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TOPIC HIGHLIGHT

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# Direct effects of hepatitis C virus on the lymphoid cells

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## Abstract

It has been reported that the direct binding of hepatitis C virus (HCV) and/or the replication of HCV in the extrahepatic organs and, especially, lymphoid cells, might affect the pathogenesis of extrahepatic diseases with HCV infection. More than one decade ago, several reports described the existence of HCV-RNA in peripheral blood mononuclear cells. Moreover, many reports describing the existence of HCV in B lymphocytes and B cell lymphoma have been published. In addition to B lymphocytes, it was reported that HCV replication could be detected in T lymphocytes and T cell lines. Among the extrahepatic diseases with HCV infection, mixed cryoglobulinemia-related diseases and autoimmune-related diseases are important for understanding the immunopathogensis of HCV persistent infection. Moreover, HCV persistent infection can cause malignant lymphoma. The biological significance of lymphotropic HCV has not yet become clear. However, several candidates have been considered for a long time. One is that lymphotropic HCV is an HCV reservoir that might contribute to the recurrence of HCV infection and difficult-to-treat disease status. The other important issue is the carcinogenesis of the lymphoid cells and disturbances of the immune responses. Therefore, the extrahepatic diseases might be induced by direct interaction between HCV and lymphoid cells. In this article, we summarize various studies showing the direct effect of HCV on lymphoid cells and discuss the biological significance of lymphotropic HCV.



**Key words:** Hepatitis C virus; Lymphotropism; T cell; B cell; Immunology

**Core tip:** In this article, we summarize various studies showing the direct effect of hepatitis C virus (HCV) on lymphoid cells and discuss the biological significance of lymphotropic HCV.

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## INTRODUCTION

An estimated 130-170 million people are infected with hepatitis C virus (HCV) worldwide[1]. Around 75% of the patients with acute HCV infection undergo chronic HCV infection and are subsequently at risk of progressing to hepatic fibrosis, cirrhosis and hepatocellular carcinoma (HCC)[1,2]. Persistent infection of HCV involves not only the liver but also various extra-hepatic organs[3-7]. HCV can infect hepatocytes, lymphoid cells, and probably other cells through CD81 and receptor candidates[8]. Moreover, the expression of microRNA (miR)-122 facilitates efficient replication of HCV in nonhepatic cells[9]. These reports indicated that the direct binding of HCV and/or the replication of HCV in the extrahepatic organs, especially lymphoid cells, might affect the pathogenesis of

extrahepatic diseases with HCV infection. Among the extrahepatic diseases with HCV infection, mixed cryoglobulinemia (MC)-related diseases and autoimmune-related diseases are important for understanding the immunopathogenesis of HCV persistent infection[10-13]. Moreover, HCV persistent infection could cause malignant lymphoma[4]. The status of a disease might depend on the direct interaction between HCV and lymphoid cells[6,14-17]. The biological significance of lymphotropic HCV has not yet become clear. However, several candidates have been considered for a long time. One is that lymphotropic HCV is an HCV reservoir that might contribute to the recurrence of HCV infection and difficult-to-treat disease status[18-23]. The other important issue is the carcinogenesis of the lymphoid cells and disturbances of the immune responses[8,14,24-28]. Previously, Sung *et al*[29] reported a lymphotropic HCV strain that was isolated from B cell lymphoma. This lymphotropic HCV strain can infect and replicate in established B cell lines and primary B lymphocytes[29]. Moreover, we reported that T cell lines and primary naïve T lymphocytes were infected with this HCV strain[8,25,26]. In these studies, we demonstrated that lymphotropic HCV had various effects, especially on T cell development and proliferation. Therefore, understanding of the direct effects of HCV on the lymphoid cells is needed to clarify the immunopathogenesis of HCV persistent infection. In this report, we summarize various studies showing the direct effect of HCV on lymphoid cells and discuss the biological significance of lymphotropic HCV.

## ROLE OF VIRUS RESERVOIR

### *HCV infection in peripheral blood mononucleated cells*

More than one decade ago, several reports described the existence of HCV-RNA in peripheral blood mononucleated cells (PBMCs)[30,31]. The detection rate of HCV-RNA in PBMCs was increased if the patients were infected with human immunodeficiency virus (HIV) and HCV[31]. This phenomenon indicated that immune-suppressive circumstances and/or HIV antigen might enhance the replication activity of HCV in lymphoid cells[32]. HIV-1 accessory protein transactivator of transcription (TAT) can activate HCV replication by upregulating IP10 production. Moreover, it was reported that continuous release of HCV by PBMCs was detected in HCV-infected patients, especially in HIV co-infected patients[18]. The detection of HCV-RNA in the PBMCs from HIV-HCV co-infected patients could contribute to the recurrence of HCV viremia after pegylated-interferon and ribavirin treatment. It was reported that the presence of positive/negative strand HCV RNA at the end of treatment is associated with relapse among HCV-HIV co-infected patients[33]. In addition to HCV-HIV co-infected patients, a low level of HCV replication could be detected in peripheral lymphoid cells from HCV mono-infected patients after antiviral treatment[20,23]. Moreover, it was reported that HCV persisting at low levels long after therapy-induced resolution of chronic hepatitis C could remain infectious[20]. This continuous viral presence could result in the persistence of humoral and cellular immunity for many years after treatment and could present a risk of infection reactivation.

### *Responsible lymphocyte subsets as a viral reservoir*

It has been reported that HCV replication could be detected in various kinds of lymphoid cells. Many reports describing the existence of HCV in B lymphocytes and B cell lymphoma have been published[5,29,34]. Recently, one group reported that $CD19^+$ B lymphocytes had significantly higher viral loads than $CD14^+$ monocytes[35]. Among B lymphocytes, $CD27^+$ memory B lymphocytes were more resistant to apoptosis than $CD27^-$ B lymphocytes. $CD27^+$ B lymphocytes might be a candidate subset of the HCV reservoir in chronic hepatitis C (CH-C)[36]. In addition to B lymphocytes, it was reported that HCV replication could be detected in T lymphocytes and T cell lines[20,37,38]. We also reported that a lymphotropic HCV strain could infect T cell lines and primary human naïve $CD4^+$ T lymphocytes[8,25,26]. HCV infects hepatocytes, lymphoid cells, and probably other cells through CD81 and several candidate receptors. The expression of CD81 could be detected in B cells, T cells, and monocytes, indicating that these types of cells are potential targets of HCV infection. Recently, one group reported that HCV infection of human T lymphocytes is mediated by CD5[39]. In contrast to T lymphocytes, hepatocytes do not express CD5. Therefore, the mechanism of HCV lymphotropism might be different from that of HCV hepatotropism. Moreover, the other candidate receptors were analyzed using HCV-prone and resistant T cell lines, PBMCs, primary T cells, Huh7.5 cells and HepG2 cells[40]. CD5 and CD81 expression coincided with lymphotropism and that of occludin with the permissiveness of T cell lines, but probably not primary T lymphocytes[40].

In addition to B and T lymphocytes, it has been reported that HCV can infect monocytes, especially $CD14^+CD16^+$ monocytes, but not $CD14^+CD16^-$ monocytes[41]. The detection of HCV-RNA in monocytes was reported in HCV-HIV co-infected patients and HCV-monoinfected patients[19]. HIV might facilitate the infection/replication of HCV in human macrophages[42]. One group reported the frequent compartmentalization of HCV in circulating $CD19^+$ B lymphocytes and $CD14^+$ monocytes[43]. Moreover, it was reported that immature and mature dendritic cells are susceptible to HCV genotype 1 infection, supporting at least HCV RNA replication *in vitro*[44]. Another group reported that replicative-strand HCV-RNA was detected in peripheral blood dendritic cells[28]. Although other lymphoid cells might be susceptible to HCV infection[45,46], these reports suggested that B and T lymphocytes, monocytes, and dendritic cells could be reservoirs for HCV.

## DIRECT EFFECT OF HCV ON THE CARCINOGENESIS OF LYMPHOID CELLS

Many reports have focused on the relevance of HCV infection and B-cell lymphoma, especially non-Hodgkin lymphoma (NHL)[4,47]. Compared to the high association between HCV infection and HCC, epidemiologic reports on the relationship between HCV and NHL show a moderate risk for the development of lymphoma. However, no association between HCV and NHL was also reported in low HCV prevalence countries[48,49]. Different hypotheses have been suggested to explain the difference in the HCV-NHL prevalence: (1) Geographic differences in the HCV genotype distribution might contribute to differences in the HCV-NHL prevalence; (2) The duration of persistent infection of HCV might influence the carcinogenesis of lymphoid cells; and (3) Studies in low prevalence countries might not have included enough patients to detect the association. However, meta-analyses indicated a significant association between HCV and B-NHL[48,50].

Many groups reported the mechanisms of lymphomagenesis. However, we have to understand that HCV-infected patients with MC are at a higher risk of developing HCV-NHL[51]. MC could be an intermediary step in the development of NHL. Although, different theories have been proposed to explain the mechanism of HCV-induced lymphomagenesis, we can classify most of the theories into two categories. One of them is direct HCV binding with B lymphocytes. The external stimulation of lymphocyte receptors (CD19, CD21, CD81, B-cell receptor) by HCV antigen might induce a proliferation signal[52]. The HCV-core protein induces the production of interleukin (IL) 6 in $CD14^+$ cells *via* Toll like receptor 2 and leads to increased B cell proliferation[53]. In addition to the classical cytokine proliferation signal, the down regulation of miR-26b, an miRNA known to have tumor-suppressive properties, was found in splenic marginal zone lymphoma with HCV persistent infection[54]. This theory was supported by the phenomenon of lymphoma remission when the HCV antigens are removed by treatment. In addition to the proliferation signal, HCV-E2 CD81 on B cells triggers the enhanced expression of activation-induced cytidine deaminase (AID), which could contribute to enhancing the mutation frequency[14]. The other category of lymphomagenesis mechanism is HCV infection and/or replication in B lymphocytes. It has been reported that the replication of HCV in B lymphocytes could induce error-prone DNA polymerase zeta, polymerase iota, and AID, which contribute to enhancing the mutation frequency[14]. Moreover, the cellular DNA damage and mutation were mediated by nitric oxide and reactive oxygen species[55,56]. In addition to *in vitro* study, interferon regulatory factor-1-null mice with inducible and persistent expression of HCV structural protein showed a high incidence of lymphoma and lymphoproliferative diseases[57]. In this mouse model, the overexpression of apoptotic related genes and aberrant cytokine production were detected in the first step of carcinogenesis. Another group also reported that the expression of HCV-core protein could increase the incidence of lymphoma in transgenic mice[58]. Moreover, it has been reported that persistent expression of the full genome of HCV in B cells induces the spontaneous development of B-cell lymphoma *in vivo*[59]. HCV transgenic mice that expressed the full HCV genome in B cells showed a 25% incidence of diffuse, large B-cell non-Hodgkin lymphomas. Although the relationship between HCV persistent infection and lymphomagenesis could become clarified by various epidemiological studies, the mechanism of lymphomagenesis still needs to be considered carefully.

## DIRECT EFFECT OF HCV ON THE IMMUNE EVASION

Many studies have described a failure of the innate and cellular immune response, including type 1 helper T cells (Th1) hypo-responsiveness, cytotoxic T lymphocytes (CTL) exhaustion, excessive function of $CD4^+CD25^+$ $FOXP3^+$ regulatory T cells, failure of dendritic cell function, occurs in HCV persistent infection[60-69]. Among the numerous mechanisms, the lymphoid cells, *via* direct binding and/or infection in B cells, T cells, NK cells and DCs *etc*., should be considered, especially in HCV persistent infection[8,25-28,70-73]. In our previous study, we used SB-cell lines that continuously produce infectious HCV virions in culture. The virus particles produced from the culture had a buoyant density of 1.13-1.15 g/mL in sucrose and could infect primary human PBMCs and an established B-cell line *in vitro*[29]. This lymphotropic HCV strain was useful to investigate the biological significance of HCV replication in lymphoid cells. In this *in vitro* system, HCV could infect and transiently replicate in T cells and HCV replication suppressed the interferon (IFN)-γ/STAT-1/T-bet signaling due to the reduction of STAT-1 and inhibition of its activation[26]. Moreover, HCV replication in T cells suppressed cellular proliferation and enhanced susceptibility to Fas signaling by inhibiting CD44v6 signaling and expression[25]. In addition to cell lines, we used primary T lymphocytes to analyze the biological meaning of lymphotropic HCV[8]. Another group reported that HCV core protein modulates the transcription of *IL-2* promoter in T lymphocytes by activating the nuclear factor of activated T lymphocyte pathway[74,75]. Moreover, the expression of HCV core protein could induce $Ca^{2+}$ oscillations that regulate both the efficacy and information content of $Ca^{2+}$ signals[74]. In addition to HCV replication in T cells, Yao *et al*[76] reported that the direct binding of HCV core to gC1qR on $CD4^+$ and $CD8^+$ T cells leads to impaired activation of Lck and Akt. We could also detect a relationship between HCV core protein and immune suppression in HCV persistent infection[77]. Double filtration plasmapheresis for CH-C patients could reduce the amounts of HCV core proteins in the peripheral blood and on the surface of T lymphocytes[77]. Moreover, it has been reported that the

engagement of gC1qR on DCs by HCV core limits the induction of Th1 responses and may contribute to viral persistence. Another group reported that NK cell-derived cytokines secreted in the presence of HCV cc showed a diminished antiviral effect that correlated with a reduction of IFN-γ[72]. DCs play essential roles in the triggering of primary antiviral immune reactions. DCs are the most potent activators of CD4 T cells for supporting Th1 differentiation, which is important for the cellular immune response. Several reports described that persistent HCV infection is associated with an allostimulatory defect of monocyte-derived DC[67,70]. These reports supported that HIV/HCV co-infected patients were difficult-to-control in comparison with HCV mono-infected patients, since lymphotropic HCV is frequently detected in HIV/HCV co-infected patients[78]. Co-infection with HCV and HIV is associated with increased HCV replication and a more rapid progression to severe liver disease, including the development of cirrhosis and HCC.

## DIRECT EFFECT OF HCV ON IMMUNE STIMULATION

We need to focus not only on the suppression of the immune system but also on the stimulation of the immune system, since the prevalence of cryoglobuline-related and autoimmune-related diseases is much higher than in healthy subjects[10,79]. HCV core protein activates interleukin-2 gene transcription through the nuclear factors of activated T cells pathway[75,80]. IL-2 has a role in T cell proliferation. Recently, we reported that lymphotropic HCV and high frequency of Th17 cells were detected in CH-C patients with pyoderma gangrenosum-like lesions[16]. In that report, the eradication of HCV could improve the immunological status and pyoderma gangrenosum-like lesions. A study regarding the relationship between lymphotropic HCV and autoimmune diseases is ongoing in our laboratory. Another group reported that HCV-core induced STAT3 activation might play a role in the alteration of inflammatory responses in human monocytes[81]. Moreover, HCV infection of macrophage/monocytes *in vitro* might be associated with the induction of cytokines tumor growth factor-α and IL8. In addition to T lymphocytes and monocytes, Machida *et al*[17,27] reported that HCV could induce immunoglobulin hypermutation in B lymphocytes. These reports together suggest that HCV could stimulate an unfavorable immune response. As for the understanding of autoimmune diseases, HCV persistent infection might be one of the representative models of viral-induced autoimmune diseases.

## CONCLUSION

Although various reports have described the direct effects of HCV on lymphoid cells, few have addressed whether the disturbance of the immune system induced by the direct binding and/or infection of HCV on lymphoid cells might coordinately influence the pathogenesis of HCV persistent infection. In this article, we summarized various reports indicating the direct effects of HCV on lymphoid cells. In addition to the direct effect of HCV, the indirect effects of HCV on lymphoid cells could influence the pathogenesis of HCV persistent infection. Therefore, we must treat a vast array of data to clarify the real pathogenesis of HCV persistent infection. Recently, the technologies of deep sequencing, immunoassays with increased numbers of multicolor flow cytometry analyses, and chimera mice with human lymphocytes have been developed. These technologies, together with previous data, might be able to clarify the direct effects of HCV on lymphoid cells.

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