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The biological functions, Structure and sources of CXCL10 and its outstanding role: As biomarker in both hepatitis B and hepatitis C

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Abstract
Hepatitis is the major cause of inflammatory condition of liver. It is commonly caused by both infectious (viral, bacterial, fungal and parasitic organism) and non-infectious (alcohol, drugs, auto immune disease and metabolic diseases). Hepatitis has many types, amongst all hepatitis B and hepatitis C are more prevalent pan world.
HBV infection caused by hepatitis B virus which is responsible for different liver stages such as acute and chronic liver disease. It is water borne disease. HCV infection caused by hepatitis C virus, responsible for different stages of liver such as chronic liver disease, fibrosis, cirrhosis and liver carcinoma.
Chemokines are a sub family of cytokines, acts as a chemo attractant for different cells, includes immune cells. CXCL10 is a small protein with 10 KD size binds with CXCL3 to mediate immune response by activating and recruiting leukocytes such as T cells, eosinophils, monocytes and NK cells.
The aim of the review is to address recent finding regarding the relation between CXCL10 in both hepatitis B and hepatitis C.

Keywords: Hepatitis B virus, Hepatitis C virus, Jaundice, Liver, Hepadnaviridae, cirrhosis, IP-10, CXCL10, C, CC, CX3C, IFN- γ, IFN-α, IFN-β, CXCR3, Chemokines, Cytokines, NF-κB-α, cholecystokinin (CCK8), CXCR3-A, CXCR3-B, CXCR3-alt, Cytokeratin 17, fibrosis, cirrhosis, hepatocellular carcinoma, IL-28B, proapoptotic signaling, TLR2, CD44, apoptosis, chemoattractant

Introduction

An inflammatory condition of the liver known to be said as Hepatitis. It's commonly caused by a viral infection. (https://www.healthline.com/health/hepatitis) [1] Short-term (acute) hepatitis often has no visible symptoms, so you may not realise you have it, such as muscle and joint pain, a high temperature, feeling and being sick, feeling unusually tired all the time, a general sense of feeling unwell, loss of appetite, tummy pain, dark urine, pale, grey-colored poo, itchy skin, yellowing of eyes and skin (jaundice) (https://www.nhs.uk/conditions/hepatitis/) [2].

Hepatitis, may result from various causes, both infectious (i.e., viral, bacterial, fungal, and parasitic organisms) and on the flip side non-infectious (e.g., alcohol, drugs, autoimmune diseases, and metabolic diseases) (https://emedicine.medscape.com/article/775507-overview) [3]. Viral infections of the liver that are classified as hepatitis include hepatitis A, B, C, D, and E. A different virus is responsible for each type of hepatitis (https://www.healthline.com/health/hepatitis) [1]. Amongst them Hepatitis B and C are more prevalent in India.

It is estimated that currently approximately 250 million people are infected chronically with hepatitis B virus (HBV). (Schweitzer *et al*., 2015) [4]. Hepatitis B causes due to infection with the hepatitis B virus (HBV), causing both acute and chronic liver injuries (Ryder *et al*., 2001; Lai *et al*., 2003) [5]. HBV is a member of Hepadnaviridae family i.e., a small DNA virus which leads to a different liver disease ranging from acute to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Acute HBV infection can be of 2 types- asymptomatic or symptomatic acute hepatitis. (T. Jake *et al*., 2009) [6]. The genome of HBV is organized as an encapsidated circular partially double-stranded DNA, covalently attached to HBV polymerase, a specialized reverse transcriptase. (Churin *et al*., 2015) [7].

The tendency of acute viral B hepatitis is for a few weeks that occur in less than 1%, and may lead up to death as a result. (López *et al*., 2013) [8]. Chronic forms may be silent, but the association with a chronic liver inflammation (chronic hepatitis) over a period of several years, may lead to cirrhosis (Xia X *et al*., 2008) [10] and can also increase the incidence of liver cancer (Fernández-Rodríguez *et al*., 2014; Xu C *et al*., 2014) [9].

As HCV is a blood borne RNA virus, the main route of HCV transmission is through blood, blood products, tissue and organs; unsafe medical procedure; healthcare exposure e.g. needle stick injury, (Owusu-Ofori S- *et al*., 2005) [14]; it can also be transmitted by intravenous drug use. (Tohme *et al*., 2010) [11]; sexual transmission (Jafari *et al*., 2010) [12]; body piercings (Lam NC *et al*., 2010) [13] and vertical transmission (Owusu-Ofori *et al*., 2005) [14]. Prevention of this can be done primarily by screening and testing of blood, plasma, tissue, organ and semen donors; virus inactivation of plasma derived products; risk reduction counseling services and implementation of infection-control practices. Secondary activities can be prevented by identification of people who are at risk (https://www.cdc.gov/mmwr/preview/mmwrhtml/00055154.htm) [15].

Concerning viral hepatitis, liver damage by pathogenesis as well as on the extra-hepatic indication either protecting or promoting infection, determined on host immune status and

genetic background, CXCL10 seems to be involved (S. Fabiani *et al*, 2015) [16].

Chemokines, which are a family of small cytokines, or signaling secreted proteins by cells. Chemokines or CXCL10 (IFN-inducible protein are chemotactic cytokines of 8-10 kDa, CXCL10) is a proinflammatory chemokine (S. Fabiani *et al*, 2015) [16]. Chemokines, a subfamily of the cytokines, which acting as chemoattractant for a wide diversified cell, including immune cells (Moser B *et al*., 2004) [19]

Chemokines and CXCL10 (chemotactic cytokines) are small heparin binding proteins which compose of a large family of peptides (60-100 amino acids) structurally analogous to cytokines, which can regulate leukocytes, as well as non-hematopoietic cells trafficking (Luster *et al*., 1998) [17]. They are sub-classified into four families: C, CC, CX3C, and CXC (Rollinset *et al*., 1997) [18]. Apart from structural criteria, chemokines may be categorized into several functional groups (25): inflammatory chemokines, homeostatic chemokines, and dual-function chemokines (S. Fabiani *et al*, 2015) [16]. CXCL10 binds with CXCR3 receptor which induces chemotaxis, apoptosis, cell growth and angiostasis. Inflammatory diseases including infectious diseases, immune dysfunction and tumor development alters expression level of CXCL10. CXCL10 is also act as a biomarker to predict severity of various diseases (Mingli Liu *et al*., 2011) [20].

IFN- γ inducible protein is defined as CXCL10 hence, in response to IFN- γ, it is secreted from different cells such as endothelial, monocyte, fibroblast, and keratinocyte (Zlotnik A *et al*., 2012) [21]. CXCL10secretion can also be induced by other different inflammatory stimuli, including IFN-α and IFN-β as well as tumor necrosis factor (TNF)-α (Ohmori Y *et al*., 1994) [22]. CXCL10 levels and their elevated peripheral fluids are a marker of Th1 orientated immune response, recruited as Th1 lymphocytes lead to increase in IFN- γ and TNF-α production, which in turn stimulates secretion of Th1 lymphocytes CXCL10, producing positive feedback and finally perpetuating the immune cascade (Antonelli A *et al*., 2014) [23]. In pathogenesis and progression of different disorders (autoimmune, neoplastic, and infectious diseases), Th1 immune response are involved (S. Fabiani *et al*, 2015) [16].

CXCL10 signal transduction

Different cell systems such as keratinocytes and hepatocytes show synergy between tumor necrosis factor (TNF) and IFN regarding CXCL10 expression induction.

In the promoter of CXCL10, this synergistic effect is facilitated by NF-κB and ISRE. (Majumder S *et al*., 1998) [24]. A mechanism which repressed inhibitor of NF-κB-α degradation and in turn caused induced CXCL10 expression, whereas cholecystokinin (CCK8) was shown to increase CXCL10 via a pathway regulated by NF-κB activation which was blocked by PDTC (pyrrolidine dithiocarbonate, an NF-κB inhibitor) in isolated and cultured pancreatic acinar cells. [34]. Protein kinase C in parallel with increased intracellular Ca 2+ mediates the activation of NF-κB and subsequent CXCL10 expression, in response to CCK8. (Han B *et al*., 1999) [25].

Evidence indicates that stimulation of IFN- γ and TNF- α with keratinocytes induced CXCL10 in time dependent manner and a concentration, mediated by activation of the protein kinase C pathway (Kaplan G *et al*., 1987) [26] CXCL10 also produced, primary human kidney mesangial cells, stimulated by TNF- α and/ or IFN- γ, in an NF-κB-dependent pathway and co-operation between NF-κB sites and the ISRE on the CXCL10 promoter were responsible for this action (Romagnani P *et al*., 2002) [27]. For expression of CXCL10 in human fibroblast cell lines Majumder S *et al*., 1998; Romagnani P *et al*., 2002) [24, 27] as well as LPS-stimulated Kupffer cells (Kopydlowski KM *et al*., 1999) [28], TNF-α and IFN- γ employ STAT1α (signal transducer and activator of transcription 1α) and NF-κB, respectively. (Majumder S *et al*., 1998; Romagnani P *et al*., 2002) [24, 27].

Cell growth has double effects on CXCL10 (Aksoy MO *et al*., 2006) [29]. The CXCL10 is either cell-type dependent, or may depend upon its CXCR3 receptor subtype for its proliferative or anti-proliferative action of CXCL10. Three differentially expressed CXCR3 subtypes have been reported: CXCR3-A, CXCR3-B, and CXCR3-alt by different cell types, when it bound to its ligand CXCL10, divergent effects on proliferation occurs (Aksoy MO *et al*., 2006) [29]. Cytokeratin 17 (K17), a cell proliferation marker, in tumor cells co-localizes with CXCL10 (Lo BK *et al*., 2010) [30].

Role of CXCL-10 in hepatitis B

Each year HBV infection causes about 700,000 deaths world-wide, either by acute infection or by chronic infection (GBD *et al*, 2013) [31]. One compelling host biomarker for hepatitis B perhaps the chemokine C-X-C motif chemokine 10 (CXCL10) also named as interferon gamma-induced protein (IP-10). CXCL10 is also suggested as a promising target for immunotherapy of cancer (Liu M *et al*., 2011) [32]. CXCL10as a matter of fact play a role in the pathogenesis of viral hepatitis. (Narumi *et al*., 1997) [33] demonstrate that in chronic hepatitis B CXCL10 mRNA was mainly synthesized by hepatocytes around periportal piecemeal necrosis and intralobular focal. The effect of this kind of high concentrations in those inflammatory areas could assist to an accumulation of T-cells and stimulated NK cells to produce IFN- γ which results in a self-perpetuating activating immune pathway which may be important for the non-cytolytic elimination or degradation of intrahepatic ccc DNA mediated by cytokines (Xia Y *et al*., 2016) [34].

Chronic hepatitis B (CHB) is a life-threatening liver disease originated by hepatitis B virus (HBV). Approximately 2 billion people worldwide are roughly calculated to be infected with HBV (Wang Y *et al*., 2014) [35]. The major feature of Chronic Hepatitis B virus is the infiltration of inflammatory cells, including neutrophils, monocytes, natural killer cells and lymphocytes, into the liver (Gong L *et al*., 2015) [36]. CXCL10 has been discussed as a treasure predictor of the patient's response to treatment with interferon (IFN- γ) in hepatitis C virus (HCV) treatment (Jaroszewicz J *et al*., 2011) [37].

As antiviral therapy becomes progressively individualized, CXCL10 may be an effective predictive maker of treatment outcomes, but the levels of CXCL10expression in patients with CHB and diverse stages of inflammation and fibrosis and the predictive value of CXCL10are yet not resolved (Kai Zhao *et al*., 2017) [38].

Role of cxcl-10 in hepatits C

Hepatitis C is an infectious disease caused by the HCV which in turn affecting 150-200 million people worldwide (Lemoine M *et al*., 2014) [39]. Studies reveal that in the liver

CXCL10 mRNA expression was prominently associated with lobular neuro inflammatory grade and HCV genotype 1 (Zeremski M *et al*., 2008) [40]. In compare to CXCL9 and CXCL10 the expression of CXCL10 increased strongly with a higher stage of fibrosis. The suggested data reported in two ways, Firstly, in CHC, CXCL10 could be determining factor in the development of necro inflammation and fibrosis in the liver (Zeremski M *et al*., 2008) [40]. Moreover, in advanced fibrosis patients CXCL10 plasma levels had increased significantly and secondly, in HCV genotype 1 patients chemokines associated with CXCR3 are the promising noninvasive markers of hepatic fibrosis (Zeremski M *et al*., 2009) [41].

It has been reported that in CHC, for detection of liver fibrosis CXCL10 can be considered a marker of liver fibrosis (Zeremski M *et al*., 2011) [42]. Moreover, it has been observed that CXCL10 induced by HCV can cause of raising hepatocyte turnover and development of fibrosis, cirrhosis and Hepatocellular Carcinoma (HCC) (Brownell J *et al*., 2013) [43]. In many HCV patients, circulating CXCL10 is an enzymatic process to generate a CXCL10 antagonist form, introducing chemokine antagonism role during HCV infection (Brownell J *et al*., 2013) [43]. It is also confirmed that CXCL10, in presence of IL-28B, could be a helpful marker to predict HCV patient's treatment failure (Fattovich G *et al*., 2011) [44].

Articles showed that in CHC, expression of CXCL10 was highly associated with the total transcripts of IFN- γ(Mihm S et.al 2003) [45]. CXCL10 can be induced by HCV in hepatocytes, which took part in the CHC pathogenesis (Harvey C *et al*., 2003) [46]. Another article reported that upregulation of CXCL9 and CXCL10 expression in human hepatocyte-derived cells can be done by NS5A and core proteins, alone, or in combination with cytokines (Apolinario A *et al*., 2005) [47]. Other publication confirmed by inducing the release of CXCL10 with HCV in hepatocytes (Brownell J et. al.,2013) [48], along with TLR2 and CD44 (Apolinario A *et al*., 2005) [47]. During liver injury TLR4, a noncognate receptor of CXCL10, which induces a proapoptotic signaling cascade for hepatocytes (Sahin H. *et al*., 2013) [49].

Table 1: Relation between Hepatitis B and hepatitis C with CXCL 10 (IP 10)

S. no	No. of Patients	Stages of hepatitis	IP 10 level		Reference
1.	72	Chronic Hepatitis B	G>2	IP 10 level is significantly higher	38. Kai Zhao1,4, Tao Yang2,4, Mimi Sun3, Wei Zhang3, Yong An3, Gang Chen3, Lei Jin2, Qinghua Shang3,*, and Wengang Song1* IP-10 Expression in Patients with Chronic HBV Infection and Its Ability to Predict the Decrease in HBsAg Levels after Treatment with Entecavir Mol. Cells 2017; 40(6): 418-425
			G≤2	in patients with CHB rated as G > 2 than in patients rated as G ≤ 2	
		Fibrosis stage with Chronic Hepatitis B	S>3	Serum IP-10 concentration was higher in patients with CHB rated as S > 3 than in patients rated as S1-2	
			S= 1 & 2		
2.	103	Acute hepatitis C		IP 10 level, irrespective of sex, increases in acute hepatitis C patients compare to healthy individuals	50. Jason Grebely1,*, Jordan J. Feld2,*, Tanya Applegate1, Gail V. Matthews1,3, Margaret Hellard4,5, Alana Sherker2, Kathy Petoumenos1, Geng Zang6, Ineke Shaw1, Barbara Yeung1, Jacob George7, Suzy Teutsch8, John M. Kaldor1, Vera Cherepanov2, Julie Bruneau6, Naglaa H. Shoukry6, Andrew R. Lloyd8, and Gregory J. Dore1, Plasma interferon-gamma-inducible protein-10 (IP-10) levels during acute hepatitis C virus infection Hepatology. 2013 June; 57(6): 2124–2134
3.	52	HBV infected patients and HCV gt 1 infected patients		The IP-10 level, irrespective of sex and age, were significantly slower in patients with HBV infection than in HCV patients' genotype1.	51. Nina Nikolova, Krasimir Antonov, Deian Jelev, Lyudmila Mateva, Zahariy Krastev, THE CYTOKINE IP-10 IN CHRONIC HBV AND HCV INFECTION, Journal of IMAB. 2013 Jul-Dec;19(3):442-447

Conclusion

Overall, based on the latest information available in the literature for the role of CXCL10 in the Hepatitis infection, the authors of the present article propose that CXCL10 plays a promising role in targeting for immunotherapy of cancer. On other hand, CXCL10 may be one of the useful predictive bio-maker of HBV treatment, but the CXCL10 expression levels in different stages of patients are unknown.

CXCL10 which can be considered as a biomarker for HCV induced fibrosis, cirrhosis & hepatocellular carcinoma. It is also confirmed that CXCL10 with IL-28B could be one of the helpful bio-marker for HCV patient treatment failure. Upon Core protein and NS5A expression of HCV, CXCL10 may up-regulate.

In a nutshell it can be concluded CXCL10 can be treated as a biomarker for HBV and HCV with its different stages.

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