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Chronic Inflammation as a Result of Hepatitis C Virus Infection: A Review of the Literature

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ABSTRACT  Approximately 170 million people are infected with Hepatitis C virus (HCV) worldwide. It is estimated that roughly 80% of those infected suffer from persistent infection with HCV; this persistence of infection is progressive, and over time can lead to fibrosis, cirrhosis, and hepatocellular carcinoma. Chronic inflammation and apoptotic deregulation are both hallmarks of chronic HCV infection, and many molecular pathways are initiated in both the innate and adaptive immune responses during infection with this viral pathogen. This review surveys some of the major molecular mechanisms responsible for the induction of chronic inflammation that occurs during HCV infection.

Abbreviations: HCV, Hepatitis C virus; HSC, hepatic stellate cells; KC, Kupffer cells; HCC, hepatocellular carcinoma; TNF, tumor necrosis factor; AIM, apoptosis inhibitor of macrophage; IL-1β, Interleukin-1beta; PRR, pattern recognition receptor; TNF-α, tumor necrosis factor-alpha; NLR, Nod-like receptor; NLRP3, Nod-like receptor P3; TLR, toll-like receptor; NF-κB, nuclear factor-κB; HSPB8, heat shock protein 8; AID, activation-induced cytidine deaminase.

INTRODUCTION

Hepatitis C virus (HCV) is a single-stranded, positive-sense RNA virus that belongs to the family flaviviridae. During replication, a single polyprotein is cleaved into three structural (core, E1, and E2) and seven nonstructural (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) proteins, some of which studies have shown to mediate inflammatory processes during infection. Inflammatory stimuli are responsible for causing the synthesis and secretion of various cytokines and chemokines. Inflammatory stimuli can also cause responses in a number of liver cells, such as hepatocytes, hepatic stellate cells (HSCs), and Kupffer cells (KCs).

It is estimated that approximately 170 million people worldwide are infected with HCV. Nearly 80% of those infected are unable to clear the acute HCV infection, which results in chronic infection with the virus. This can lead to fibrosis, liver cirrhosis, and hepatocellular carcinoma (HCC).
It has been reported that the most important cause of chronic hepatitis, liver cirrhosis, and HCC is HCV infection. Currently, it is thought that as the severity of fibrosis increases so too does the incidence of HCC, and the progression of fibrosis is thought to be attributed to inflammation and steatosis.

Inflammation is an important component of the innate immune response. Under physiological conditions, inflammation is of vital importance in order to maintain a homeostatic environment in the body; this protective immune response warrants the removal of detrimental stimuli and also repairs damaged tissue.

However, chronic inflammation has the ability to cause destructive effects. The mechanisms that are responsible for chronic inflammation in chronic HCV infection are extremely complex, not yet fully understood, and include direct viral effects as well as indirect molecular pathways. HCV can evolve and generate mutations such that it is able to evade the immune responses of the host. Furthermore, the fact that HCV is capable of establishing a persistent chronic infection showcases its ability to escape both the innate and adaptive immune responses during the course of infection.

The Liver: A Major HCV Replication Site

The liver acts as a filter for toxins and food antigens that may be ingested. Interestingly, the liver may be considered a site that is relatively tolerant to harmless antigens that are consumed. Under normal physiological conditions, the liver can selectively remove activated CD8+ (cytotoxic) T cells that have specificity for food antigens upon entry. These T cells are inactivated and subsequently undergo apoptosis. Under physiological conditions, this helps to maintain immunological homeostasis. However, some hepatic pathogens may gain the ability to establish infection in such an immunologically tolerant environment.

The liver is a major replication site for HCV. Upon infection, hepatocytes may die in an apoptotic or necrotic manner. This phenomenon is clinically recognized as liver inflammation and fibrosis. In addition to this major site of replication, alternative sites have been recognized. It has been reported that peripheral blood mononuclear cells, monocytes, and B and T lymphocytes are also sites for the replication of HCV.

APOPTOTIC FACTORS

Fas-FasL Interactions

Apoptosis is a cell-intrinsic mechanism that triggers cell suicide through a variety of cellular signaling pathways. The process of apoptosis involves nuclear condensation, fragmentation, and packaging of the deceased cell into apoptotic bodies. These apoptotic bodies are subsequently removed by phagocytic cells. Activation of immune responses is circumvented by the process of apoptosis. Unlike apoptosis, necrosis results in vacuolation of the cytoplasm, degradation of the plasma membrane, and release of cellular contents. This process has been reported to induce inflammation around the necrotic cell, due to the release of the cell contents and proinflammatory molecules.

Apoptosis of hepatocytes and leukocytes seems to be a key element in the pathogenesis of chronic HCV infection. Even though the process of apoptosis is usually considered a defense mechanism used by host cells, in chronic HCV infection this may actually be a viral shedding mechanism used by HCV.

A membranous protein belonging to the family of tumor necrosis factor (TNF) receptors called Fas receptor has been found to trigger a major cell pathway of apoptosis. This occurs by the binding of Fas to a particular ligand, which causes activation of the pathway. Fas is inherently expressed in small amounts in hepatocytes. However, its expression in HCV-infected hepatocytes is increased significantly. This increase in Fas expression results in an increase in the elimination of hepatocytes. The particular ligand that participates in binding to Fas is called FasL. FasL is part of the family of TNF ligands, and is expressed on the surface of leukocytes, as well as on lymphocytes that ultimately infiltrate liver tissue. It is thought that Fas-FasL interactions may be responsible for an increase in apoptosis of hepatocytes in HCV infection.
There is a high risk of progression towards chronic liver inflammation and damage resulting from the hepatocytotoxicity that is mediated by T lymphocytes (T cells)\(^\text{17}\). The ability of the immune system to clear HCV infection often fails due to an intermediate cytotoxic T-cell response\(^\text{18}\). In this response, T cells are unable to eliminate HCV infection, and simultaneously cause hepatocyte destruction\(^\text{18}\).

It has also been reported that T-cell apoptosis in both CD4\(^+\) and CD8\(^+\) lymphocytes can occur as a result of the influences of HCV proteins\(^\text{15}\). FasL ligand expression on hepatocytes can be amplified by HCV proteins, while in turn Fas expression is amplified (by the virus) on CD4\(^+\) and CD8\(^+\) lymphocytes. This can over time result in the impairment of immune responses through the insufficient elimination of infected cells, thereby leading to persistent HCV infection\(^\text{19}\). Increased expression of Fas on leukocytes can cause an increase in the susceptibility of immune cells to apoptosis, subsequently causing immunological impairment\(^\text{15}\). Over time, this impairment can inhibit the elimination of infected hepatocytes, thus allowing HCV to persist in host cells, and cause chronic infection\(^\text{15}\).

**Apoptosis Inhibitor of Macrophages**

A recent study has brought to light yet another molecular mechanism that may contribute to advanced hepatic fibrosis. Apoptosis inhibitor of macrophage (AIM) belongs to the scavenger receptor cysteine-rich superfamily\(^\text{20}\), and is secreted exclusively by tissue macrophages\(^\text{21}\). AIM has shown a positive association with hepatic fibrosis\(^\text{8}\). Initially, AIM was identified as a defense mechanism, providing protection from apoptosis for macrophages\(^\text{20}\). However, serum AIM levels in patients with severe HCC seem to be higher than levels tested in patients with no or mild hepatic fibrosis\(^\text{8}\). It appears that as the severity of fibrosis increases, so too do the serum AIM levels. Although this mechanism remains somewhat unclear, the possibility of revealing another marker to test the state of hepatic fibrosis that results from chronic HCV infection may aid in further understanding the pathways that lead to the progression of this disease.

**INFLAMMATORY MEDIATORS**

The Pivotal Role of Interleukin-1\(\beta\)

Liver disease progression that is mediated by HCV infection has a strong association with persistent inflammation\(^\text{22}\). An increase in the expression of inflammatory cytokines and chemokines is fundamental to the disease process; this can happen through direct signals as well as by recruiting immune cells\(^\text{23}\). Interleukin-1\(\beta\) (IL-1\(\beta\)) plays a distinctive role in the induction of inflammation, and in the progression of disease.

Inflammasomes are the activating platforms of IL-1\(\beta\)\(^\text{24}\). They comprise a family of cytoplasmic pattern recognition receptors (PRRs) that are altogether known as Nod-like receptors (NLRs), and are known to sense viral nucleic acids and proteins\(^\text{24}\). Upon activation, NLRs form a multi-protein complex that includes pro-caspase-1. Following cleavage of pro-caspase-1 into fully functional mature caspase-1, this molecule is responsible for the cleavage of IL-1\(\beta\). Studies have shown that Nod-like receptors such as NLRP1, NLRP3, and NLRC4 can sense viral infections\(^\text{1}\). This leads to the activation of inflammasomes, and ultimately to the release of the proinflammatory cytokines IL-1\(\beta\) and IL-18\(^\text{1}\). The activation and subsequent release of these cytokines are strictly regulated processes, which require two distinct signals\(^\text{25}\). The first signal occurs in a TLR signal-dependent fashion. NF\(\kappa\)B is activated, and in turn synthesizes pro-IL-1\(\beta\) and pro-IL-18 mRNAs\(^\text{1}\). The activation of caspase-1 is involved in the second signal. Caspase-1 is responsible for the cleavage of pro-IL-1\(\beta\) as well as pro-IL-18 into their mature forms\(^\text{1}\).

Studies have shown that HCV induces the production and secretion of IL-1\(\beta\)\(^\text{26}\). It appears that several cell types in the liver participate in IL-1\(\beta\) production as a result of HCV infection. Hepatic macrophages within HCV-infected liver tissues have been found to produce IL-1\(\beta\) in high concentrations\(^\text{9}\). Between 80% and 90% of
tissue macrophages in the body consist of Kupffer cells, which reside in liver tissue. PRRs on the surface of Kupffer cells have the ability to sense HCV; in turn Kupffer cells can inflict inflammatory responses. Specifically, the production of inflammatory cytokines TNF-α and IL-1β occurs in Kupffer cells as a result of induction by nonstructural viral proteins NS3, NS4, and NS5. Hepatic stellate cells (which comprise of 5-8% of total cells in the liver) also secrete IL-1β. This induces the production of pro-inflammatory cytokines and chemokines IL-6 and IL-8. Additionally, HCV has the ability to activate the Nod-like receptor P3 (NLRP3) inflammasome complex. The synthesis of proinflammatory cytokines and chemokines can result from the induced production of IL-1β via activated NLRP3.

SHIP TLR Pathway Inhibitor
Various cytokines, chemokines, and transcription factors contribute to chronic inflammation. This can be described as a continuous active inflammatory response and tissue destruction, which subsequently leads to irreversible tissue remolding. Persistent inflammation is a major determining factor in the progression of liver fibrosis in chronic HCV infection. It has been reported that this inflammation is subject to regulation by components of the innate immune system through toll-like receptor (TLR) signaling. Activation of TLR pathways trigger the production of proinflammatory cytokines when challenged with specific ligands such as HCV proteins, dsRNA, and ssRNA. In turn, TRLs will subsequently activate NF-κB, which is responsible for the transcription of inflammatory genes. Viral proteins core and NS3 have been found to activate TLR2. Studies have also shown a correlation between the regulation of gene expression in a TLR2/TLR4 inhibitor called inositol polyphosphate-5-phosphatase (INPP5D, or SHIP) and an endogenous TLR4-ligand, heat shock protein 8 (HSPB8). Due to its anti-inflammatory characteristics, SHIP may be involved in the regulation of immune-related liver pathogenesis. The extent to which the TLR system is responsible for the modulation of fibrogenic mechanisms and inflammatory responses are still not fully understood. However, recent studies have generated data suggesting a significant inverse correlation between the expression of SHIP, HSPB8, and the severity of fibrosis in the liver. Taken together, the increase in biosynthesis of HSPB8 coupled with the decrease in SHIP expression may render those suffering from chronic HCV infection more susceptible to severe liver fibrosis.

GENETIC INSTABILITY
Activation-Induced Cytidine Deaminase
One of the most recognized molecules that contributes to the pathogenesis of chronic inflammation is the transcription factor NF-κB. In virus-infected cells, NF-κB plays a fundamental role in the regulation of cytokines, chemokines, and interferons. A variety of proinflammatory cytokines and microbial products are successful activators of this transcription factor; in turn, NF-κB has the ability to regulate various cytokines and chemokines that are determinants of cell fate. It has been shown that HCV core protein has the ability to induce NF-κB activation in hepatocytes. This particular molecule has recently been identified to be responsible for the direct activation of the nucleotide-editing enzyme activation-induced cytidine deaminase (AID). It has been reported that AID is directly involved in DNA instability. The accumulation of genetic alterations in various genes can occur as a result of abnormal expression of AID in hepatic tissues. Due to its dangerous capabilities of causing changes to somatic DNA, AID is tightly regulated under physiological conditions. Although under physiological conditions AID expression is restricted to activated B-cells, the abnormal expression of AID results in the accumulation of genetic alterations in hepatoma cells; thus suggesting a correlation between the inappropriate expression of AID and increased genetic susceptibility to mutagenesis in hepatocytes. It has been reported that through the mutagenesis of inappropriate target genes,
AID has shown direct oncogenic potential. This cascade of molecular events may subsequently lead to the development of HCC.

**DISCUSSION**

There are a plethora of molecular mechanisms that appear to feed into the sustained inflammatory condition that is a hallmark of chronic HCV infection. Other factors such as apoptotic pathways and genetic alterations also play pivotal roles in the progression of the diseased state. A multitude of molecular mechanisms are deregulated in the host, and both innate and adaptive immune components are affected.

The presence of persistent inflammation is a key determinant in the progression of liver fibrosis in chronic HCV infection. Increased expression of inflammatory cytokines, chemokines, and transcription factors are essential in the progression of disease. This expression can occur as a result of direct signaling, as well as indirect molecular pathways, some of which are virus-mediated. HCV can induce the production and secretion of IL-1β. Several cell types take part in HCV-triggered IL-1β production, part in HCV-triggered IL-1β production, including Kupffer cells and hepatic stellate cells. HCV is also responsible for the activation of the Nod-like receptor, NLRP3, which in turn will activate the inflammasome complex, a cascade that ultimately ends in the production of mature, biologically active IL-1β.

Although under physiological conditions apoptosis is considered a host defense mechanism, in the case in chronic HCV infection, this would-be host defense turns on itself, and apoptotic events appear to be critical in disease progression. These events can be mediated by several mechanisms, including Fas-FasL interactions as well as apoptosis inhibitor of macrophages (AIM). Fas-FasL interactions can either result in the elimination of hepatocytes, or of T lymphocytes; both cases result in the impairment of immune responses, by which host defenses are unable to adequately eliminate HCV-infected cells. In AIM, the protection from apoptotic events in macrophages causes serum AIM levels to rise; this correlates with increasing severity in fibrosis.

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