Research Article

The Role of Dendritic Cells During HCV Infection

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Abstract

Hepatitis C virus is a highly mutable RNA virus that exists in patient blood as quasispecies, a population of dynamic strains closely related to each other. It is primarily transmitted by contaminated blood, and the major host cell supporting HCV replication is the human hepatocyte. In the natural course of HCV infection, more than 75% of patients develop chronic hepatitis after acute infection. Strong, multi-faceted and sustained T-cell responses are essential for HCV clearance. However, HCV is mutable and could develop multiple mechanisms to evade patient immune response. T-cell responses are regulated by antigen-presenting cells among which dendritic cells (DCs) are the most potent ones. In this review, the important immune molecules expressed on myeloid DCs (mDCs) and T-cells are discussed. T-cells and mDCs could interact by molecules expressed on the cell surface. DCs can express activating molecules, which facilitate T-cell proliferation and activation, which are beneficial for virus clearance. T-cells and mDCs can also express up-regulated levels of inhibitory molecules and down-regulated levels of activating molecules, which facilitate T-cell apoptosis and anergy, and finally lead to persistent infection. During chronic HCV infection, patient T cells express up-regulated level of programmed death receptor-1 (PD-1). Compared to healthy mDCs, patients mDCs express higher levels of inhibitory molecules, the ligand 2 of PD-1 (PD-L2) and Fas ligand (FasL), and lower levels of activating molecules, human leukocyte antigen (HLA)-DR and CD86. The altered expression of these immune molecules during HCV infection plays a crucial role in determining the infection outcome. With the outcome of HCV infection depends on the interaction of HCV and host immune response, HCV has evolved multiple mechanisms to evade host immune responses. This review indicates the significance of developing immune therapy for HCV infection.

1. General background of Hepatitis C virus (HCV)

After World War II (1939-1945), transfusion-associated hepatitis became one of the major hazards of blood transfusion. Most of the transfusion-associated hepatitis cases were not caused by hepatitis A virus (HAV) or hepatitis B virus (HBV), which were the only identified hepatitis virus at that time [1-3]. Thus, the new form of blood transfusion-associated hepatitis caused by the unknown infectious agent was named the non-A, non-B hepatitis (NANBH) until hepatitis C virus (HCV) was identified by the research in 1989 [4, 5, 6].

HCV is a positive-stranded RNA virus. The HCV particle consists of an RNA genome in a nucleocapsid, which is surrounded by a lipid bilayer. The lipid bilayer is of cellular origin, and viral envelope glycoproteins are embedded in the envelope [7].

With approximately 170 million patients infected, which is 3% of the world's population, HCV is the major cause of chronic hepatitis and exerts a huge burden on public health. The standard therapy for HCV infection is a combination of pegylated IFN-α (pegIFN-α) and ribavirin. The therapy lasts 6 to 12 months, depending on the viral genotype [3].

In chronically infected patients, HCV genome exists as a dynamic population of heterogeneous closely related variants, which are called HCV quasispecies. The generation of HCV quasispecies is due to its replication enzyme, RNA-dependent RNA polymerase, which lacks proof-reading activity and is error-prone [7].

Host selective pressure however plays a dominant role in driving HCV mutations. Without selective pressure from host immune responses, HCV does not undergo high rates of mutation [8]. The selective pressures on mutants include specific anti-HCV antibodies, HCV-specific helper T lymphocytes (Th) and HCV-specific cytotoxic T lymphocytes (Tc, or CTL). These specific immune responses could neutralize HCV infection of target cells, mediate the killing of HCV-infected cells, and prevent virus dissemination.

2. Dendritic cells and Immune Molecules

Activation of an immune response in humans depends on the interaction of antigen presenting cells (APCs) and T cells. Being unable to directly recognize antigens, T cells recognize and then respond to APCs in the context of the epitope-carrier molecules of the human leukocyte antigen (HLA) molecules. Dendritic cells (DCs) are the most potent professional APCs [9].

In 1973, DCs were first identified as a type of immune cells by Ralph Steinman and Zanvil Cohn at Rockefeller University. By observing cells from mouse spleen that adhered to glass and plastic surfaces, the scientists found a cell population with special microscopic properties. Being distinct from mononuclear phagocytes, granulocytes and lymphocytes, these cells were large, refractile, contorted in shape, and contained small nucleoli [10]. For the discovery of the DCs, Ralph Steinman was awarded the 2011 Nobel Prize in Medicine [11].

In human, there are two subpopulations of DCs: myeloid DCs (mDCs) and plasmacytoid DCs (pDCs). The major function of mDCs is the uptake, processing and presentation of antigens, while pDCs are the major producers of type I interferons [12]. mDCs are also called conventional DCs due to their important role in antigen presentation.

DCs play a crucial role in regulating T-cell immune responses. This is because of their special attributes, including optimal positioning as sentinels in the periphery, rapid migration to the draining lymph nodes, their ability to acquire and present antigens in MHC molecules, and their high expression of the co-stimulatory molecules CD80 and CD86 [9, 13, 14]. In draining lymph nodes, antigen-bearing DCs interact with CD4 T cells which express the T-cell receptor (TCR) and CD28. The TCR is triggered by HLA class II carrying the antigen peptide ("signal 1") and CD28 is engaged by CD80/CD86 ("signal 2") expressed on DCs. These interactions lead to activation and clonal expansion of antigen-specific T-cells [15]. The interaction between DCs and CD8 T-cells is not emphasized. This is because that strong and long-lasting CD4 T–cell response is more associated with HCV clearance [10, 11].

3. Immune response determines the outcome of HCV infection

Immune response, especially specific CD4 T-cell response, determines the outcome of acute HCV infection. Strong and sustained T-cell responses are essential for HCV clearance. Acute HCV-infected patients with strong HCV-specific T-cell responses spontaneously clear HCV infection, while the patients with weak and impaired T-cell responses develop chronic hepatitis [8, 16-20]. An important characteristic of HCV infection is that 70% to 80% of HCV-infected patients develop chronic hepatitis C [21-24]. The rate of chronicity is much higher than that HAV and HBV.

HCV is one of the most successful human viruses in establishing chronic infections. HCV has evolved unique mechanisms to block and evade critical steps in the innate immune response of host [25]. Understanding the mechanism of HCV immune evasion is crucial for the control of HCV.

4. Activating molecules whose expression are altered during HCV infection

4.1. Decreased expression of HLA-DR and CD86 on mDCs during chronic HCV infection

Activation and expansion of antigen-specific CD4 T-cells requires at least two signals sent from APCs by their expression of HLA class II ("signal 1") and CD80/CD86 ("signal 2") [15]. If signal 2 from CD80/CD86 is lacking, antigen presentation leads to T-cell anergy, a mechanism of immunologic tolerance [15].

Patients with chronic HCV infection demonstrate impaired T-cell responses against HCV [8, 16-20]. Concomitantly, mDCs from these patients have poor capacity to stimulate T-cell proliferation [26]. This could be partly attributed to the decreased expression of HLA-DR and CD86 on patient mDCs compared to the mDCs from healthy donors.

The decreased expression of HLA-DR and CD86 of patient mDCs is responsible for decreased levels of signal 1 (HLA-DR) and signal 2 (CD86) for CD4 T-cell activation [26], and may lead to anergy as mentioned above.

4.2. NF-κB activity is diminished in mDCs from chronic hepatitis C patients

NF-κB is a transcription factor regulating immune responses. NF-κB controls the expression of HLA-DR and CD86, and functions as an anti-apoptotic factor for mDCs [27-30].

NF-κB activity in mDCs from chronically infected HCV patients is diminished compared to that in mDCs from healthy donors, and it is responsible for functional changes and increased apoptosis of mDCs in such patients [26]. Given the importance of mDCs in immune responses, NF-κB activity in mDCs plays an important role in regulating protective immune responses against HCV.

4.3. Serum level of B lymphocyte stimulator (BLyS) is increased in hepatitis C patients

BLyS, an immune molecule which is also termed B cell-activating factor belonging to the TNF family (BAFF), is a member of the tumor necrosis factor (TNF) superfamily [31-33].

BLyS was firstly identified as a cytokine crucial for B-cell maturation, function, and survival [31-33]. BLyS-knockout mice demonstrate significantly reduced spleen weight, markedly reduced numbers of peripheral blood B cells, and have a profound reduction in total serum immunoglobulins [33].

BLyS is primarily produced by myeloid cells, including monocytes, macrophages, DCs and neutrophils [34, 35]. Full-length BLyS molecule is expressed on cell surface of immune cells as membrane-bound BLyS (mBLyS). mBLyS expressed on DCs has a co-stimulatory activity on both CD4+ and CD8+ T-cells [36, 37]. The full-length mBLyS expressed on APCs provides a complete second signal for T-cell activation, which leads to T-cell division and cytokine secretion [38,39]. This discovery proves the multiple functions of BLyS.

After being cleaved by polyprotein convertases, the extracellular C-terminal fragment of the BLyS molecule (amino acids 134-285) is released as soluble BLyS (sBLyS) [31-33]. Being not capable of co-stimulating T-cell activation sBLyS regulates B-cell maturation, function, and survival [34,35].

During chronic HCV infection, mBLyS expression on mDCs is unchanged, which indicates that mBLyS on mDCs may not be one of the molecules leading to impaired T-cell response during chronic HCV infection [40]. However, mBLyS expression on other immune cells is to be further determined.

In serum of HCV-infected patients, sBLyS levels are significantly higher than those in healthy controls [41]. The serum level of sBLyS predicts the outcome of acute HCV infection [42]. sBLyS level is significantly increased in acute HCV-infected patients who evolving to chronicity compared to those with a self-limited disease course, and thus a higher serum level of sBLyS is associated with persistent HCV infection [42]. Patients with chronic HCV infection demonstrate certain extrahepatic manifestations, including mixed cryoglobulinemia, Sjogren's syndrome, B cell non-Hodgkin's lymphoma, and presence of auto-antibodies in sera [43]. The elevated serum level of sBLyS in these patients might contribute to these B cell-related manifestations [41].

5. Inhibiting molecules with altered expression during HCV infection

The impaired CD4 T-cell responses to HCV are a common feature of chronic hepatitis C [8,16,21,23]. Antigen-driven proliferation of CD4 T-cells is always observed in patients who cleared HCV infection, but is inconsistently detected in patients who develop chronic hepatitis C. Chronic hepatitis C patients could be classified into two groups depending on HCV replication patterns during the first few months of infection. Patients in the first group are unable to mount a HCV-specific CD4 T-cell response and thus remain chronically infected. The second group of patients demonstrate strong HCV-specific CD4 T-cell response and clear HCV RNA transiently from their serum. However, the CD4 T-cell activity weakens just before a rebound in HCV viremia, which results in chronic infection [8, 44]. The strong and then weakened CD4 T-cell in the second group of chronic hepatitis C patients is not well explained yet [40], however, the presence of killer DCs during chronic HCV infection probably leads to the fluctuation of T-cell response.

Besides their well-known immunogenic function of stimulating T-cell proliferation [9,13], DCs also have a tolerogenic activity by killing T-cells. Killer DCs could express Fas ligand (FasL: CD178) [40,45-51], tumor necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL: CD253) [52-55] and PD programmed death-1 (PD-1) ligand 2 (PD-L2: CD273) [40]. Killer DCs with up-regulated expression of TRAIL can be found in measles virus (MV) [52, 53] and HIV [54, 55] infections. During HCV infection, DCs demonstrate up-regulated expression of FasL and PD-L2, and are capable of inducing the apoptosis of T cells [40].

According to statistical data, male patients have more aggressive HCV infection in general than female patients. Women eliminate HCV more rapidly, have a lower rate of disease progression, and have a lower mortality rate from HCV-related liver disease [56]. Although the mechanisms are not fully understood, killer DCs might contribute to this phenomenon. mDCs of male patients chronically infected with HCV display more killing activity of than those of females. mDCs from female patients chronically infected with HCV do not demonstrate altered expression of FasL or PD-L2, and have a poor killing activity on T cells [40].

5.1 Up-regulated expression of FasL on mDCs of chronic hepatitis C patients

DCs expressing Fas ligand (FasL: CD178) are called killer DCs since they are capable of inducing T-cell apoptosis. CD4 and CD8 T cells express Fas. The interactions of FasL/Fas induce

T-cell apoptosis [40, 45-51]. Patients mDCs demonstrate increased expression of FasL compared to healthy donor mDCs, and are capable of killing both autologous and allogeneic CD4 and CD8 T-cells [40].

Of note, Formation of immunological synapse, which facilitates the cell-cell contact, determines the FasL-Fas interaction between APCs and target T-cells and drives the specific killing of mDCs. The FasL-expressing killer DCs in hepatitis C patients are not capable to kill T-cell lines which lack TCR expression [40]. TCR interacts with HLA molecules and are crucial for the formation of the immunological synapse between a T cell and a DC [57].

TRAIL expression by DCs during HCV infection was also reported. The expression of membrane-bound TRAIL (mTRAIL) on mDCs is comparable in chronically infected HCV patients and healthy donors, and the concentrations of soluble TRAIL (sTRAIL) in patient serum and in culture supernatants of patients' mDCs are also comparable to those of healthy donors [40]. This is different from what is observed in MV [52] [53] and HIV [54,55] infections, when TRAIL expression was up-regulated.

5. 2 Up-regulated expression of PD-L2 on mDCs of chronic hepatitis C patients

The ligands for PD-1 are PD-L1 and PD-L2, which differ in their expression and activity. Firstly, PD-L1 is expressed much more broadly than PD-L2. PD-L1 is present on multiple blood cells and a wide variety of non-hematopoietic cells. PD-L2 is only expressed on DCs, macrophages and cultured mast cells [58]. Secondly, PD-L2 may have stronger biological activity than PD-L1. Blocking PD-L2 on DCs results in enhanced T-cell proliferation, which is more modest when PD-L1 is blocked [59].

Blocking PD-L1 could restore T-cell functions in HCV-infected patients [60]. However, the level of PD-L1 expression on patient mDCs is the same as that on healthy mDCs. PD-L2 expression on patient mDCs is significantly higher than that seen on healthy mDCs [40]. PD-L2 could therefore be more important than PD-L1 in regulating CD4 and CD8 T-cell apoptosis during HCV infection.

5.3 Up-regulated expression of programmed death receptor-1 (PD-1) on T-cells of chronic hepatitis C patients

The killing effect of mDCs could partly be mediated by PD-1 expression on target T-cells [40]. Being an important molecule regulating T-cell response, PD-1 is a target of virus immune evasion, and thus could also be a target for immunotherapy against viral infections, e.g. HCV [61,62] and HIV [63].

Compared to healthy donor CD4 T-cells, CD4 T-cells from chronic hepatitis C patients have up-regulated expression of PD-1 and a higher level of spontaneous apoptosis. The increased expression of PD-1 on patient T-cells correlates with their up-regulated sensitivity to apoptosis compared to healthy donor T-cells [40]. Furthermore, HCV-specific CD8 T-cells undergo significant apoptosis in the peripheral blood during acute HCV infection and in the liver during chronic HCV infection [64]. These studies indicate that PD-1 is an important molecule associated with functional T-cell deficits in chronic HCV-infected patients [40, 64].

CD8 T-cells are effector T-cells which directly kill virus-infected cells, and thus are critical for virus clearance. Two major mechanisms may lead to the poor CD8 T-cell response in chronic hepatitis C patients: (1) mDCs in these patients can directly kill CD8 T-cells through Fas/FasL and PD-1/PD-L2 interactions [40]. (2) Patient mDCs impair CD4 T-cells activity [26], and thus can indirectly weaken CD8 T-cell responses since CD4 T helper cells are critical for the initiation and maintenance of CD8 T-cell responses.

In addition, several other molecules, such as Toll-like receptors and DC-SIGN, are also involved in the process of HCV infection although they may not directly mediate immune cell interactions. With multiple TLR being expressed on DCs, TLR-5 ligand could work as a super stimulant to enhance the inflammatory cytokine production of DCs, and thus may help developing DC vaccines to induce anti-HCV immunity [67]. DC-SIGN expressed on DCs could capture circulating HCV particles and facilitate HCV infection [68].

Of note, there were also studies showing that the function and expression of immune molecules of patient DCs are comparable to those of healthy DCs, which made the DC function of HCV a controversial research topic. The discrepancy might be due to multiple factors, such as inappropriate culture of DCs with non-autologous serum, HCV genotype, patient population, and assays used [69,70]. Here we reviewed the results from studies [26, 40] in which DCs were cultured using autologous serum, and thus the interference from heterologous serum were avoided.

In summary, immune molecules play a fundamental role in regulating T-cell responses, and thereby determine the outcome of HCV infection. DCs from chronically infected HCV patients display phenotypical and functional changes compared to healthy DCs. The ability of mDCs to stimulate T-cell proliferation is impaired in patients chronically infected with HCV compared to uninfected healthy controls [26], and the ability of mDCs to induce T-cell apoptosis is up-regulated in these patients [40]. The function of mDCs is switched from immunogenic to tolerogenic during chronic HCV infection. T cells express a higher level of PD-1, and demonstrate increased sus-

ceptibility to the killing effect of mDCs [40]. These changes are mediated by immune molecules, and eventually facilitate the immune evasion of HCV [65]. Immunotherapy designed to recover a normal profile of immune molecules expression may rescue T-cell responses and help to clear HCV infection [66].

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