Hepatitis c virus infection biology essay

Hepatitis C virus (HCV) infection is a major public health burden throughout the world (Alter and Seeff, 2000; Lauer and Walker, 2001). It is considered to be the most common blood borne infection in the U. S. with an estimated 4 million HCV infected individuals in the U. S.(Recommendations for prevention, 1998), and 180 million people are estimated to be affected by HCV globally (Davis et al., 2003; Rosen, 2011).

Hepatitis C virus (HCV) infection causes significant liver disease and severity of the disease ranges widely from asymptomatic chronic infection to liver cirrhosis and even hepatocellular carcinoma (HCC) (Lauer and Walker, 2001; Asselah et al., 2009). However both genetic and environmental factors have a major impact on the natural history of HCV infection (Asselah et al., 2009).

Acute hepatitis C is defined as the symptomatic infection and accounts for the first six months after infection with HCV. Only 15% of the individuals are affected by acute HCV infection and no anti-HCV antibody is detected at the first appearance of symptoms, in about one third of the infected people (Maheshwari et al., 2008). Viral infection elicits an initial immune response that is responsible for elimination of the virus in 15% to 45% of patients during acute hepatitis C (AHC) (Santantonio et al., 2008).

Chronic hepatitis C can be described as an asymptomatic infection with HCV that remains for more than six months. It is involved in infiltration of inflammatory cells (Leroy et al., 2003). In comparison to the other viral infections, the distinctive attribute of HCV infection is that the majority of the persons acquire chronic infection (up to 80%) after viral exposure (Lauer and Walker, 2001; McHutchison, 2004). Upon HCV infection, many patients

progress to chronic hepatitis C as their early innate immune response and later adaptive immune response have failed in clearing the virus. Furthermore, in many infected persons with chronic HCV, the ineffective inflammatory response results in the fibrogenesis and the development of cirrhosis (Heydtmann and Adams, 2009).

Hepatitis C virus (HCV) is a member of Hepacivirus genus of the Flaviviridiae family (Pedersen et al., 2007; Asselah et al., 2009), represented by six genotypes and a large number of subtypes (Simmonds et al., 2005; Pederson et al., 2007). It is a non-cytopathic and hepatotropic RNA virus (Heydtmann and Adams, 2009), that replicates in the liver (Lauer and Walker, 2001). HCV comprises of the polyprotein that is processed into structural proteins (core and envelope proteins 1 and 2), nonstructural proteins (NS2 to NS5), and a protein of unknown function (p7) (Lauer and Walker, 2001; Dustin and Rice, 2007).

The HCV virion is made up of 9. 6 kb single stranded positive RNA genome with highly invariant 5′ and 3′ untranslated regions (Rehermann and Nascimbeni, 2005; Wieland and Chisari, 2005). It is contained in a capsid and is enveloped by a lipid bilayer, within which two different glycoproteins are anchored (Asselah et al., 2009).

When the host cell is infected with virus, the viral genome is uncoated and functions as a template for the translation of single polyprotein that is processed by host and viral proteases. The synthesis of negative-strand RNA is initiated by the non-structural viral proteins and then negative-strand RNA acts as a replication template for the propagation of new positive-strand viral

genomes (Rehermann and Nascimbeni, 2005; Wieland and Chisari, 2005). Viral replication is exceedingly fast; more than ten trillion viral particles are estimated to be produced per day, even in the chronic phase of infection (Neumann et al., 1998).

Viral replication is carried out through an RNA-dependent RNA polymerase that lacks proof-reading capability, contributes to the generation of sequence diversity but related quasispecies within an infected individual, presenting a major challenge with respect to host immune response and chronic infection (Bowen and Walker, 2005; Rehermann and Nascimbeni, 2005; Dustin and Rice, 2007).

Hepatocytes are the major target of HCV, but the other targets of virus may include monocytes, lymphocytes and endothelial cells (Lai et al., 2006; Pham et al., 2008). HCV is considered to be the common cause of chronic hepatitis and is one of the most crucial aetiologic agents of postransfusional hepatitis (Balanescu et al., 2012). Studies on HCV infection had been carried out in infected patients (Lechner et al., 2000; Takaki et al., 2000) and chimpanzees (Thimme et al., 2002; Shoukry et al., 2004).

CYTOKINES:

Cytokines; molecular weight of less than 30 kDa; are defined as regulatory proteins or glycoproteins; secreted by white blood cells and various other cells in the body in response to various stimuli. More than 200 cytokines have been identified (Goldsby, 2003). Cytokines play an indispensable role in regulating the host responses to infection, immune responses, inflammation and trauma (Dinarello, 2000).

Structural studies have indicated that cytokines are classified into four groups: the hematopoietin family, the interferon family, the chemokine family and the tumor necrosis factor family (Goldsby, 2003).

Cytokines can be categorized as pro-inflammatory and anti-inflammatory cytokines. Proinflammatory cytokines are involved in making the disease worse by promoting inflammation whereas anti-inflammatory cytokines function to reduce inflammation and promote healing process (Dinarello, 2000). According to some researchers; cytokines are responsible for both immunoregulation and immune impairment (Woitas et al., 1999; Cianci et al., 2005; Wright et al., 2005).

CYTOKINES AND HEPATITIS C VIRUS:

Hepatitis C virus (HCV) is considered to be the main cause of hepatocellular injury that is related with the complicated immunologic systems (Zekri et al., 2005). In order to regulate immune responses, cytokines have major influence in controlling the underlying pathogenesis and the resulting effect of HCV infection (Amini and Poustchi, 2012).

Host immune defense against HCV infection is regulated by both humoral and cell-mediated immune responses but it is indicated that cell-mediated immune response to the cytokine system is involved in the immunopathogenesis of chronic hepatitis C (Jacobson et al., 2001).

Cytokines consist of a complicated network of molecules that are responsible for regulating the inflammatory response and the homeostasis of organ functions. Furthermore, cytokines participate in many physiological and pathological actions occurring in the liver; which include regulation of liver

growth, regeneration and other inflammatory processes such as viral liver disease, liver fibrosis and cirrhosis (Zekri et al., 2005). During chronic HCV infection, cytokines play a central role in the regulation of hepatic inflammation and fibrogenesis (Zhang et al., 2012).

It is indicated that cytokines themselves are manipulated by polymorphisms in their genes. However most of the genetic variants that confer a significant risk for chronic HCV infection have been localized in genes responsible for cytokine synthesis and the ultimate immune response (Amini and Poustchi, 2012).

ROLE OF INTERFERONS IN HCV INFECTION:

Interferons belong to the multigene family of inducible cytokines (Blatt et al., 1996; Diaz et al., 1996; Young, 1996; Roberts et al., 1998; Stark et al., 1998). Interferon was first discovered as an antiviral agent by Isaacs and Lindenmann more than 50 years ago (Isaacs and Lindenmann, 1957). More than 10 mammalian IFN species and several subspecies have been reported (Pestka, 2007) and all IFNs possess antiviral activity (Pestka et al., 1987; Samuel, 1988; Stark et al., 1998).

IFNs are categorized into three main groups: type I, type II and type III IFNs (Heim, 2012). The type I IFNs comprises all IFNαs, IFNβ, IFNε, IFNκ, IFNω and IFNν (Pestka, 2007). Type II IFNs include only one class i. e., IFNγ (Heim, 2012), and type III IFNs have been identified as IFNλ1, IFNλ2 and IFNλ3 and these are also known as IL29, IL28A and IL28B respectively (Kotenko et al., 2003; Sheppard et al., 2003). Upon viral infection, cells produce IFNαs, IFNβ and IFNλs (Heim, 2012).

Two major pathways have been reported that are involved in the detection of the viral genomes and in the induction of type I and type II interferons: the toll-like receptor (TLR) dependent pathway (Iwasaki and Medzhitov, 2004; Akira et al., 2006) and the cytosolic pathway involving the binding of viral genome to the RNA helicases retinoic acid inducible gene-I (RIG-I) and melanoma differentiation antigen 5 (MDA5) (Yoneyama, 2004; Yoneyama and Fujita, 2007).

Interferons are not only involved in the initial host response to HCV, but also play crucial role in an immune response to chronic phase of hepatitis C which lasts for many years and subsequently results in the cirrhosis and hepatocellular carcinoma (Heim, 2012). The constantly activated endogenous IFN system has been observed in the liver of many infected patients with chronic hepatitis C and the expression of hundreds of IFN stimulated genes (ISGs) in hepatocytes have been indicated (MacQuillan et al., 2003; Asselah et al., 2003; Chen et al., 2005; Asselah et al., 2008; Sarasin et al., 2008).

Role of type I interferons including IFN-α, -β and -ω against viral infection are related with innate immune responses (Ding et al., 2012). The products of interferon-stimulated genes (ISGs) include the cellular factors that mediate this defense mechanism. However little information is available about antiviral potential, target specificity and the mechanism of action of most ISG products (Schoggins et al., 2011). Direct signaling pathways by viral infection are involved in the IFN gene transcription and IFN activates the innate cellular antiviral response which serves to inhibit the viral replication (Yang et al., 2011).

Suppression in production of HCV virion by affecting the viral RNA and protein synthesis, encouragement of immune lysis of HCV infected cells, inhibitory actions on hepatic fibrosis and negative effect on HCV induced carcinogenesis; are some of the prominent functions of type-II interferon i. e. IFN- γ (Cecere et al., 2004). In addition to these, spontaneous viral elimination is also related with IFN-γ production in HCV infection (Major et al., 2002; Thimme et al., 2002).

Type-III interferon (IFN- λ, including IL-29, IL-28A and IL-28B); a new subfamily of interferon; are associated with the inhibition of viral replication in vitro and in vivo (Ding et al., 2012). However genes encoding these type-III interferon members are found to be clustered on human chromosome 19q13. Structurally, they are related to IL-10 superfamily of cytokines but their functions are similar to type-I interferons as they are also activated by viral infections and possess anti-viral activity in vitro (Kotenko et al., 2003; Sheppard et al., 2003).

Recent studies have shown that there is an association of genetic variants near the IL28B gene and ISG expression in the liver (Honda et al., 2010; Urban et al., 2010; Dill et al., 2011) but the mechanism of induction of ISGs linked with IL28B genotype is still obscure (Heim, 2012). Moreover, viral eliminating processes that are responsible for HCV to persist, in spite of such powerful activation of hepatic IFN system, are not well understood. It is indicated that activated endogenous IFN system is not only involved in HCV clearance, but also suppresses the response to IFN- based therapies (Chen et al., 2005; Asselah et al., 2008; Sarasin et al., 2008).

ROLE OF CHEMOKINES IN HCV INFECTION:

Chemokines are a super family of cytokines; molecular weight of 8-10 kDa. These are chemotactic cytokines that induce leukocyte migration and are involved in orchestrating the immune response to viruses, including hepatitis C virus (Murdoch and Finn, 2000; Rossi and Zlotnik, 2000; Heydtmann and Adams, 2009). In order to promote the cell migration, chemokines bind to specific G-protein coupled receptors, expressed on different target cells that ultimately enhance the immune responses during acute and chronic inflammation (Murdoch and Finn, 2000; Rossi and Zlotnik, 2000). Although chemokines are essential for elimination of virus, but these are also responsible for inflammation and tissue damage due to inappropriate persistence of their expression in chronic hepatitis C infection (Heydtmann and Adams, 2009).

On the basis of different number of amino acids between the N-terminal cystein residues, chemokines are classified into four families: the CC, the CXC, the CX3C, and the XC families (Kang and Shin, 2011).

Chemokines in acute HCV infection:

The role of chemokines in acute HCV infection is not well defined and in order to study regulation of chemokines in acute HCV infection HCV-infected chimpanzee models had been used (Landford et al., 2004; Major et al., 2004; Shin et al., 2011).

In response to HCV RNA, pattern recognition receptors induce the production of type I interferon (IFN) in early phase of HCV infection RNA (Havey et al., 2003; Helbig et al., 2004; Shin et al., 2006; Decalf et al., 2007; Takahashi et

al., 2010; Shin et al., 2011) that is followed by production of Th1-associated chemokines after two to eight weeks of HCV infection (Shin et al., 2006; Shin et al., 2011). In acute phase of HCV infection, CXCR3-associated chemokines (CXCL9, CXCL10, and CXCL11) and CCR5-associated chemokines (CCL3, CCL4, and CCL5) are considered to be essential for efficient antiviral T cell response (Kang and Shin, 2011).

Chemokines in chronic HCV infection:

The role of chemokines in chronic HCV infection is completely different from their roles in acute phase of HCV infection. During acute HCV infection, chemokines take part in recruitment of antiviral T cells that leads to viral clearance whereas in chronic HCV infection chemokines are responsible for inflammation.

The increased level of chemokines in the peripheral blood and the liver during chronic HCV infection, results in the development of inflammation (Qin et al., 1998; Loetscher et al., 1998; Shields et al., 1999; Kunkel et al., 2002; Boisvert et al., 2003; Leroy et al., 2003; Heydtmann et al., 2006).

Due to persistent HCV virus, there is constantly augmented production of chemokines to the liver and results in chronic liver injury without viral clearance. It is observed that many of the liver-infiltrating HCV-specific T cells isolated from chronic HCV-infected patients may involve in the persistence of chronic inflammation that directs to continuous hepatic injury, despite being exhausted. There are many chemokines associated with liver inflammation in chronic HCV infection. It is indicated that during chronic HCV infection, the virus replicates persistently within the hepatocytes thus

prolonging the production of chemokines and as a consequence leads to continuous hepatic injury without viral elimination by recruitment of inflammatory cells to the liver (Kang and Shin, 2011).

ROLE OF Th1 AND Th2 CYTOKINES IN HCV INFECTION:

Immunoregulatory cytokines and T lymphocytes are of vital importance in the host defense against HCV infection (Zekri et al., 2005). On the basis of differences in cytokine secretion, activated CD4+ T cells can be classified into two subsets: Th1 and Th2 subsets (Gioia et al., 2005; Lanzilli et al., 2005).

Th1 and Th2 cytokines are important in viral infections and disturbances in the regulation of these cytokines result in viral persistence and emergence of chronic disease. Recent studies have shown that Th1 cytokines are predominant in chronic hepatitis C and are associated with liver immunopathology (Gigi et al., 2008).

The unsuccessful event of spontaneous clearance of virus and chronic persistence of virus is associated with an inadequate Th1 immunity as well as weak HCV-infected T cell response at an inflammatory site. In order to induce the Th1 immunity, production of interleukin-12 (IL-12) is required, leading to the elimination of pathogens and viruses (Cecere et al., 2004).

T-helper type 1 (Th1) cytokines (IL-2, IFN-γ) are needed for host anti-viral responses, while T-helper type 2 (Th2) cytokines (IL-4, IL-10) can suppress the development of these effectors. Cacciarelli et al. observed increased levels of IL-2, IL-4, IL-10, and IFN-γ in patients infected with chronic HCV. It

was reported that after treating HCV-infected patients with interferon therapy, levels of IL-4 and IL-10 had decreased and resulted in diminished activity of HCV RNA (Cacciarelli et al., 1996).

Another study has indicated that patients infected with chronic HCV infection exhibited augmented levels of Th1 cytokines, including IL-2, IL-2R, and IFN-γ; whereas levels of Th2 cytokines IL-4 and IL-6 were lower in the patients as compared to control subjects (Cribier et al., 1998).

Experimental studies have indicated that antigen-specific Th1 immunity and pro-inflammatory cytokines are involved in liver injury related to HCV and viral clearance (Schvoerer et al., 2003; Wright et al., 2005; Katia et al., 2006), however little is known about pathogenesis of chronic HCV infection (Wang et al., 2012).

ROLE OF PRO-INFLAMMATORY CYTOKINES IN HCV INFECTION:

In chronic hepatitis C, an elevated serum level of pro-inflammatory cytokines has been observed (Tilg et al., 1992; Larrea et al., 1996). TNF-α and IL-1 (α and β) are considered to be crucial pro-inflammatory cytokines that are expressed by kupffer cells and T-cells in the liver (Beutler and Cerami 1989; Winwood and Arthur 1993; Hoffmann et al., 1994). Apart from the kupffer cells, newly recruited macrophages from circulating monocytes may also act as a source of cytokines (Tsukamoto, 1999).

It has been demonstrated that pro-inflammatory cytokines also produce in endothelial cells of liver sinusoids, activated hepatic stellate cells (HSCs), and biliary epithelial cells (Hoffmann et al., 1994; Tsukamoto, 1999).

The function of cytokines derived from hepatocytes, is not yet clearly defined. Although studies carried out on intrahepatic inflammatory cytokine genes in human chronic HCV infection have pointed out that an augmented hepatic expression of the Th1 cytokines (IL-2 and IFN- γ) is related with HCV liver injury (Napoli et al., 1996; Bertoletti et al., 1997; McGuinness et al., 2000). As compared to healthy persons, the untreated chronic HCV-infected patients had shown an elevated level of TNF-α mRNA in the liver and mononuclear cells (Larrea et al., 1996; McGuinness et al., 2000).

Pro-inflammatory cytokines may include IL-6 and IL-18, where IL-6 serves in immune responses (Li et al., 2004) and levels of IL-18 are associated with metabolic and viral hepatic diseases (Vacchiet et al., 2005).

As the pathogenesis of chronic HCV infection is concerned, an increased level of pro-inflammatory cytokines had been observed in serum of patients (Tilg et al., 1992; Larrea et al., 1996) and upregulation of intrahepatic Th1-like cytokines had also indicated (Napoli et al., 1996). It was reported that HCV becomes resistant to inhibition by cytokines and due to this reason; cytokines play a prominent role in liver damage rather than controlling viral replication (Shapiro et al., 1998; Koziel, 1999).

ROLE OF OTHER INTERLEUKINS IN HCV INFECTION:

Interleukins (IL) belong to one of the families of cytokines and these are secreted by some leukocytes and may act upon other leukocytes (Goldsby, 2003). Some of the interleukins associated with HCV infection are discussed here.

Interleukin-17 (IL-17) cytokine family has recently been identified; involved in host immune responses against intracellular pathogens and chronic inflammatory conditions. Although little information is available about the function of IL-17 producing cells in HCV infection but it is indicated that T cells producing IL-17/IL-22 are found in liver and circulating levels of IL-17 are not associated with liver fibrosis (Foster et al., 2012). However, Chang et al. had reported positive correlation between IL-17 and severity of liver inflammation. In chronic HCV infected patients, serum IL-17 levels are found to be higher (Balanescu et al., 2012).

Interleukin-33 (IL-33) is a newly described cytokine; belongs to the family of IL-1. Epithelial tissues and vascular endothelial cells may produce IL-33 (Schmitz et al., 2005). However, less information is available on contribution of IL-33 to the pathogenesis of HCV infection.

Wuang et al. reported that IL-33 is considered to be a pathogenic agent leading to chronic hepatitis C related liver injury and is associated with the development of Th2 response (Wuang et al., 2012).

The biological role of IL-33 is associated with the induction of Th2 cell differentiation and activation of mast cells, resulting in Th2 cytokine production and Th2 response. Moreover, the effects of IL-33 also include pulmonary and mucosal Th2 inflammation (Schmitz et al., 2005).

ROLE OF TGF-β CYTOKINE IN HCV INFECTION:

Transforming growth factor beta (TGF-β) is described as a major profibrogenic cytokine and HCV-specific CD8+T cells are involved in production of TGF-β. It has a protective role in HCV-infected liver along with

other T-cell derived factors, involved in ameliorating HCV liver disease progression (Li et al., 2012).

TGF family of proteins has important roles in regulation of cellular processes including growth, differentiation, extracellular matrix formation and immune-suppression (Blobe et al., 2000; Hayashi and Sakai, 2012). TGF-β and pro-inflammatory cytokines are known to be essential mediators of progressive fibrosis and carcinogenesis (Zhang et al., 2012).

In chronic infection, HCV-specific immune effector responses may lead to liver damage and hepatic stellate cells (HSC) are considered as main effectors of liver fibrosis (Li et al., 2012). During acute phase, adaptive effector T cells play a crucial role in controlling HCV infection (Missale et al., 1996), whereas in chronic infection, persistence of inefficient effector T cell responses is responsible for tissue damage and inflammatory reactions, directing to fibrosis and finally cirrhosis (Li et al., 2012). It is reported that TGF-β produced locally by regulatory/immunosuppressive T cells (Tregs) inhibits rather than enhances hepatic fibrogenesis. Tregs are related with HCV pathogenesis; however Treg roles in HCV disease progression are not well understood (Li et al., 2012).

TGF-β is a cytokine with several roles, including capability of directing T cell lineage commitment towards either pro-inflammatory Th17 T cells or anti-inflammatory Treg, depending on presence of additional factors, such as IL-6 (Wahl, 2007).

TGF-β mediated suppressive activity against HCV-specific effector function had previously been detected in peripheral blood of patients infected with

chronic hepatitis C and a new population of non-classical human Tregs responsive to HCV that produced the Treg-associated cytokine TGF-β, had identified (Alatrakchi et al., 2007).

According to some studies, Tregs are considered to be related with HCV persistence in chronic HCV infection (Billerbeck et al., 2007; Li et al., 2008; Alatrakchi and Koziel, 2009). Although TGF-β may play an indispensable role in anti-inflammation by locally protecting against surrounding tissue damage (Li et al., 2012).

It is concluded that in response to infection with HCV, cytokines are either involved in regulating the immune response in order to eliminate the virus or in liver damage by impairing the immune system. Cytokines are considered to be both positively and negatively correlated with HCV infection.