

## HBV/HCV Infection and Inflammation

Mohammad Khalid Zakaria<sup>1†</sup>, Anurag Sankhyan<sup>1†</sup>, Ashraf Ali<sup>2</sup>, Kaneez Fatima<sup>3</sup>, Esam Azhar<sup>4,5</sup> and Ishtiaq Qadri<sup>2\*</sup>

<sup>1</sup>Department of Biochemistry, All India Institute of Medical Sciences, New Delhi, 110029, India

<sup>2</sup>Department of Medical Biotechnology, King Fahad Medical Research Center, King Abdul Aziz University, Jeddah, Saudi Arabia

<sup>3</sup>IQ Institute of Infection and Immunity, Lahore, Pakistan

<sup>4</sup>Special Infectious Agents Unit-Biosafety Level 3, King Fahad Medical Research Center, King Abdul Aziz University, Jeddah, Kingdom of Saudi Arabia

<sup>5</sup>Medical Laboratory Technology Department, Faculty of Applied Medical Sciences King Abdul Aziz University, Jeddah, Kingdom of Saudi Arabia

<sup>†</sup>Equal Contributors

### Abstract

Liver is a key organ involved in the regulation of both systemic as well as local inflammatory responses. Hepatic inflammation is the hallmark of viral hepatitis caused by non-cytopathic Hepatitis B and C viruses (HBV and HCV). Both HBV and HCV induce several inflammatory responses, causing persistent liver injury, which manifests into progressive diseased state. This ultimately leads to fibrosis, cirrhosis and eventually hepatocellular carcinoma. The disease progression is mediated by a complex interplay of molecular pathways involving both viral and hepatic factors. The complex cellular crosstalk, involving pro-inflammatory cytokines, during the liver injury also causes extra hepatic disorders such as atherosclerosis, glomerulonephritis, arthritis, cardio vascular and brain disease. In addition, these viral infections have been reported to contribute to non-Hodgkin lymphoma, cholangio carcinoma and pancreatic cancer. Host genetics also play an important role in the HBV/HCV mediated viral hepatitis and the accumulation of mutations in the host genes responsible for mounting antiviral effects (cytokines and interferon receptors) has been shown to produce differential immune responses among individuals and increase susceptibility to chronic infections. Viral proteins are known to modulate the host immune response by a variety of mechanisms such as by exerting direct or indirect effects on the cytokine pathways, oxidative stress, miRNAs and other cellular processes. However, the complete network of cytokines involved in the disease pathogenesis is yet not fully understood. This review analyzes the interplay of inflammatory molecules and viral proteins, the impact of local and systemic inflammation during HBV and HCV infection and the contribution of host genetics to such responses.

**Keywords:** Inflammation; Hepatitis; HBV; HCV; Fibrosis; Hepatocellular carcinoma; Cytokines

### Introduction

Hepatitis B and C viruses (HBV and HCV) are the two global causes of hepatitis with 5 to 10 % of HBV infected and more than 70% of HCV infected patients developing chronic infection [1]. HBV/HCV infection alters the state of liver homeostasis inducing inflammatory responses. However, sustained presence of such stimuli leads to chronic inflammation with hazardous implications. Liver is the central organ involved in the regulation of inflammation, both local and systemic *via* synthesis and secretion of a number of proteins [2]. HBV and HCV viral proteins and nucleic acids provide the inflammatory stimuli to the hepatocytes, Kupffer Cells (KCs), bile duct epithelial cells, Hepatic Stellate Cells (HSCs) and sinusoidal endothelial cells, thereby inducing local and systemic inflammatory responses [3,4]. Also, several reports indicate that both HBV/HCV can mediate inflammatory responses by modulating the level of various microRNAs [5,6]. Host genetic background has also been implicated in the viral persistence and clearance. Majority of the gene mutations and polymorphisms have been located within the genes responsible for mounting inflammatory and anti-viral responses during HBV/HCV infection. Thus virus persistence is likely to prolong as a result of alteration in such genes [7].

During acute HBV and HCV infection, robust CD4+ and CD8+ cellular responses against multiple viral proteins lead to spontaneous viral clearance. The inability to mount such strong virus-specific response causes chronic illness. Persistence of virus specific and non-specific immune cells, during chronic illness, is responsible for the observed inflammatory responses [8-15]. Liver injury, due to prolonged inflammatory state, manifests into progressive diseased state leading to fibrosis, cirrhosis and eventually hepatocellular carcinoma (HCC). Hepatic cells (HSCs, hepatocytes, etc) along with

innate as well as adaptive immune effector cells – Natural Killer (NK) cells, KCs and macrophages are involved in the differential secretion of a network of cytokines. Interferon (IFN)- $\alpha$ ,  $\beta$ ,  $\gamma$ , interleukin (IL)-6, 8, 29 and intrahepatic chemokines - regulated upon activation normal T cell expressed and presumably secreted (RANTES), Macrophage Inflammatory Protein 1 (MIP1), interferon-inducible protein 10 (IP10) and Monokine Induced by Gamma-Interferon (MIG) contribute to both HBV and HCV associated inflammatory manifestations and liver injury [16,17].

In addition to the cytokines and chemokines, regulation of other host factors, directly or indirectly, by various viral proteins generates inflammatory environment within the liver. As the disease progresses, further systemic inflammation also adds on. Reactive Oxygen Species (ROS) and reactive nitrogen species (RNS) which generally maintain the physiological homeostasis of hepatocytes [18] are also involved in inflammatory responses. Hepatic as well as systemic Oxidative Stress (OXS) has been reported both in chronic hepatitis B (CHB) and Chronic Hepatitis C (CHC) infection. The stimuli for ROS generation in mitochondrion is provided by HBV/HCV proteins

**\*Corresponding author:** Ishtiaq Qadri, Department of Medical Biotechnology, King Fahad Medical Research center, King Abdul Aziz University, Jeddah, Saudi Arabia, Tel: +966 53 516 8434; E-mail: [ishtiaq80262@yahoo.com](mailto:ishtiaq80262@yahoo.com)

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[19] and the resulting oxidative stress causes widespread hepatic cell damage [18,20]. HBV/ HCV also regulate the expression of various non-coding small RNAs; the microRNAs (miRNAs) which serve as an intermediates and generate inflammatory responses. The modulation of the miRNA levels by HBV/HCV infection involves the activation of various inflammatory mediators and related pathways [5,6].

The outcome of HBV/HCV related disease progression, pathogenesis and treatment is also dependent on the host genetic background [21]. Particular haplotypes and alleles as well as single nucleotide polymorphisms (SNPs) among particular gene loci also determine the susceptibility of individuals to the chronic infections. [22–24]. These mutations in the host cytokine and interferon receptor genes directly or indirectly affect inflammatory responses during HBV/ HCV infection [22,25,26].

The liver parenchyma of CHB/CHC patients contains high levels of inflammatory cytokines and chemokines. The HSCs, activated by Transforming Growth Factor Beta (TGF-β) and ROS, and activated KCs release Tissue Inhibitor of Metalloproteinases (TIMP) which inhibits collagen-degrading Matrix Metalloproteinases (MMP), resulting in collagen (Type I) deposition and fibrosis [27]. Viral protein HBx, is associated with fibrosis development by transcriptional up-regulation of TGFβ1 [28-31]. HSC activation accompanied with increased ROS production and lipid peroxidation are also responsible for HBV and HCV mediated hepatic steatosis. An increased inflammatory state in the liver can possibly contribute to the neoplastic transformation of hepatocytes. Cancerous/precancerous cells are suppressed *via* CXCL10 dependent cytotoxic and inflammatory immune responses by the recognition of the tumor specific antigens [32]. These responses are, however, impaired in CHB and CHC patients. Oxidative or nitrosative stress and free radical generation, induced by inflammation, contribute to mutations in the cellular DNA and the resulting genomic injury alters DNA methylation, genomic integrity, protein stability and cytokine production ultimately leading to HCC development [30].

In addition to the liver injury inflicted by the HBV or HCV infection, viral proteins and their immune complexes may extend the disease pathogenesis. Viral proteins are able to cause several inflammation inflicted systemic injuries by modulating the host transcriptional machinery, cellular signaling, metabolic pathways and the immune responses [33,34]. This results in deleterious consequences on nervous, vascular, renal and other systems resulting in extra-hepatic manifestations such as insulin resistance, neurological dysfunction, vascular neuropathies, increased atherosclerosis risk, membrane proliferative glomerulonephritis, arthritis, arthralgia, skin rash, and popular acrodermatitis [35–42]. HBV/HCV is also significantly associated with Non-Hodgkin Lymphoma (NHL), cholangio carcinoma and pancreatic cancer development [43–46].

This review analyzes the interplay of such inflammatory molecules

and viral proteins and their impact on hepatic/systemic inflammation during HBV and HCV infection. We also enumerate the various host genetic factors that contribute to such responses and disease susceptibility.

## Materials and Methods

PubMed database was searched for research articles, reviews and case reports related to HBV and HCV involvement in liver and systemic inflammation and the molecular mediators of such inflammatory responses using the search terms “HBV and liver inflammation”, “molecular pathways in HBV mediated inflammation”, “HCV and liver inflammation”, “HCV and HBV inflammation mediated systemic and local diseases”, “inflammatory pathways of HBV” inflammatory pathways of HCV”, “modulators of liver inflammation during HBV and HCV infection” etc. Relevant articles were grouped under the HBV and HCV infection and the information has been translated topic-wise in the review. The molecular mediators and pathways affected by viral proteins, during HBV and HCV infection, obtained from the search were classified as per the regulating viral protein and have been listed in Table 1. An overview of the mechanism of liver and systemic inflammation and disease progression caused by HBV and HCV virus was prepared from these articles (Figure 1). Various drugs, approved by FDA, for HBV and HCV treatment are also compiled in Table 2.

## Molecular interplay in HCV/HBV mediated inflammation of Liver

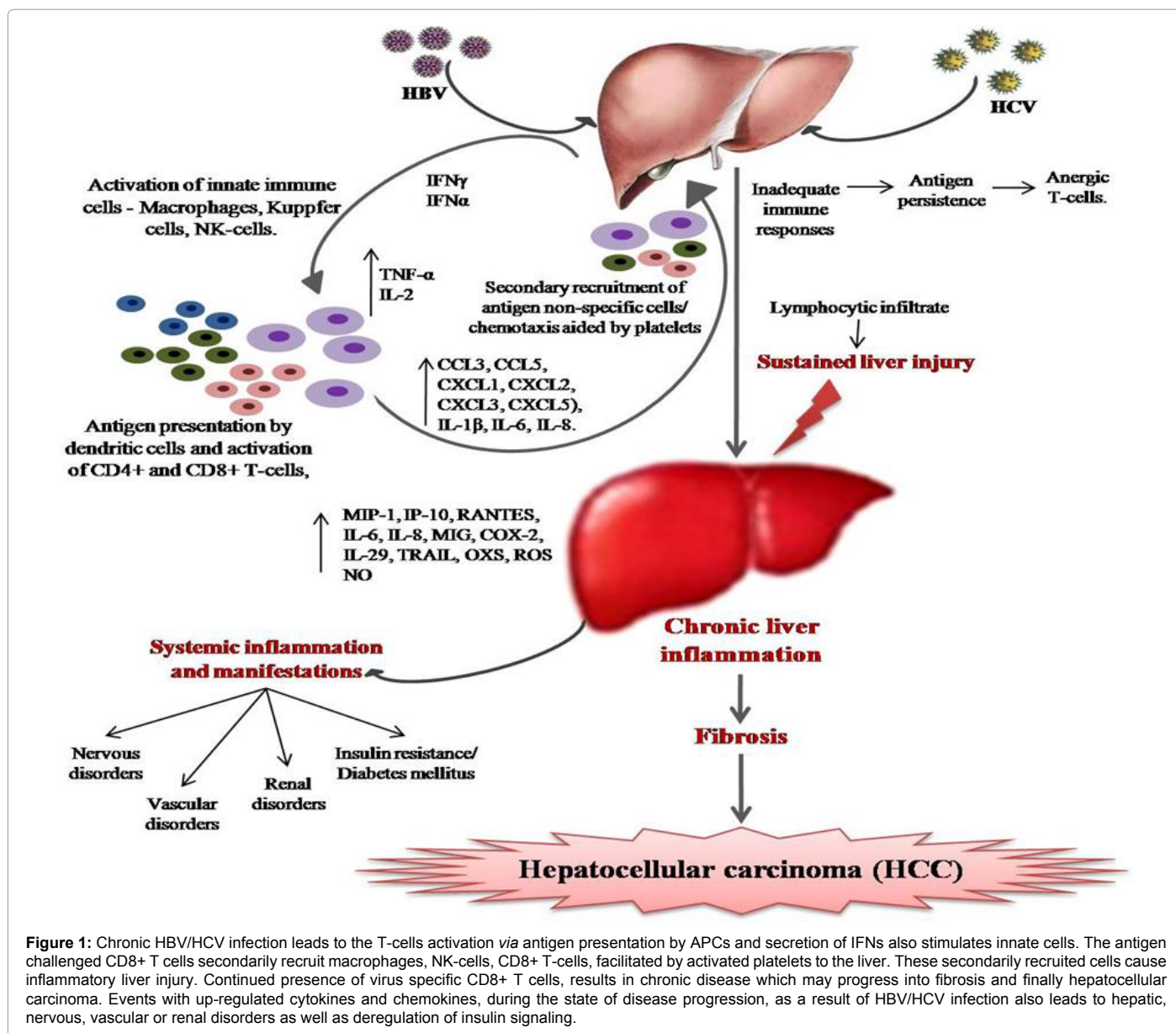
Chronic inflammatory state, during HBV and HCV infection, is associated with activated inflammatory cells and is mediated by various cytokines [47,48]. A concomitantly low grade systemic inflammation is also sometimes observed, in addition to the hepatic inflammation, with elevated pro-inflammatory cytokine levels [4,49].

**Cytokines during HCV infection:** Cytokines belong to a category of small proteins required in cell signaling events and inflammatory responses. These include interferons, interleukins, chemokines, tumor necrosis factor, lymphokines etc. Additionally, intra-hepatic pro-inflammatory cytokine levels corroborate with the degree of liver inflammation and fibrosis [50]. Increase in intra-hepatic chemokines, such as MIP-1, IP-10 and RANTES is observed in people infected with HCV [51].

HCV core proteins stimulate hepatocytes to produce multiple cytokines through STAT3 signaling cascade [52]. It is also established that c-jun, along with STAT3, potentiates the progression of HCC through HCV infection [53]. Additionally, retinoic acid inducible gene I (RIG-I) and toll-like receptor-3 (TLR-3) recognizes dsRNA of HCV, leading to the generation of RANTES, IL-8, MIP1α and MIP1β [54]. These receptors, when bound to their ligands, converge on common inhibitor kappa beta (IκB)-kinase dependent kinases, thereby activating

	HCV	HBV
Viral components modulating host responses	Viral RNA, Core NS5A, NS3,NS4B (Ref 27, 28)	Viral dsDNA, I-IBX, I-IBsAg, I-IBeAg (Ref 72-75, 77, 110)
Altered host pathways	RIG, MAPK, JNK, Wnt/B-catenin, Akt/mTOR, JAK-STAT, (Ref 23, 25)	JNK, Pyk2, MAPK, Wnt, Ras, P13K/Akt, c-Raf-1/Erk2 (Ref 31, 34, 77, 85)
Key up-regulated molecules	TGF-β, TNF-α, AP1, STAT3, c-jun,NFκB, TRIP, IRF-3/IRF-7, ISGs, (Ref 24, 25, 49, 66)	AP1,NF-AT, NFκB, Erb2, SOCS3, ISGs (Ref 30, 34)
miRNAs	miR-449a, miR-107, miR-155, miR146a miR-I25b (Ref 5, 49)	miR-155, miR-210 miR-29 family (Ref 50, 51)

**Table 1:** HCV/HBV components effecting various pathways, molecules and miRNAs which indirectly or directly are implicated in inflammation.



interferon regulatory factor 3/7 (IRF-3/IRF-7) and Nuclear Factor Kappa Beta (NFκB). This network ultimately triggers the synthesis of Type I IFN (IFN α/β), Interferon Stimulatory Genes (ISGs) and proinflammatory cytokines, ultimately leading to inflammation [55].

An alternate mechanism for HCV based inflammation has been reported recently. It is described that NS5A (viral RNA dependent RNA polymerase) catalyzes the production of small RNA species which trigger IFNs and inflammatory cytokines [56]. Also, NS4B and NS3A are known to interfere with the host defense and modulate cytokine function [57]. Nishitsuji et al. have demonstrated that the conditioned medium, derived from HSCs, could stimulate hepatocytes to secrete chemokines and cytokines (IL-6, IL-8 and MIP1 α/β). This possibly indicates that the HCV infection associated inflammation of liver is an outcome of crosstalk between HSCs and infected hepatocytes. Moreover, CAAT Enhancer Binding Protein (C/EBPβ) production is enhanced during HCV infection and the HSC dependent IL-

1α production is responsible for the stimulation of C/EBPβ target cytokines and chemokines in the infected hepatocytes [58].

**Cytokines during HBV infection:** HBV infection induces a network of inflammatory cytokines that work in tandem causing inflammatory responses. A key mediator of HBV associated liver inflammation is IL-8 which maintains an inflammatory environment within the liver during HBV infection. This is also thought to be implicated in HCC development [59]. IL-8 gene expression is trans-activated by HBV's HBx protein through NFκB and C/EBP-like cis-elements [60]. *In vitro* studies have shown that IL-8 activates cyclooxygenase (COX)-2 gene, by CREP and C/EBP binding to COX promoter, through the induction of Extracellular-Signal-Regulated Kinase (ERK) and c-Jun N-terminal kinase (JNK) signaling pathways. Activation of COX-2 gene ultimately induces inflammation [61].

Another inflammatory factor stimulated by HBV infection is IL-29. It has been shown to inhibit HBV replication through enhanced

	Drug Name	Target
HBV	Peg-Interferon $\alpha$ -2A	Activates CD8 <sup>+</sup> T
	Interferon $\alpha$ -2B	Up-regulates the expression of MHC I proteins
	Entecavir	Block viral replication
	adefovir dipivoxil	Block viral reverse transcription
HCV	Telaprevir	HCV NS3-4A inhibitor
	Interferon alfacon-1	Increases MHC I expression
	Interferon $\alpha$ -2A	Activates CD8 <sup>+</sup> T cells
	Boceprevir	HCV protease inhibitor
	Simeprevir	NS3/4A protease inhibitor
	Sofosbuvir	HCV NSSB polymerase inhibitor

**Table 2:** FDA approved drugs and their targets in the treatment of HBV/HCV infection. (Source: Food and Drug Administration).

production of protein kinase R (PKR) and oligo adenylate synthetase (OAS). During the flares of liver inflammation, NK cells are activated and enriched in the HBV infected Liver. A subset of NK cells, activated in liver, is a potent source of IFN- $\gamma$  [62].

Moreover, in HBV mediated inflammation, the cellular JAK/STAT/SOCS signaling pathway mediate anti-HBV effects by enhancing IFN- $\gamma$  secretion [63]. During HBV infection, cellular gene expression is also regulated by the viral HBx protein through the activation of signal transduction cascades including proline-rich tyrosine kinase 2 (PYK2), Src tyrosine kinases and Mitogen-Activated Protein Kinase (MAPK), leading to the activation of NF $\kappa$ B, AP1 and NF-AT transcription factors [64]. HBx activated NF $\kappa$ B further mediates transcription of MIG, which acts as an attractant for leukocytes at the site of infection in liver causing inflammation [65].

**Oxidative stress:** ROS and RNS are important for maintaining physiological homeostasis of hepatocytes [18]. Several reports have established a link between oxidative stress and inflammatory processes. HCV replication activates p38 MAPK (mitogen-activated protein kinase) and JNK (c-Jun N-terminal kinase), *via* AP-1, which is linked to increased oxidative stress [66]. Both CHB and CHC infection involves hepatic as well as systemic OXS. HBV/HCV acts as a stimuli to induce oxidative stress and lead to the generation of ROS in mitochondrion [19]. ROS causes damage to the hepatic cells by inducing inflammation, necrosis and apoptosis [18,20].

HBx is the key HBV protein involved in increasing the cellular production of ROS. Its expression activates a number of transcription factors such as NF $\kappa$ B, AP1, and NF-AT which respond to alterations in OXS levels [67]. HBx is also reported to orchestrate apoptosis through the loss of anti-apoptotic protein Mcl1, in cells with high levels of OXS, helping in the inflammatory resolution [68–70]. Some reports suggest that the truncated mutants of preS/S polypeptide elevate ROS levels and oxidative DNA damage *via* activation of ER stress pathways and 8-oxoguanine glycosylase (Ogg1) production [71–73]. High and sustained ER stress levels are also known to induce unfolded protein response (UPR), which further leads to the induction of OXS and inflammation.

**Modulation of miRNAs:** Micro RNAs (miRNAs) belong to a category of non-coding small RNAs (21-25 nucleotides). Being complementary to the target mRNA, they regulate the expression of a variety of genes [74]. Alteration in the miRNA levels has been reported during HBV or HCV infection, suggesting their close association. A group has recently demonstrated that HCV alter the levels of miR-449a and miR-107 in order to generate inflammatory responses. These miRNAs activate an inflammatory cytokine, CCL2, *via* IL-6 signaling pathway [5]. Levels of other miRNAs, miR-155, 146a and 125b, are also altered in response to HCV infection. HCV infected patients show increased levels of miR-155, which is a positive regulator of TNF- $\alpha$

while miR-125b, a negative regulator of inflammation, was shown to be down-regulated [75].

Su and coworkers showed that, during HBV infection, miR-155 activates JAK/STAT pathway ultimately resulting in inflammatory responses [6]. Up-regulation of miR-210, an inflammatory miRNA, has also been observed in CHB patients [76]. Furthermore, HBV infected patients showed reduced expression of miR-29 family, which is the negative regulator of inflammation [77].

It has been shown that HBx protein could alter the expression of miRNA 16 family in transformed hepatocytes. Repression of miRNA 15a/16 is mediated by proto-oncogene c-Myc. Such repression is critical for HCC development. Thus, miRNA 16 family could be a potential target for HBV-induced HCC [78]. HBx protein also modulates miRNA 181 family. This occurs through  $\beta$ -catenin which alters MMP2 and MMP9, helping in the metastasis of tumor [79]. Micro array study has shown differential expression of miRNA 181 family under inflammatory state. miRNA 181a binds to the 3' un-translated region (UTR) of an important inflammatory molecule, IL-8, and regulate its expression [80].

HBV/HCV mediated up-regulation of miRNA 21, along with oxidative stress, leads to liver inflammation and metastasis of tumour [79]. Elevated levels of miRNA 21 are seen in HCC patients associated with CHC infection when compared to non-CHC ones. It is established that such elevation in miRNA 21 is potentially due to Chronic Hepatitis (CH) rather than HCC. Level of miRNA 21 in the sera is also correlated with the necroinflammatory activity in the liver of CHC patients [81]. miRNA 21 inhibits apoptosis related genes such as programmed cell death 4 and phosphatase and tensin homolog [82].

Peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) binding complex epigenetically regulates miR-122 in neoplastic liver cells. This is achieved by binding of HBx to PPAR $\gamma$  inducing transcriptional repression of miRNA 122. However, HCV has no significant effect on miRNA 122 through PPAR $\gamma$  [83]. miRNA 146 and 155 are inflammatory mediators. miRNA 146 level is up-regulated by pro-inflammatory agents such as IL-1 and TNF- $\alpha$  [84]. Since IL-1 and TNF- $\alpha$  are regulated by HBV/HCV infection, indirect regulation of inflammation could occur through these miRNAs.

Bruni et al. have shown the association of miRNA 223 with HCV infection [85]. Zhou et al. demonstrated a correlation between HBV related HCC by differential expression of miRNA 223 [86]. Expression of miRNA 223 is de-regulated during HBV infection. Validated targets for miR-223, that have effects on inflammation and infection, include granzyme B, IKK $\alpha$ , Roquin and STAT3 [87]. Such reports indicate that HBV/HCV also impose inflammatory responses through several miRNAs, serving as an intermediates.

## Host Genetic Factors, Inflammation and HBV/HCV Infection

Host genetic background plays an important role in the persistence and resolution of viral hepatitis. Studies based on this could help to elucidate disease progression, pathogenesis and treatment outcome [21]. Upon HBV/HCV infection, both innate (complement, IFN, macrophage, NK cells, dendritic cells etc.) and adaptive (CD4<sup>+</sup>, CD8<sup>+</sup> T cells and antibodies) arms of the host immunity are activated. Directly or indirectly, these could be related to inflammatory responses during HBV/HCV infection as most of the host mutations are observed in the genes responsible for mounting antiviral effects (cytokines and interferon receptors; [7]).

## HBV

Killer cell-immunoglobulin like receptor (KIR) facilitates the function of NK cells. Hosts with KIR2DL3 and group I HLA-C are resistant whereas with KIR2DL1 and group II HLA-C are susceptible to HBV infection [88]. A study demonstrated that subjects with TNF $\alpha$ , a pro-inflammatory cytokine, 238A allele are associated with long lasting HBV infection [24]. Also, polymorphism in the receptor for IL-10, another molecule implicated in inflammation, is linked with HBV infection and disease progression. Mutations in IL-10 gene could lead to decreased immune response, decreased inflammation and persistent HBV infection. Type I IFN is implicated in the inflammatory responses during viral infection and mutations in the Interferon- $\alpha$  receptor II (IFNAR2) was shown to be associated with chronic HBV infection [89,90]. This also could be due to the failure in the generation of inflammation required in the resolution of infection. Single nucleotide polymorphism (SNP) studies have linked mutation with the gene loci of Type II cytokine receptor. IFNAR2 and IL-10 receptor (IL-10RB) were found to be associated with CHB infection [22].

## HCV

In the case of HCV infection, TNF-238A allele was associated with the chronic HCV infection in European population [91]. Polymorphism in the IFN $\gamma$ A promoter and p40 subunit of IL-12 has been linked with HCV clearance [92,93]. A study on 343 individuals, with cleared HCV infection, and 547 HCV infected patients have revealed that the large number of SNPs are associated with 112 immune response genes [23]. Polymorphism in the promoter region of IL-10 gene [25] and SNPs in the IL-28B [26] have been linked with the outcome of the anti-HCV therapy.

HCV induces the activation of Type I IFN response resulting in inflammation. This signals the immune cells to mount an anti-viral response. Therefore, HCV has other mechanisms to counter and evade such responses [94]. Additionally, some host genetic factors also aid HCV virus in escaping such anti-viral response. Genes eventually effected by Type I interferon, MxA, OAS and PKR, were found to be associated with HCV outcome [95]. Type I IFN dependent protein, called TRAF family member-associated NF $\kappa$ B activator (TANK), was also associated with the course of HCV infection [23].

Polymorphic genes significantly participate in the HBV/HCV infection outcomes. Genes involved in inflammation, as a consequence of HBV/HCV infection, are often found to be mutated and hence support viral persistence. This could be due to the lack of mounting a strong inflammatory immune response required for viral clearance. Although such studies have provided an insight in understanding the disease progression associated with either HBV or HCV, yet any applicable therapeutic benefits are still to be found.

## Inflammation and liver implications as a result of HCV/HBV infection

High expression levels of inflammation associated cytokines and chemokines are found in the liver parenchyma of CHB/CHC patients. Activated KCs keep releasing TGF- $\beta$  and ROS which further activates HSC and collagen (Type I) deposition. Furthermore, these activated HSCs release TIMP, which inhibits collagen-degrading MMPs, resulting in fibrosis [27]. CXCL10 dependent cytotoxic and inflammatory immune responses suppress cancerous/precancerous cells by recognizing their specific antigens [32]. However, these responses, involved in immune defense, are impaired in CHB and CHC patients indicating the decreased likelihood in the removal of

such tumorigenic cells. A diagrammatic illustration (Figure 1) shows the events and cytokines involved in the development of chronic liver injury as a consequence of HBV/HCV infection.

HBV and HCV mediated hepatic steatosis is shown to be associated with increased production of ROS, lipid peroxidation and HSC activation. This in turn, increases pro-inflammatory and pro-fibrotic cytokine production. Steatosis also renders the liver more sensitive to apoptosis, injury and inflammation mediated by TNF- $\alpha$  [96]. All these factors along with insulin resistance (IR) orchestrate fibrosis development during HCV infection but the exact mechanisms are still not fully understood. The association between HBV infection and hepatic steatosis development is still an unresolved issue, with some groups affirming no relation between the two [97], while others suggest that the lipids accumulate in the liver through several mechanisms that activate sterol regulatory element-binding proteins (SREBP) and PPAR $\gamma$  [98].

Fibrosis associated with viral hepatitis (HCV and HBV) is a result of disturbed balance between extracellular matrix production and degradation, due to chronic inflammation, that follows failure in the resolution of infection. Fibrosis develops as a result of complex mechanisms of fibrinogenesis, cell proliferation, contractility, chemotaxis, degradation of matrix, and cytokine release [99]. HBx protein causes transcriptional up-regulation of TGF $\beta$ 1 and ultimately fibrosis [28–31]. Up-regulation of TGF $\beta$ 1 is proposed to be potentiated by the decreased expression of alpha-2-macroglobulin ( $\alpha$ 2M) by HBx [100]. This event is either by the activation of NF- $\kappa$ B through STAT3, and/or by blockage of  $\alpha$ 2M by phosphatidylinositide 3-kinases (PI3K). Stimulation of a plethora of signaling cascades (NF- $\kappa$ B, PI3K, MAPK, Wnt, ras, src, etc.) by HBx, in combination with altered SMAD signaling, results in heightened pro-fibrogenic environment [101]. ROS and other pro-inflammatory molecules such as hepatic neomatrix are also known to cause liver fibrosis [102]. Elevated level of circulating miR-122, observed in acute viral hepatitis, is associated with high inflammatory activity and minimal fibrosis. However, its levels are low in chronic disease with high fibrotic activity and hepatocyte death [103]. CHC patients are predisposed to a higher degree of hepatic inflammation and fibrosis, due to a higher frequency of gene polymorphisms in alleles of key inflammatory mediators, such as CCR5, RANTES, monocyte chemotactic protein 1 (MCP-1), COX-2 etc. [104,105].

Mutations in the cellular DNA, by oxidative or nitrosative stress, could be induced by inflammation [30]. Genomic injury, by OXS and free radical generation, alters DNA methylation, genomic mutations, protein stability and cytokine production ultimately leading to HCC development. A study compared expression levels of various pro-inflammatory molecules in 26 HCC patients previously having chronic HCV based hepatitis. Interestingly, the results indicated that such pro-inflammatory factors were significantly up-regulated in HCC patients. This suggests that an increased inflammatory state could possibly have contributed to the neoplastic transformation of hepatocytes. Moreover, IL-6 and IL-8 levels correlated with the tumor load [106].

CHB patients show a significant induction of the genes involved in control of liver proliferation and inflammation along with unfolded protein response (UPR). UPR causes OXS and increase in production of intracellular ROS by up-regulating the oxidative folding machinery, thereby contributing to the HCC development [107,108]. Contrastingly, HBV mediated HCC progression is largely dependent upon the activation of signaling cascades independent of the inflammatory network. Truncated form of HBs-L protein can increase upregulation

of cyclin A expression, and truncated M surface protein can specifically activate c-Raf-1/Erk2 signaling, both leading to an increase in hepatocyte proliferation [109]. HBx maintains hepatocellular growth and survival during decades of infection by stabilizing  $\beta$ -catenin and up-regulation of ErbB2 [110].

### Inflammation and Extra Hepatic Manifestations as a result of HBV/HCV Infection

HBV and HCV proteins and immune complexes are the major molecular players in the disease pathogenesis and extra-hepatic disorders. Viral proteins are able to cause several inflammation inflicted systemic injuries by modulating the host transcriptional machinery and the immune responses. The HBV/HCV infection can have deleterious consequences on nervous, vascular, renal and other systems by interfering with several cellular signaling and metabolic pathways.

The commonly observed obesity among CHC patients is a risk factor for both inflammation and hepatic fibrosis. In obese HCV subjects, hepatocellular injury is associated with an enhanced T helper-1 (Th<sub>1</sub>) cytokine profile and increased hepatic expression of IP-10 and monocyte chemoattractant protein 1 (MCP1). Both are T-cell chemo attractants and increases the recruitment of inflammatory cells to the liver [111]. Elevated IL-6 and TNF- $\alpha$ , in obese CHC patients, results in the development of IR through inhibition of insulin signaling and reduction of adiponectin levels [42]. During the development of IR, both hyperglycemic state and TNF- $\alpha$  could contribute to OXS and ROS generation, altering IRS activity [112]. The scientific community has not yet arrived at a consensus regarding the relationship between type 2 DM and HBV infection, with some groups reporting no relation between insulin resistance and HBV infection [97,113]. However, HBx has been demonstrated to interfere with the activation of insulin signaling by activating STAT3 and C/EBP. This results in the increased expression of suppressor of cytokine signaling 3 (SOCS3) at the transcriptional level [114].

Nearly 50% of HCV patients suffer from neuropsychiatric symptoms with impaired quality of life [115]. An alteration in the blood brain barrier is caused due to the apoptosis of brain cells by HCV [116]. This allows the circulating pro-inflammatory cytokines and chemokines to reach the brain causing neurological dysfunction [117]. Significant correlation between increased IL-1 and IL-6 in the peripheral circulation, prefrontal cortex and hippocampus has been observed, which is possibly related to the impairment of neurocognitive function [118]. HCV possibly induces a local inflammatory response within the brain and *in vitro* infection of macrophages, increasing TNF- $\alpha$  and IL-8 production [119,120]. But unlike HCV, direct involvement of HBV in any brain disease has yet not been reported. However, CHB has been frequently linked with several peripheral neuropathies of either vascular or immune mediated pathology [121,122]. Cases of hepatitis B patients, with vascular neuropathies, such as Poly Arteritis Nodosa (PAN) or demyelinating neuropathies, chronic inflammatory demyelinating polyneuropathy and Guillain-Barré syndrome have been reported [123]. Also, HBV is associated with chronic immune-mediated non-vasculitic Mononeuropathy Multiplex (MM; [124]). These neuropathies are as a result of accumulation of immune complexes involving viral proteins and specific antibodies. HBV infection may trigger the production of antibodies, cross-reactive with self-proteins, through molecular mimicry and mononuclear cells involved in inflammation [125].

HCV infection is capable of enhancing the risk of atherosclerosis

and vascular disease development *via* induction of systemic inflammation [39–41]. CHC infection associated pro-inflammatory cytokines up-regulate several intracellular adhesion molecules, anti-endothelium antibodies and increase the risk of atherosclerosis and vascular diseases [38]. Even the non-obese and non-diabetic HCV infected patients are at a risk of cardiovascular diseases, since they have elevated pro-inflammatory cytokine levels (IL-6 and TNF- $\alpha$ ) and increased pro/anti-inflammatory cytokine ratio (TNF- $\alpha$ /IL10 and IL-6/IL-10 [126]. In HCV infected patients, increased level of systemic and liver inflammatory markers, such as fibrinogen and C-Reactive Protein (CRP), have been demonstrated to be associated with atherosclerosis [39,127]. HBV infection has also been suggested to induce vasculitis but owing to differential T-cell responses to HBV in contrast to HCV, atherosclerotic activity is more profound in CHC [128]. Cryoglobulinaemic vasculitis has also been linked to CHB infection with HBsAg-Ab complexes in circulation as well as its deposition in muscular arteries and dermal vessels [129]. Hypo-complementemia (decreased serum complement), with increased serum C1q binding activity, has also been demonstrated to accompany HBV-associated vasculitis and inflammation [130,131]. However, the frequency of HBV associated vasculitis has declined several folds over the decades owing to the successful vaccine and therapeutic regimen in place [132].

Membranoproliferative glomerulonephritis (MPGN) is one of the major manifestations of the HBV and HCV related liver injury. The renal injury in both diseases has been proposed to be a result of immune complex mediated inflammation with cryoglobulinemia [35–37]. In HBV and HCV infection, cryoglobulins may induce endothelitis and inflammation, *via* anti-endothelial antibody and complement activation, causing platelet aggregation through over-expression of vascular cell adhesion molecule 1 (VCAM-1) [133]. Immune complexes, involving HBV/HCV surface and core antigens, damage glomerular structures by acting as chemo-attractants for circulating inflammatory cells and/or by mediating the release of vaso-active substances and cytokines [134]. The expression levels of absent in melanoma 2 (AIM2), during HBV infection or replication, have been found to be elevated. This generates inflammatory state and contributes to renal damage [135]. Also, TLR3-signalling has been implicated in HCV-related glomerular disease [136]. HBx protein and HCV core proteins reduce IRS1 levels and promote insulin resistance, which is thought to cause excess intra-renal production of insulin-like growth factor 1 (IGF-1) and TGF $\beta$ . This results in renal cell proliferation and up-regulation of angiotensin II type 1 receptor expression in mesangial cells, consequently enhancing the deleterious effects of angiotensin II in the kidney [33,34].

HBV infection can also cause extra-hepatic disorders as a result of immune complex (viral antigen-antibody) deposition and is clinically expressed as an autoimmune phenomena accompanying inflammation [137]. Arthritis, arthralgia, skin rash, and popular acrodermatitis (Gianotti-Crosti Syndrome) etc. are some of the manifestations of such inflammatory autoimmune phenomenon. Cannabinoid receptor (CB2-63 QQ variant) present in high concentrations within liver, has been reported to be linked with severe necro-inflammatory responses in HCV patients [138,139].

Strong possible correlation between HCV infection and Non-Hodgkin Lymphoma (NHL) has been demonstrated [43]. Generally, HCV causes lympho-proliferative cryoglobulinemia, which eventually leads to B-cell NHL (B-NHL). Also, there is association of HCV with T-cell NHL (T-NHL) and primary sites of NHL presentations. Such dependency is strongly related to the regional areas. Moreover, linkage

between nodal and extra-nodal NHL with HCV infection has also been demonstrated [140]. NHL development, by lympho-proliferation, occurs through continuous viral antigenic stimulation and possibly persistent inflammatory state [141]. Association between HBV and NHL has not been extensively studied as compared to HCV. However, a group demonstrated that the HBV patients are three times more prone in developing NHL after excluding other factors such as HCV co-infection, comorbidity and regional occurrence [142]. Marcucci and coworkers also showed positive association between HBV and NHL [44].

Cholangio Carcinoma (CCA) is bile duct epithelial cell cancer and could be present within the intra-hepatic or extra-hepatic biliary network. Both HBV and HCV infection are significantly associated with CCA [143]. Mechanistic study revealed that CCA development takes place as a result of HBV/HCV mediated chronic inflammation, cirrhosis and fibrosis [45].

Pancreatic AdenoCarcinoma (PAC) is certainly one of the lethal cancers due to its asymptomatic nature and poor prognosis. It is highly metastatic and the lack of early detection procedures makes it difficult to treat. Some reports hypothesized that there might be a correlation between pancreatic cancer and pathogenic infection involving HBV/HCV [144]. Earlier, other groups ascertained significant association between HBV and pancreatic cancer [145,146]. Moreover, Wang and coworkers showed a possible linkage between A blood type, HBV infection and development of pancreatic cancer [147]. Patients positive for HBsAg or anti-HBc are more prone to Pancreatic Ductal Adenocarcinoma (PDAC). This is further aggravated in patients, with DM, having HBV infection [148]. Previous findings have already established the role of HCV in intra-hepatic cholangiocarcinoma (ICC), but its association with Extra-Hepatic Cholangiocarcinoma (ECC) or pancreatic cancer is less extensively studied. However, El-Serag et al. reported more than two fold increase in the risk of developing pancreatic cancer with HCV infection [149]. Xu et al. also confirmed that HBV/HCV could increase pancreatic cancer development [46]. Exact mechanism in HBV mediated pancreatic cancer is not fully understood but the persistence of HBV DNA, in pancreatic cancer patients, suggest its possible role in the etiology of the disease [150]. Various factors, participating in the inflammation, altered as a consequence of HBV/HCV infection are enlisted in Table 1.

## Targeting Inflammatory Molecules for Therapeutic Means

Some of the commonly used drugs, approved by FDA, targeting HBV/HCV are mentioned in Table 2. Inflammatory responses have a definite role in the progression CHB and CHC along with their local and systemic effects. Hence, an anti-inflammatory approaches for controlling such processes could prove useful for therapeutic purpose. Sorafenib, a chemotherapeutic agent, inhibits Raf/ERK pro-inflammatory and pro-fibrotic signaling pathways [151]. TNF $\alpha$  inhibitors have been used to reduce IL-6 and TGF- $\beta$  in animal models [152]. However, using such anti-inflammatory drugs could interfere with the IFN therapy for HCV based hepatitis.

HCV based inflammation has been controlled by blocking pro-inflammatory IL-1 $\beta$  by Canakinumab, an IL-1 $\beta$  specific human monoclonal antibody [153]. PTX acts by down-regulating the expression levels of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1, IL-6, TGF- $\beta$  and IFN- $\gamma$ ), in liver, as well as Peripheral Blood Mononuclear Cells (PBMCs). Targeting the endocannabinoid system (CB1 and

CB2 receptors), for reducing inflammation and fibrosis, has shown promising results [139,154].

For treatment of HBV infection, the antiviral nucleoside/nucleotide analogues targeting the viral reverse transcriptase efficiently suppress replication of HBV and reduce cirrhosis associated liver inflammation [155]. CHB is a necro-inflammatory liver disease and treatment of CHB by inhibiting mediators of inflammation has also been tested. Transgenic mice experiments which involved the use of anti-platelet therapy to suppress intrahepatic CTL activity have been successful in preventing disease progression to HCC. Activated platelets are known to facilitate hepatic CD8+ T-cell accumulation and anti-platelet therapies block this process, thereby reducing liver injury and fibrosis [156]. Several groups have shown that inhibition of platelet activation pathways by specific inhibitors: aspirin (Asp; blocks thromboxane (TX) A2 production), and clopidogrel (Clo; blocks P2Y12 ADP receptor) influence CD8+ T-cell and virus-nonspecific inflammatory cells infiltration in liver [157,158]. The current immunotherapeutic strategies for HBV replication control and suppression are restricted by our limited knowledge, and a better understanding of the virus in its hepatic niche will certainly facilitate the development of novel approaches.

## Conclusion

The development of inflammatory environment within the liver during HBV or HCV infection is crucial for the reversal of disease as well as its pathogenesis. The evidences highlighted earlier, indicates that CHB and CHC based inflammation has a paramount role in the local and systemic effects. In addition, host genetic factors also contribute to the viral persistence and resolution. The exact mechanisms, underlying HBV and HCV based inflammation, is still not known. Therefore, discovery of novel therapeutic targets, for effective treatment of CHC/CHB is highly desirable. Targeting "inflammation" in CHB/CHC is a very attractive therapeutic option and could be particularly useful in antiviral treatment non-responders. These kinds of therapies could have high implications in the chronically HBV/HCV infected patients, with last stage liver disease, in the near future. Additionally, such therapies directed against host could be advantageous against non-viral liver diseases involving inflammation.

## Conflict of Interest

The authors declare that they have no competing interests.

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