, HCV viral particles are less efficient in stimulating the MPS[57]. Nevertheless, they can activate macrophages, leading to production of proinflammatory cytokines like IL-6, IL-1β, and TNF-α rather than the antiviral cytokines including IL-12 and type Ⅰ IFN[57].

IMPACT OF HCV ON THE MPS

HCV and monocytes

Effect of HCV on TLR signaling: TLR signaling is associated with the outcome of acute HCV infection as well as the therapeutic outcome[66]. Accumulating evidence suggests that HCV infection can influence the expression of TLRs[67-69]. Particularly, the expression levels of TLR2 and TLR4 are elevated after HCV infection in monocytes[67-69]. The expression of TLR2 is significantly correlated with serum TNF-α and alanine transaminase (ALT) levels[67], indicating that the inflammation associated with HCV infection is partially attributed to production of proinflammatory cytokines in a TLR2-dependent manner. Similarly, HCVc can activate the MPS in a TLR2-dependent manner[58]. In contrast, TLR3 and TLR4 in monocytes are compromised after HCV infection[70]. In healthy individuals, the repeated stimulation of monocytes *via* the TLR ligands leads to tolerance, thereby providing a protective mechanism to limit inflammation. However, this tolerance is disrupted in HCV-infected patients[71]. Therefore, monocytes from HCV-infected patients are hyper-responsive, and their expression of TNF-α is upregulated. The loss of TLR tolerance can be attributed to IFN-γ[71]. Alternatively, other reports demonstrated that HCVc can induce down-regulation of IL-6 production after stimulation with TLR2 and TLR4 ligands[72,73]. We hypothesize that HCVc induces hyporesponsiveness, leading to the evasion of immunity in the early period of infection, whereas IFN-γ-induced loss of tolerance may contribute to inflammation and subsequent liver damage in chronic infection.

Impact of HCV on cytokine production from monocytes: IL-10, an anti-inflammatory cytokine, can be produced by monocytes[74]. IL-10 has several immunoregulatory functions after HCV infection. It is involved

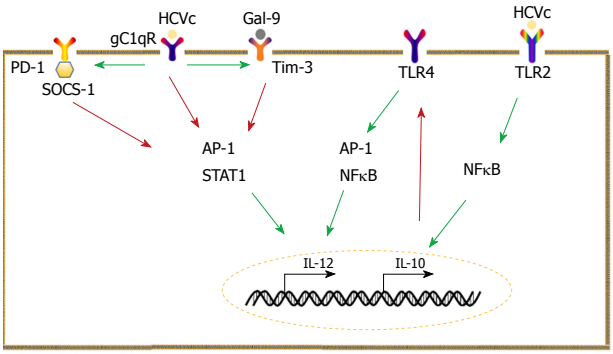

Figure 1 Mechanisms underlying aberrant interleukin-10 and interleukin -12 expression. Monocytes are a main producer of interleukin-10 (IL-10) in hepatitis C virus (HCV) infection. HCV core protein (HCVc) can stimulate monocytes to produce IL-10, which selectively inhibits Toll-like receptor 4 signaling, leading to impairment of interleukin -12 (IL-12). Programmed cell death 1 (PD-1)/ ligand of PD-1 (PD-L1) signaling and the galectin-9 (Gal-9)/ T cell immunoglobulin and mucin domain 3 (Tim-3) pathways suppress IL-12 production by inhibiting activator protein 1 and signal transducer and activator of transcription 1 activation. The interaction between HCVc and receptor for the globular heads of C1q also inhibits IL-12 production but promotes PD-1/PD-L1 and Gal-9/Tim-3 pathways. The red arrow represents inhibition, whereas the green arrow indicates promotion. HCVc: HCV core protein; IL: Interleukin; TLR: Toll-like receptor; PD-1: Programmed cell death 1; PD-L1: Ligand of PD-1; Gal-9: Galectin-9; TIM-3: T cell immunoglobulin and mucin domain 3; AP-1: Activator protein 1; STAT: Signal transducer and activator of transcription; gC1qR: Receptor for the globular heads of C1q; SOCS: Suppressor of cytokine signaling; NFκB: Nuclear factor-κB.

in HCV-specific $CD8^+$ T cell regulation; specifically, IL-10 can reduce the frequency of $CD8^+$ T cells and impair their differentiation[75]. Furthermore, IL-10 preferentially targets TLR4 signaling[76]. The inhibitory role of IL-10 against the production of proinflammatory cytokines was preferentially mediated by TLR4 signaling, *i.e.*, the stimulation of chronic hepatitis C (CHC) patient-derived monocytes by lipopolysaccharide (LPS) (a TLR4 ligand) rather than R848 (a TLR8 agonist) led to lower TNF-α and IL-12 production[76].

Analysis of serum samples collected from CHC patients often shows higher IL-10 levels either produced spontaneously or after stimulation with HCV antigens[77,78]. Particularly, CHC patients have high IL-10 levels and relatively low levels of IFN-γ and IL-2[79], whereas patients with the self-limiting HCV produce lower IL-10 levels in response to both viral antigens and unspecific stimulation[80].

HCV NS4 can stimulate peripheral blood mononuclear cells (PBMCs) to produce IL-10 and transforming growth factor (TGF)-β[81]. TGF-β cooperates with IL-10 to inhibit the host-protective immune responses[82]. Additionally, supernatants of NS4-stimulated monocytes can inhibit DC maturation and DC stimulatory function[81].

In our lab, we studied the network of cytokines that regulate IL-10 production and the cytokines regulated by IL-10 upon HCV infection[74]. The stimulation of monocytes with HCVc and polyI:C induces the secretion of TNF-α, IL-1β, IL-10, and type Ⅰ IFN. Interestingly, TNF-α, IL-1β, and IFN promote the IL-10 production, whereas high IL-10 levels inhibit TNF-α, IL-1β, and IFN production[74]. Furthermore, receptors for IL-10 on monocytes are also elevated during HCV infection and the type Ⅰ as well as type Ⅲ IFNs upregulate the IL-10 monocyte receptors, leading to higher sensitivity of monocytes to IL-10[83].

Programmed cell death-1 (PD-1) is primarily expressed on activated lymphocytes, whereas its ligand (PD-L) is widely expressed by many cells[84]. PD-1/ PD-L interactions can affect responses against self and foreign antigens[84]. Consistently, PD-1/PD-L1 signaling in monocytes has critical roles in HCV infection. Monocytes from CHC patients are endowed with high levels of PD-L1, which enables the suppression of T cell proliferation, reduces the frequency of HCV-specific effector T cells, and downregulates the production of type 1 help T cell (Th1) cytokines as well[85]. PD-L1 signaling downregulates IL-12 expression, leading to low Th1 cytokine production[86]. HCVc interacts with the receptor for the globular heads of C1q (gC1qR) to increase PD-1 expression by monocytes[87]. PD-1 is associated with suppressor of cytokine signaling 1 (SOCS-1), and they work together to inhibit the activation of signal transducer and activator of transcription (STAT)-1 and the subsequent IL-12 production[87].

The galectin-9 (Gal-9) and T cell immunoglobulin and mucin domain 3 (Tim-3) pathway in monocytes is also vital for HCV infection. Monocytes express Gal-9 upon exposure to HCV-infected cells or the subgenomic replicon cells and exosomes from infected cells[88]. Consistently, Tim-3, receptor of Gal-9, is constitutively expressed on resting monocytes and can be up-regulated in CHC patients[89]. HCVc upregulates Tim-3 in a c-Jun N-terminal kinase (JNK) and T-bet-dependent manner[90]. The Gal-9/Tim-3 pathway is involved in the dysfunction of IL-12, IL-23, and IL-17[89,91]. Crosstalk between PD-1 and SOCS-1, Gal-9, and Tim-3 inhibits IL-12 production by limiting STAT-1 phosphorylation[89].

In conclusion, imbalance between IL-10 and IL-12 is a key feature of HCV infection. High levels of IL-10 combined with low IL-12 levels lead to a poor antiviral microenvironment. To make matters worse, HCV-infected patients and healthy controls show different responses to IL-10 and IL-12, *i.e.*, IL-10 can suppress IFN-γ production in both HCV-infected patients and healthy controls, whereas the stimulatory effect of IL-12 on IFN-γ is compromised in HCV-infected patients[92] (Figure 1).

Regulatory function of monocytes following HCV infection: Following HCV infection, monocytes modulate the functions of other immune cells, such as NK cells and T cells. Additionally, NS5A can upregulate IL-10 and TGF-β expression in monocytes, and in turn, these cytokines suppress NK cell function by downregulating the expression of NKG2D, an activating receptor expressed on the surface of NK cells[93]. Furthermore, monocytes secrete the IL-18 and IL-36 inhibitory proteins, which can reduce NK cell activation, TNF-related apoptosis-inducing ligand (TRAIL) expression, and the ability to kill target cells[94]. Monocyte-derived Gal-9 upregulates the cytotoxicity of NK cells, leading to HCV-specific T cell apoptosis and liver injury[95]. Co-culture of

monocytes with T cells leads to elevated mortality rate of T cells[96]. In addition to these detrimental functions, monocytes were found to be beneficial in the following situation: elevated OX40L expression, which is involved in the $CD4^+$ T cell response. Blocking OX40L expression from monocytes leads to HCV-specific $CD4^+$ T cell impairment[97]. Upon co-culture with JFH-1/HuH7.5 cells, NK cells from PBMCs produce high levels of IFN-γ. pDC-derived IFN-α is indispensable for IFN-γ production, whereas the monocyte-derived IL-15 can augment IFN-γ production to the maximum[98].

HCV and DCs

Impaired functions of DCs following HCV infection: *In vivo* study showed that gene expression in DCs from acute HCV resolving patients and from patients who become chronically infected is different[99]. The same result is also confirmed in healthy controls and CHC patients[99]. All these indicate that DCs play an important role in HCV infection.

DCs derived from peripheral blood progenitors *in vitro* enabled the extensive study of DC populations. Compared to healthy control DCs, HCV-DCs (derived from CHC patients) exhibit a normal phenotype and morphology but stimulate allogeneic T cells poorly[100,101]. Owing to the low expression of IL-12 in HCV-DCs, they induce lower amounts of IFN-γ from T cells compared with control DCs in co-cultures of allogeneic DCs and T cells[102]. Additionally, HCV-DCs are refractory to maturation stimuli and maintain an immature phenotype[103]. Interestingly, the observed defects in HCV-DCs are improved after viral clearance[100,103]. In agreement, transfection of DCs from a healthy donor with adenovirus encoding HCV E1 and HCVc resulted in poor ability to stimulate the allogeneic and autologous T cells[104].

To confirm the results obtained from *in vitro* generated DCs, researchers evaluated the functions and phenotypes of blood DCs *ex vivo* directly during chronic HCV infection[105-109]. Compared to those among healthy controls, the frequencies of mDCs, pDCs, and DC progenitors are significantly lower in HCV-infected patients[106,108-110]. DCs from HCV-infected patients have a reduced ability to stimulate allogeneic $CD4^+$ T cells[105,107,110]. Additionally, they show abnormalities in the production of cytokines, such as reduced IFN-α and IL-12 levels[107,110] and increased IL-10 production[107,108]. Interestingly, these defects are resolved after viral elimination, indicating that HCV can indeed infect DCs and alter their function[106,108,109]. Additionally, the tryptophan-catabolizing enzyme indolamine 2,3-dioxygenase (IDO), an inducer of immune tolerance, was found to be significantly increased in mDCs of CHC patients[111]. Moreover, HCV-infected patient monocyte-derived DCs and infected control monocyte-derived DCs (infected *ex vivo* with HCV) show an inability to mature, and this impairment can be reversed by IDO inhibitors[111].

The anti-HCV immune response mainly occurs in the liver; therefore, it is reasonable to speculate that the behavior of circulating DCs can be different from that of liver-resident DCs. Therefore, studies were designed to isolate and characterize human liver DCs[112]. In contrast to the circulating DCs, mDCs from livers of HCV-infected patients did not show noticeable defects in stimulating T cells and produced lower levels of IL-10 than mDCs from healthy individuals[112]. However, the livers of HCV-infected patients harbored decreased numbers of pDCs compared to the livers of healthy individuals[112], and thus, the amount of IFN-α was lower in the HCV-infected patients[112]. In summary, lower amount of IFN-α and lower levels of IL-10 can contribute to persistent viral infection and inflammation in HCV infection, respectively[112].

Additionally, DCs from HCV-infected patients showed lower production of IFN-λ[113], abolished cytotoxic activity[114], upregulated levels of Fas ligand as well as PD-L2[115], and imbalanced expression between the co-stimulatory and co-inhibitory markers[116,117].

HCV-derived mechanisms underlying DC impairment: The mechanisms underlying DC impairment as well as the HCV proteins modulating DC functions have been previously investigated[118]. HCVc and NS3 proteins are involved in the impairment of DC maturation, lower levels of T cell stimulation as well as higher levels of IL-10 production from DCs in HCV-infected patients[64] (Table 1). Additionally, HCVc protein can engage gC1qR to inhibit IL-12 production and further restrain Th1 responses[119]. HCV E2 protein interacts with CD81 of DCs to alter DC migratory behavior, thereby incapacitating the recirculation of DCs to the lymphoid tissue, which can cause impairment of T cell priming[120] (Table 1). In our lab, we isolated liver-derived pDCs from normal liver tissues collected from benign tumor dissections and liver transplant donors. We observed that the interaction of E2 with CD81 inhibits pDC maturation, activation, and IFN-α production[121]. HCV NS4 protein can change the DC phenotype and is involved in the reduction of Th1 cytokine production and impairment of T cell stimulation[122]. NS3 and E2 proteins can hinder IFN-λ production from DCs[113]. NS5A increases IL-8 production from DCs and influences the phosphorylation of STAT1 and STAT2[123] (Table 1).

On the other hand, a number of studies failed to find defects in DCs during HCV infection[124-128]. It was reported that both HCV patients and chimpanzees infected with HCV harbor phenotypic and functional intact mDCs and pDCs[124,125]. DCs (both pDCs and monocyte-derived DCs) from healthy donors and HCV patients show comparable functions[127]. These discrepancies can be attributed to the inhomogeneous disease state of the patient cohorts, technicalities in methods used for DC purification, stimuli used to induce maturation, and the evaluation of discrepant effector functions.

HCV and macrophages

Fundamental functions of macrophages after HCV infection: The number of proinflammatory macrophages is increased significantly in HCV-infected livers, highlighting the importance of macrophages in HCV infection[129-131]. This increase is dependent

Table 1 Hepatitis C virus-derived mechanisms underlying dendritic cell impairment

HCV protein	Target cells	Functional change	Mechanism	Ref.
HCV core and NS3	mDCs	Impaired maturation Impaired T-cell stimulation	Increased IL-10 and decreased IL-12 production	[64]
E2	mDCs	Alter DC migratory behavior	Interacts with CD81	[120]
	pDCs	Inhibited maturation Impaired activation Decreased IFN-α production		[121]
E2 andNS3	mDCs	Impaired IFN-λ production	Not shown	[113]
NS4	mDCs	Th1 cytokine reduction T-cell stimulatory impairment	Not shown	[122]
NS5A	mDCs	Increased IL-8 production Impaired interferon signaling	Not shown Influence the phosphorylation of STAT1 and STAT2	[123]

HCV: Hepatitis C virus; NS: Nonstructural protein; mDC: Myeloid dendritic cell; pDC: Plasmacytoid dendritic cell; IL: Interleukin; Th1: Type 1 help T cell; IFN: Interferon; STAT: Signal transducer and activator of transcription.

on the proliferation of resident KCs and recruitment of monocytes[129]. Macrophages express TRAIL, Fas-ligand, granzyme B, perforin, and reactive oxygen species, which cause direct cytotoxicity to the infected hepatocytes[132,133]. Furthermore, macrophage-derived IL-6 and IL-1β can inhibit HCV replication[134,135]. Moreover, TLR3 and TLR4 ligands can activate KCs to secrete IFN-β, therefore restricting HCV replication[136]. This observation is in agreement with the results obtained by our group. We isolated KCs from living donor allografts and stimulated them with TLR ligands and/or HCVc. Indeed, we observed that TLR3 induced KCs to secrete type Ⅰ IFNs, and this effect was blocked by HCVc[133]. Additionally, KCs were reported to produce TGF-β, IL-10, Gal-9, PD-L1, and PD-L2 during CHC, which suppresses the antiviral functions of T cells[133,137-139].

HCV infection can influence the macrophage phenotype: Burgio *et al*[140] observed that the immunophenotypes of KCs can change during HCV infection. The expression of CD80, CD40, and MHC-Ⅱ was aberrantly regulated during HCV infection. Those KCs form clusters with T cells (mostly $CD4^+$) in the livers from HCV-infected patients. In contrast, in healthy livers, the KC-T cell clusters are scarce and the T cells are mostly $CD8^+$. Taken together, these results indicate that HCV infection can change the phenotype of KCs from efficient antigen endocytic cells to professional antigen-presenting cells[140]. Additionally, the HCV E2 protein can polarize monocyte-derived macrophages to the M2 phenotype by enhancing STAT3 and inhibiting STAT1 activation[141]. In our group, we observed that HCVc can also affect the differentiation states of cells from monocytes to macrophages. Both M1 and M2 polarization are inhibited in a TLR2-dependent manner[142].

Role of macrophages in mediating HCV-associated inflammation: HCV proteins and RNA can activate macrophages, leading to the production of proinflammatory cytokines such as IL-1β, IL-6, IL-18, and TNF-α[62,63,133,143]. It is noteworthy that upon macrophage activation with HCV viral particles, the response is proinflammatory rather than antiviral[57]. This could be attributed to the polyU/UC sequences of HCV RNA, which activate the NLRP3 inflammasome of macrophages. Additionally, macrophage-derived TNF-α was reported to promote HCV entry into polarized hepatoma cells[144]. In HCV-infected patients, LPS can induce significantly high levels of TNF-α, because macrophages of HCV-infected patients are deprived of TLR-tolerance[71,130]. The combination of increased TNF-α production along with the enhanced HCV entry may represent an important mechanism by which macrophages enhance HCV infection and infection-associated inflammation (Figure 2).

Macrophages play an important role in HCV-associated liver fibrosis and/or cirrhosis: Progressive fibrosis and/or cirrhosis is a characteristic of CHC, and macrophages play an important role in this process[145]. In CHC, the role of macrophages in fibrosis is mediated by the pro-inflammatory cytokines IL-1β and TNF-α, which have a well-established pro-fibrotic function[146-149]. Additionally, conditioned medium from HCV-exposed macrophages can modulate the primary human hepatic stellate cells (HSC) and LX2 cell line. CCL5 derived from macrophages activates HSCs, leading to the increased expression of inflammatory and pro-fibrogenic markers such as NLRP3, IL-1β, IL-6, CCL5, TGFβ1, COL4A1, matrix metalloproteinase 2 (MMP2), and α-smooth muscle actin (SMA)[150].

HCV-infected patients have elevated serum levels of macrophage colony-stimulating factor (M-CSF) and IL-34[151], and these proteins are intensely expressed around the liver lesions. *In vitro*, hepatocytes produce IL-34, M-CSF, and inflammatory cytokines in response to HCV infection[151]. IL-34 and M-CSF promote the differentiation of monocytes into macrophages and endow the macrophages with profibrotic properties[151]. These profibrotic macrophages recruit monocytes to the liver and activate HSCs *via* platelet-derived growth factor, TGF-β, and galectin-3[151].

CONCLUSION

Components of the MPS have redundant but non-identical roles in HCV infection. Monocytes act as progenitors for DCs as well as macrophages, and they play an important role in blunting the immune system by

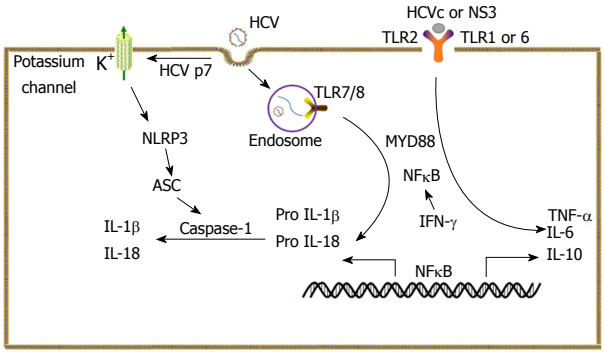

Figure 2 Role of macrophages in hepatitis C virus infection-associated inflammation. During hepatitis C virus (HCV) infection, macrophages are the main source of the proinflammatory cytokines [interleukin (IL)-1β, IL-18, tumor necrosis factor (TNF)-α, and IL-6] and the anti-inflammatory IL-10. The production of IL-1β and IL-18 requires two signals, which are initiated by the uptake of intact HCV particles. Signal 1: Following dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin-mediated endocytosis, the HCV genome is released into cytoplasm and the uridine-rich HCV RNA is recognized by endosomal Toll-like receptor 7 (TLR7). This recognition leads to pro-IL-1β and IL-18 production in a myeloid differentiation primary response gene 88 and nuclear factor-κB (NFκB)-dependent manner. Signal 2: Pro IL-1β and IL-18 become activated in this pathway. HCV p7, an ion channel protein, promotes potassium efflux that activates the nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome. Utilizing apoptosis-associated speck-like protein containing a CARD as an adaptor protein, NLRP3 activates caspase-1, which induces the maturation of pro-IL-1β and pro-IL-18 into their active forms. HCV core and NS3 proteins interact with TLR1 or TLR6 and TLR2 to activate NFκB, which results in the production of TNF-α, IL-6, and IL-10. Additionally, HCV particles can also be recognized by TLR7/8, inducing TNF-α production. TLR tolerance is a protection mechanism against uncontrolled inflammation. In HCV infection, it can be abrogated by interferon-γ through NF-κB signaling, leading to the production of high levels of proinflammatory cytokines. HCV: Hepatitis C virus; HCVc: HCV core protein; IL: Interleukin; TLR: Toll-like receptor; TNF-α: Tumor necrosis factor α; DC-SIGN: Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; TLR: Toll-like receptor; MYD88: Myeloid differentiation primary response gene 88; NF-κB: Nuclear factor-κB; NLRP3: Nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3; ASC: Apoptosis-associated speck-like protein containing a CARD; NS3: Nonstructural protein 3; IFN-γ: Interferon-γ.

secreting large amounts of IL-10 and decreasing IL-12 production. Altered TLR signaling is the most probable cause for abnormal cytokine production in HCV infection. Results from studies examining the impairment of DCs during HCV infection are still controversial. In this review, we adopt the argument that mDCs show a reduced ability to stimulate T cells, whereas pDCs produce decreased amounts of IFN-α in HCV infection. However, a definitive conclusion requires further investigation. Macrophages are a double-edged sword in HCV infection, with both beneficial and detrimental effects. Macrophage-derived proinflammatory cytokines can control the viral spread in acute infection. However, if HCV infection is not controlled, these proinflammatory cytokines contribute to persistent inflammation and complications, including fibrosis and cirrhosis. Persistent inflammation is a characteristic of HCV infection, and thus, the differentiation of monocytes into DCs and macrophages should happen frequently. Will the impairments of the precursor monocytes be inherited by DCs and macrophages? Or will those impairments be reversed during differentiation? These questions remain to be investigated.

The majority of previous studies focused on only one component of the MPS, and thus, data on the interplay and cooperation between MPS components are scarce[98,152,153]. For instance, the recruitment of DCs to the liver requires KCs and the majority of the recruited DCs bind to KCs. This DC-KC binding is indispensable, because KC depletion leads to the inhibition of DC migration to the liver[152]. Furthermore, monocytes produce IL-10 and TNF-α, leading to the apoptosis of pDCs and consequently inhibiting the production of IFN-α by pDCs[153]. Additionally, pDC-derived IFN-α and monocyte-derived IL-15 work together to maximize the IFN-γ induction by NK cells and NKT cells during HCV infection[98]. Other forms of interplay and cooperation involving the MPS remain to be analyzed.

In this review, we describe the impact of HCV infection on each population of the MPS. As a precursor of DCs and macrophages, monocytes are the major contributors to the regulation of the immune system following HCV infection. Monocytes produce high levels of IL-10 and low levels of IL-12, which leads to a blunted microenvironment. On the other hand, DCs demonstrate an impaired ability to stimulate T cells that inhibit efficient anti-HCV T-cell function. As tissue-resident cells, macrophages are tightly associated with HCV-induced inflammation and cirrhosis.

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