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**Hepatitis-related hepatocellular carcinoma: Insights into cytokine gene polymorphisms**

Dondeti MF *et al.* Cytokine gene polymorphism in HCC

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**Abstract**

Hepatocellular carcinoma (HCC) is a primary liver cancer, which is one of the most prevalent cancers among humans. Many factors are involved in the liver carcinogenesis as lifestyle and environmental factors. Hepatitis virus infections are now recognized as the chief etiology of HCC; however, the precise mechanism is still enigmatic till now. The inflammation triggered by the cytokine-mediated immune response, was reported to be the closest factor of HCC development. Cytokines are immunoregulatory proteins produced by immune cells, functioning as orchestrators of the immune response. Genes of cytokines and their receptors are known to be polymorphic, which give rise to variations in their genes. These variations have a great impact on the expression levels of the secreted cytokines. Therefore, cytokine gene polymorphisms are involved in the molecular mechanisms of several diseases. This piece of work aims to shed much light on the role of cytokine gene polymorphisms as genetic host factor in hepatitis related HCC.

**Key words:** Hepatitis C virus; Hepatitis B virus; Hepatocellular carcinoma; Cytokines; Polymorphism

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**Core tip:** Cytokines have a decisive role in the pathophysiology of many infectious, autoimmune and malignant diseases. Changes in cytokine secretion profile are involved in one way or another in susceptibility to hepatitis B virus (HBV) and hepatitis C virus (HCV) infection and eventualy are thought to influence the disease phenotype and the rapid progression to HCC. Individual variation in cytokine profile might, at least partially, to genetic alteration within the regulatory regions of cytokine genes. One of the most studied phenomena is the allelic polymorphism and its implication in cytokine gene expression, and the susceptibility to infection, clinical severity of diseases and response to treatment. This review concentrates on the cytokine gene polymorphism case-control and meta-analysis studies performed all over the world on HCC patients (as a consequence to HBV or HCV infection).

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**INTRODUCTION**

Hepatocellular carcinoma (HCC) is deemed as one of the most life threatening malignancies. It is developed after prolonged and persistent chronic hepatitis infection [hepatitis B virus (HBV) or HCV infection]. Cytokines represent the key immune-modulatory molecules involved in the defense mechanism against viral infection. Its production is genetically controlled. Variations resulted from single-nucleotide polymorphisms (SNPs) in the cytokine genes’ could extremely affect the cytokine production, which in turn disturbs the all over immune response either to viral infection or in HCC production. In this review article, we summarized the documented population-based variability in cytokine gene polymorphisms, that might implicate in hepatitis infection and participate in the development of HCC.

**INCIDENCE OF HEPATITIS-RELATED HEPATOCELLULAR CARCINOMA**

Hepatocellular carcinoma (HCC) is a global health dilemma. It is the third prevalent cancer among humans with a high rate of mortality[1,2]. It is the primary liver cancer as it represents 83% of liver cancers[3-5]. It mostly occurs in patients with chronic liver diseases like cirrhosis, which is primarily a set of the hepatotropic viruses as hepatitis B (HBV) or C (HCV) virus. Therefore, the highest rate of HCC incidence is high in areas with high endemic level of hepatitis viruses as in African and Asian countries[6] ­, on contrary to Europe and United State of America in which there is a low incidence rate of hepatitis infections[1,7-9]. World health organization (WHO) suggested that HCC is assumed to be in a growing till 2030 which re-ranks HCC to be the second preval ent cancer among humans[10].

HCC is a multistep and multifactorial process (Figure 1) as there are many factors involved like environmental factors, alcohol abuse, carcinogens as aflatoxins, obesity-related hepatitis, and hepatotropic chronic viral infections[11-14]. However, there is no individual cause of HCC[15] indicating to the implication of other unknown factors such as the host genetic elements. Therefore, it is highly important to give a closer look at the molecular level of HCC development to attain a better understanding of the underlying intricate mechanisms of the hepatocarcinogenesis.

Hepatitis is a critical player in the initiation, promotion, and progression of HCC. HBV and HCV were reported to be the commonest risk factors of HCC[16-19]. Nearly 70%-80% of HCC cases are attributed to hepatitis viruses[2]. Generally, HCC is more prevalent among HBV patients than HCV ones as 75%–85% of HCC patients have chronic HBV infection[1,7,20]. Both HBV and HCV patients develop liver cirrhosis in which 20% of cirrhotic patients develop HCC. On the other hand, only a minor fraction of hepatitis viruses’ carriers develops HCC in their lifetime, indicating to the presence of other cofactors involved in liver carcinogenesis[5,21]. The exact mechanism of hepatitis-related HCC is still controversial and unknown at the mean time as there is a plethora of intracellular and extracellular factors involved in the process of carcinogenesis. To date, one of the most implicated factors in carcinogenesis is the inflammation, which stimulates angiogenesis, DNA damage, and malignant tumor cell growth[22,23]. Interestingly, inducible nitric oxide synthase (iNOS) was reported to be the culprit of disease progression and HCC development among HCV patients through induction of nitric oxide (NO) production[24-26]. Inflammation is highly dependent on the potential of the immune response mediated by the cytokines, in which strong immune response induces chronic hepatitis and weak response can be an oncogenic cofactor in HBV or HCV carriers as the persistent infection in the hepatic microenvironment promote the progression of HCC[7,20,27,28].

**ROLES OF CYTOKINES IN THE HEPATITIS VIRUS INFECTIONS**

Cytokines, what are they? Cytokines are immunomodulatory glycoproteins, which orchestrate the immune response and modulate the activities of the immune cells. Cytokines are produced by a wide range of cell types whether immune and non-immune cells. Cytokines in the terms of ligands bind to specific receptors promoting the signal transduction within the target cell. The transducer signals activate key genes responsible for mitotic cell division, growth and differentiation, migration, or even apoptosis. In addition, they play a critical role in modulation of the innate and adaptive immune systems during viral infections and direct inhibition of viral replication. Cytokines are classified according to many criteria as the producing cells, the function, the receptors and the target cells. They are classified into monokines (monocyte lineage) or lymphokines (lymphocytes) according to the producing cells[29-31]. They are also classified according to the function into T helper (Th) 1, Th2, and Th17 cytokines. Th1 cells secrete proinflammatory cytokines as IL-2, IFN-γ and TNF-α. Otherwise, Th2 cells secrete IL-4, IL-5, IL-10 and IL-13. Th17 cells produce IL-17, IL-17F and IL-22, all of which regulate inflammatory responses of tissue cells. Overproduction of Th2 cytokines typically promotes B-cell hyperactivity and humoral immune responses, whereas T cell hyperactivity and inflammation frequently associate with an excess of Th1 and Th17 cytokines. According to the criterion of classification, cytokines are classified into either pro-inflammatory as IL-1, IL-6 and TNF-α or anti-inflammatory as IL-4 and IL-10 in addition to other cytokines which have pleiotropic roles in the immune response such as TGF-β1[32,33].

In the hepatic microenvironment, cytokines play an important role in the defense against hepatitis viruses and immunopathogensis of hepatitis infections. They are prominently involved in the liver damage during HCV infection, while they have been reported in previous studies to be determining factor of the HBV infection’s outcome. Proinflammatory cytokines as IL-1β and TNF-α were reported to be elevated among hepatitis patients. HCV-specific T cells mediate ongoing viral clearance and liver injury by either directly killing infected hepatocytes or releasing pro-inflammatory cytokines, such as IFN-γ and TNF-α. Increased mRNA levels of IFN-γ and TNF-α are found in the livers of chronic HCV-infected patients. Importantly, the expression of these pro-inflammatory cytokines correlates with both the extent of hepatic inflammation and the development of fibrosis[34-38].

The resolution of hepatitis virus infections through inhibition of viral replication is associated with enhanced CD8+T-cells response which is mediated by Th1 cytokines. Thus, the alterations in Th1 cytokines are involved in the liver injury and fibrosis resulted from chronic inflammation, which leads to enhanced remodeling of the hepatic tissue due to subsequent regeneration, subsequently proto-oncogenes activation leading to HCC development[39-43].HCC development is a complex and a multidimensional process so there are many theories about the involvement of cytokines in the HCC. Nevertheless, Cytokines were reported to suppress the tumor formation through controlling the inflammatory response against infection[44]. Cytokines are traditionally attracted of inflammatory cytokines, which may be the first step in inflammation-based carcinogenesis, in addition cytokines may trigger the hepatocarcinogenesis itself through growth signaling, angiogenesis and invasive metastasis[45-47]. Previous studies reported higher levels of different cytokines in HCC patients as IL-1β, IL-6, IL-10, IL-15, IL-18, TNF-α, IFN-α, IFN-γ, and TGF-β1[48-55], which may represent a mounting proof of the involvement of cytokines in liver carcinogenesis. Therefore, looking in depth at the molecular levels of hepatocarcinogenesis may give a clear view of what actually happens during hepatitis-related HCC.

**CYTOKINE GENE POLYMORPHISMS AS THE PROTAGONIST OF HEPATITIS-RELATED HCC**

DNA sequence between two randomly opted human genomes is 99.9% identical. The other 0.1% represents polymorphic regions that differ among individuals and occurs at a frequency of at least 1% in population so it is different from the mutations. Gene polymorphisms are characterized by the presence of multiple alleles for a given gene due to alterations in the nucleotide sequence. The polymorphisms take the following main forms: single nucleotide polymorphisms (SNPs), variable number of tandem repeats (VNTRs) and microsatellites also known as Simple Sequence Repeats (SSRs) or short tandem repeats (STRs)[44,45]. The genes of cytokines and their receptors have been shown to be highly polymorphic. So what can such variations affect the cytokines and their function? The answer comes to surface when gene polymorphisms were found to inﬂuence the expression of cytokines controlling the immune response which open the gate to understand the intricate mechanisms of diseases at the molecular level. In recent years, several studies have demonstrated that cytokine gene polymorphisms correlated with susceptibility to, or protection from, disease development[56,57].

The polymorphisms of cytokine and cytokine receptor genes occur either in the coding or the non-coding regions. The genetic polymorphisms within the coding region that lead to amino acid substitution are not common, on the other hand, the genetic polymorphism are so common in the non-coding region as the promoter, intron and the untranslated regions. There is a growing evidence of that cytokine production capacity is genetically determined by the cytokine gene polymorphisms either in coding or non-coding regions. Given that the functional consequences of polymorphisms may contribute to the establishment of a given disease phenotype, reports have focused on discovering associations between speciﬁc gene polymorphisms and disease status with the main target of identifying susceptibility groups[29,58,59]. Many reports focused on the genetic polymorphisms of cytokines as host genetic factors in hepatitis-related HCC as they may clear the complexity of HCC occurrence due to HBV or HCV as etiological factors (Table 1). In addition to disease development, polymorphisms in the cytokine genes have been reported to be significantly associated with response to therapies and spontaneous HCV/HBV clearance[5,60-62].

**INFLAMMATORY CYTOKINE GENES POLYMORPHISMS**

***IL-1 gene polymorphisms***

IL-1 gene family is located on chromosome 2q13 spanning a region of 430 kb, consists of IL-1α and IL-1β in addition to IL-1 receptor antagonist (IL-1RN). IL-1α and IL-1β are potent pro-inflammatory which produced by macrophages and their inflammatory mediated response is inhibited by IL-1RN and the acute phase protein[63,64]. The genes of this family have been reported to be highly polymorphic in which the polymorphisms modulate IL-1β production. The most studied SNPs of IL-1 gene family are IL-1β -511T/C, -31C/T and +3593C/T, in addition to the 86bp of VNTR in intron 2 of IL-1RN gene which has 5 different alleles (1/1, 1/4 and 1/3 and 1/2 and 2/2, allele1 with 6 repeats, allele2 with 4 repeats, allele3 with 5 repeats)[65]. IL-1β-31C/T is located in TATA box which reported to affect the DNA-protein interactions as it is associated with increased binding to transcription initiation factor. It was reported to be in strong linkage disequilibrium (LD) with IL-1β -511T/C. Those genetic polymorphisms were suggested to be involved in the hepatocarcinogenesis[66-68]. Chen *et al*[68] reported that the synergistic interaction between IL-1β -511T allele and -31C allele leads to increase of IL-1β production. Both alleles were reported to be associated with high level of IL-1β in the plasma of chronic HBV patients[69-71].

IL-1RN-allele2 was also reported to be linked to increased IL-1β production[72]. In the study of Chen *et al*[65] allele2 was found to be a risk factor for HBV-related HCC in the presence of IL-1β (-511CC and -31TT) genotypes. Nevertheless, both genotypes did not be risk factors for HCC in the absence of allele2 suggesting the synergistic effect of them on the production of IL-1β. The IL-1β -511C allele was found to be a risk factor while IL-1RN was not a risk factor for HBV-related HCC[73]. On the other hand, several studies found no association between IL-1β -511C allele and HBV-related HCC. Sexena *et al*[74] stressed on the importance of IL-1RN allele 1 and 2 as a risk factor for HCC. On contrary, Zhang *et al*[71] reported that allele 2 isn’t a risk factor for HBV-related HCC. In the study by Wang *et al*[75] IL-1β -31TT genotype and IL-1β -511/-31CT haplotype were found to be associated with an increased risk for HCV-related HCC and the IL-1RN VNTR polymorphism was not a risk factor. This is also demonstrated by Tanaka *et al*[76] as they found that IL-1β -511TT genotype was a possible risk factor in HCV-related HCC. Thus, some studies promote the role of IL-1β in HCC incidence as it is associated with high levels of IL-1β which reported to be determined genetically. In addition, IL-1β-31C/T and IL-1β-511T/C are suggested to be modulating factors of IL-1β production, therefore they may be candidate genetic factors in the liver hepatocarcinogenesis and they need to be further investigated to verify them as cofactors in hepatitis-related HCC.

***TNF-α gene polymorphisms***

TNF-α is a proinflammatory cytokine that affects the growth, differentiation, and survival of various cells. It is mainly produced by macrophages, in addition to other array of cells, including neutrophils, keratinocytes, mast cells, endothelial cells, neurons, NK cells, fibroblasts, T and B lymphocytes and tumor cells[77]. TNF-α has been reported to promote chronic inflammation-related carcinogenesis. TNF-α gene is located on chromosome 6p21.3 of the major histocompatibility complex (MHC) class III region. The most studied polymorphisms in TNF-α gene lies in the promoter region TNF-α (-1031T/C, -863C/A, -857C/T, -308G/A and -238G/A). These polymorphisms have been reported to modulate the production of TNF-α[2,78].

TNF-α-308G/A is considered a critical risk factor for liver carcinogenesis[79,80], but TNF-α-238G/A was found to have a passive role in HCC risk[81]. TNF-α-308GG genotype has been reported to be associated with a decrease of HCC incidence[82]. On the other hand, other studies reported higher risk of HCC in patients carrying TNF-α-308A allele[78]. Many studies reported the correlation between TNF-α promoter alleles as TNF-α-308A and TNF-α-238A and the different capacity levels of TNF-α production[83,84]. Additionally, it was reported that the TNF-α promoter alleles as TNF-α-308A and TNF-α-238A which were correlated with high TNF-α levels and the resolution of HBV infection, suggesting the protective roles of them[85,86]. In the meta-analysis study of Wei *et al*[87], they found that TNF-α (-308G/A, -238G/A, and -863C/A) polymorphisms are associated with the risk for HCC. On the other hand, -857C/T and -1031T/C polymorphisms weren’t associated with risk to HCC. In a meta analysis of shin *et al*[2] no single TNF-α polymorphisms (-1031 T>C, -863 C>A, -857 C>T, -308 G>A, and -238 G>A) are associated with HCC cases with HBV infection..

Haplotype studies also revealed some surprising results concerning the risk of HCC. The homozygous haplotype (CGG/CGG) of the TNF-α (-863A/C, -308G/A and -238G/A) was reported to be protective against HCC[88], while, TCGG haplotype of the TNF-α (-1031T/C, -863A/C, -308G/A and -238G/A) was associated with HCC[89]. Additionally, GGCCT haplotype of the TNF-α (-238G/A, -308G/A, -857C/T, -863A/C and -1031T/C) was reported to be associated HBV clearance[90]. Therefore, the haplotypes containing GG represent protection factors against HCC, while AG of -308G/A and -238G/A implies high risk for hepatitis-related HCC[91].

***IL-6 gene polymorphisms***

IL-6 is a pluripotent cytokine which is a central player in regulating several cellular processes as proliferation and differentiation in addition to its pivotal role in the acute phase response. It is also the control balance valve between proinflammatory and anti-inflammatory responses[92]. IL-6 is reputed to be the lost ring between the inflammation response and liver carcinogenesis[93] as IL-6 was reported to inhibit apoptosis and induce metastasis[1,41,94]. It has also been reported to be the main player at the first stage of the immune response, whereas IL-6 promotes the secretion of acute phase proteins and the proliferation of lymphocytes[95]. Moreover, IL-6 was found to be associated with liver fibrosis and cirrhosis[96]. Therefore, IL-6 is a chief player in the viral infection and the counteracting inflammatory response. IL-6 gene, located on chromosome 7p21 with 5kbp length, has five exons interspersed with four introns[97]. The most studied genetic polymorphisms in IL-6 gene lie in the promoter region (-597G/A, -572G/C, -174G/C, and -373A/T). These SNPs, which are in a strong linkage disequilibrium, has a heavy impact on the production capacity of IL-6 at the transcriptional level[1,62,98] and they have been reported to be associated with chronic hepatitis[27,93,99].

IL-6 -174G/C has been extensively studied; however, the results are still controversial concerning its function in hepatitis-related HCC. Nieters *et al*[100] study reported no association between IL-6-174G/C and the risk to HCC while a study by Ognjanovic *et al*[11] found that IL-6-174GG showed a great inclination to HCC risk. IL-6-174CC has been reported to coincide with low IL-6 levels, which is associated with protection against HCC in cirrhotic patients[101]. Another study reported that IL-6-174GG correlated with high levels of IL-6 while IL-6-174CC is correlated with low levels of Il-6 among HCC patients, which suggest the risk of HCC in G allele carriers[27,102]. IL-6 (-572G/C and -597G/A) were found to be not associated with hepatitis-related HCC[103]. In the meta-analysis of Chang *et al*[104], IL-6 (-572G/C, -597G/A and -174G/C) might not be significantly correlated to the progressive HBV to HCC[105]. On the other hand, IL-6 -572G/C was found to be associated with the risk of HBV-related HCC in a study on Korean population.

There is a great disparity in the correlation between IL-6 gene polymorphism and hepatitis-related HCC according to the surveyed literature.

**ANTI-INFLAMMATORY CYTOKINE GENE POLYMORPHISMS**

***IL- 10 gene polymorphisms***

IL-10, an immunosuppressor cytokine produced by macrophages, down regulates Th1 cytokines such as IL-1, IL-6 and TNFα[106,107] and it plays a role in the compromised host immune response during chronic viral infections[34,108]. Its production has been reported to be controlled at the genetic level[109]. IL-10 (-1082G/A, -819T/C and -592A/C) are the most studied SNPs of the IL-10 gene as they have been reported to have a deep impact on the production of IL-10 leading to different production capacities among individuals. That effect can be attributed to that IL-10 -1082A/G and -592A/C and their haplotypes mediate the expression of IL-10 by differences in the nuclear binding activity[110,111]. The reports suggested that -1082G allele and GCC haplotype were correlated with high expression of IL-10, however, ATA haplotype was correlated with lower expression levels of IL-10. On the contrary, other studies reported that IL-10GCC and AAGCC haplotype of IL-10 (-3575, -2763, -1082, -819, and -592) were correlated with lower expression levels of IL-10[112,113]. Therefore, there are conflicting results which may be attributed to ethnic variations and those studies were conducted in different populations. Several studies have reported the correlation between IL-10 gene promoter polymorphism and progression of HBV[114], HCV[115,116], chronic liver diseases[117,118] and hepatitis-related HCC [103,119,120]. On the other hand, other reports suggest no association between IL-10 gene promoter polymorphism and hepatitis[121].

***TGF- β1 gene polymorphisms***

TGF-β1, produced by many cell populations as T-cells and platelets, hepatic stellate cells (HSCs) and hepatocytes in the liver, is a pluripotent multifunctional cytokine involved in a plethora of cellular processes[122,123]. It regulates cell growth, differentiation and induces the fibrosis, though up regulation of collagen and extracellular matrix (ECM)[124,125]. Moreover, it has the ability to inhibit B-cells and T-cells in addition to its anti-inflammatory action by down regulation NK cells and Th1[86,126]. It normally inhibits cell growth, but in tumor cells, it promotes the progression of the tumor by suppressing the immune response[127-129]. TGF-β1 was reported to be a versatile player in the liver, whereas it is involved in many physiological processes[130] and many studies focused on the correlation between TGF-β1 and chronic liver diseases as liver fibrosis[131-133]. TGF-β1 gene, containing 7 exons separated by 6 introns, lies on chromosome 19q13.1-13.3. The production capacity of TGF-β1 has been reported to be genetically controlled[127,134,135]. Many genetic polymorphisms have been reported either in the coding or non-coding regions. The most studied polymorphisms were in both regions, whereas TGF-β1-988C/A, -800G/A, -509C/T and in an insertion/deletion at position 72 in the 5’UTR region of intron 4, in addition to +869T/C (Codon 10), +915G/C (Codon 25) in exon 1 and +788C/T (codon 263) in exon 5[136].

In the coding regions, the variations cause non-synonymous change in the amino acid sequence of the signal peptide. While codon 10 variation causes the exchange of leucine with proline, codon 25 causes the exchange of arginine with proline, and codon 263 variation causes the exchange of threonine with isoleucine[137,138] which lead to the formation of hydrophobic signal sequence and subsequently cause alternation in the export efficiency of the TGF-β1 pre-pro-protein through the endoplasmic reticulum. The correlations between chronic liver diseases and TGF-β1 gene polymorphisms have been studied extensively[119,131,139-141]. TGF-β1 (+869T/C and +915G/C) were reported to be effective SNPs[142,143] and TGF-β1 +869T allele was reported to be correlated with high levels of TGF-β1[137,138]. There are some other reports that found no association between +869T/C and TGF-β1 levels among hepatitis patients [119,139,144]. However, some studies reported the negative role of TGF-β1+869T/C in hepatitis infection [145,146], other studies reported the association between +869CC genotype and the reduced risk of HBV-related HCC[119,147].

TGF-β1-800G/A hasn’t been studied with hepatitis-related HCC but it was reported that TGF-β1-800A allele may reduce the binding affinity of cAMP-responsive element binding protein (CREB) and subsequently lower TGF-β1 levels. On the other hand, TGF-β1-509C/T has been studied with hepatitis-related HCC. It is reported that -509T allele correlates with high levels of TGF-β1 and high transcriptional activity more than -509C allele[148,149]. Moreover, Grainger *et al*[148] reported that TGF-β1-509TT genotype correlates with higher TGF-β1 levels than the genotypes -509CT or -509CC and this was attributed to that -509C/T lies within the consensus transcription factor binding site YY1 (Yin Yang 1) regulatory region[150]. While the genotype TGF-β1-509TT was reported in Ma *et al*[5] meta analysis to be associated with the risk for HCV-related HCC, the TGF-β1-509CC was reported to be associated with the risk for HBV-related HCC[140]. On the other hand, Wang *et al*[131] reported that TGF-β1-509C allele was associated with the progression of Liver cirrhosis and TGF-β1-509T allele wasn’t associated with the risk to HCC[131,151]. TGF-β1-509T allele was reported to be correlated with high levels of TGF-β1[152], while Qi *et al*[140] reported that TGF-β1-509C allele was correlated with high levels of TGF-β1 in HBV-related HCC. Controversially, some studies reported that the genotypes -509TT and -509CT were associated with reduced risk to HCC [85,140,153].

**REGULATORY TH1 CYTOKINES**

***IL- 18 gene polymorphism***

IL-18, mainly produced by the activated macrophages and kupffer cells[64], is a proinflammatory cytokine which has been reported to be involved in liver injury[41,154]. It is also reported that IL-18 mediates cellular immune response against viral infections[155,156]. It was reported to be up regulated during hepatitis infection and liver cirrhosis as well[157,158]. Therefore, it may be able to inhibit HBV and HCV replication. The antiviral activity of IL-18 was attributed to its ability to induce NK cells and T-cells to produce IFN-γ and IFN-α/β in the hepatic microenvironment so, IL-18 is frequently called IFN-γ-inducing factor[41,158,159]. IL-18 activates cellular immune response *via* Fas ligand and perforin-mediated T-cell and NK-cell cytotoxicity. Additional ly, it acts synergistically with IL-12 to induce Th1 polarization which up regulates the production of IFN-γ, IL-1, IL-6 and TNF-α in addition to its efforts to decrease IL-10 production[160-162] and it was found to promote chemokines production as IL-8. IL-18 was reported to mediate anti-tumor immune response and it may regress liver cancer, though cytotoxic T-cells and NK cells[163,164]. High levels of IL-18 were reported to be correlated with HCC[165-167].

IL-18 gene is located on chromosome 11q22.2–q22.3. The most studied SNPs in IL-18 gene are -607A/C and -137C/G which were reported to be in a strong LD[168]. These SNPs was reported to affect the expression levels of IL-18[169,170], as -137C allele disrupt H4TF-binding site and -607C/A disrupt cAMP responsive element binding site. Additionally, the haplotype AC was reported to be associated with reduced levels of IL-18[171,172]. IL-18 gene promoter polymorphisms were reported to be associated with HBV and HCV infections in addition to HCC[173-175]. In a recent study, -607AA genotype and -607A allele were reported to be protective among HBV patients[175]. Moreover, -607CC genotype and -607C allele were reported to be associated with increased risk to the progression of the infection to cirrhosis and HCC development[167], while -607AA genotype was associated with reduced risk to HCC progression[175,176]. On the contrary, it was found that IL-18 -607AA genotype is associated with risk to disease progression while IL-18 -137C allele was reported to be a protective allele[41,177]. On the other side, IL-18 -148G/C has also been studied in which IL-18-148C allele was found to be correlated with low levels of IL-18[178], which gives rise to the risk of HCC. These controversial assert that more studies needed to assess the precise role of IL-18 gene promoter polymorphism in the progression of HBV and HCV infections.

***IL- 16 gene polymorphisms***

IL-16 is a chemotactic proinflammatory cytokine produced mainly by the activated CD8+T-cells, mast cells and B-cells in addition to dendritic cells (DCs) and neural cells in addition to epithelial cells during inflammation[179,180]. It is involved in many cellular functions which is formerly known as a lymphocyte chemoattractant factor (LCF)[181]. It activates many immune cells as DCs, Monocytes, macrophages and T-cells, through binding to CD4[182,183]. It induces the production of Th1 cytokines as IL-1β, IL-6 and TNF-α by monocytes[184,185]. IL-16 also triggers a cellular mediated immune response against viral infections[180,186]. IL-16 is also able to upregulate CD25 and IL-4 during the course of viral infections[184,185]. On the other side, IL-16 was found to activate many cellular pathways as p56lck tyrosine kinase, the stress-activated protein kinase (SAPK), and the p38 mitogen-activated protein kinase (MAPK)[187,188]. Moreover, IL-16 is reported to play a role in carcinogenesis through activation of Signal transducer and activator of transcription(STAT3)[189]. All of these reports assert on the role in HBV and HCV infection in the liver carcinogenesis.

IL-16 gene is located on chromosome 15q26.3 with seven exons interrupted by six introns and it is transcribed into two versions lymphatic and neural IL-16[190,191]. SNPs of the IL-16 gene coding region was reported to affect IL-16 production and function as IL-16 (rs11556218T/G) in exon 6 which causes the exchange of asparagine with lysine, and IL-16 (rs4072111C/T) which leads to exchange of proline with serine in addition to IL-16 (rs4778889T/C) at the position of -295 in the gene promoter which reported to affect the transcriptional level of IL-16[192-195]. The studies on hepatitis-related HCC and IL-16 gene polymorphisms are so far scanty so there an urgent need for further studies. In a previous study, IL-16 (rs11556218T/G), IL-16 (rs4072111C/T) and IL-16 (rs4778889T/C) were studied in HBV patients and the data showed that genotypes IL-16 (rs11556218TG and GG) and allele IL-16 (rs11556218G) are associated with high risk of HBV-related HCC. In addition, they found that IL-16 (rs4072111TT) was also associated with high risk for HCC among HBV patients[20]. In another study, IL-16 (rs4778889CC) genotype was reported to be associated with the progression of HBV infection[196].

***IL-13 gene polymorphisms***

IL-13 is a pleiotropic Th2-derived cytokine which is involved in inducing apoptosis, B-cells and mast cell proliferation, and anti-inflammatory responses through inhibition of Th1 cytokines and chemokines as IL-8. The crucial roles of IL-13 have been studied in tumors as it was reported that IL-13 was over expressed in tumor tissues and targeting IL-13 in cancer may have a potent role in cancer immunotherapy[197,198].

IL-13 gene is located on chromosome 5q31 with four exons[199-201]. IL-13 gene polymorphisms were reported to affect the IL-13 levels as IL-13 -1112C/T, -1512A/C and -1024C/T, and in the coding region IL-13 +2044G/A (in which arginine is replaced by glycine) and IL-13 +130G/A. Moreover, it was found that -1024C/T may affect the binding of STAT transcription factors which profoundly affect the expression levels of IL-13 in the activated T-cells[202,203]. IL-13 gene polymorphisms have been scarcely studied in hepatitis-related HCC but in a recent study by Deng *et al*[201] two SNPs rs1800925C/T and rs20541G/A have been studied in HBV and HCC patients. They found a significant correlation between rs2054G/A and HBV-related HCC. Moreover, they found that GA genotype was significantly associated with reduced risk for HCC, in addition to the haplotype TG which has a protective role against HCC and the haplotype CA which has an increased risk to liver carcinogenesis. Therefore, more studies are needed to assess the role of IL-13 gene polymorphisms in the hepatitis-related HCC as no conclusion can be addressed from the scrape of studied on IL-13 and HCC.

**IFNS GENES POLYMORPHISMS**

Viral infections as hepatitis viruses induce the production of IFNs through the innate immune response. There are three types of IFNs, Type I (IFN-α/β), Type II (IFN-γ) and Type III (IFN-λ, IL-28A/B and IL-29) which induce IFN-stimulated genes (ISGs) during the infection course[204]. ISGs are involved in antiviral immune response, inflammation and apoptosis[205]. IFN-γ is Th1 antiviral cytokine and it mediates inflammation and it was found to be associated with hepatitis-related HCC[206,207]. It was reported to be anti-fibrogenic cytokine, however, it is suggested to be involved in liver fibrosis[43,207]. The imbalance between Th1 and Th2 responses may be mediated by the genetic polymorphisms of both IFN-γ and IL-10 genes which affect the outcome of the hepatitis infection[123,208].

IFN-γ gene polymorphisms were studied primarily in hepatitis infections and HCC. IFN-γ+874T/A (rs2430561), +2109C/A and the microsatellite CAn repeat were the most studied polymorphisms[9,209]. IFN-γ+874T allele and +874TT genotype were reported to be in complete LD with CA12 repeat[210]. IFN-γ gene polymorphisms were found to affect the IFN-γ levels in which +874T allele correlates with high expression levels of IFN-γ[211]. On the other side, +874T allele was reported to be associated with the risk of progression of hepatitis infection, in addition, both homozygous and heterozygous genotypes IFN-γ (+874TT and +874TA) was reported to be associated with the risk to liver cirrhosis and HCC incidence among HCV patients[121,212]. On the contrary, +874A allele and +874AA genotype were reported to be associated with the risk of HBV-related HCC incidence[100]. The meta-analysis of Zhou *et al*[213,214] pointed that the IFN-γ +874A/T polymorphism might correlate to HBV related HCC risk. Other reports suggest no correlation between IFN-γ +874T/A and chronic liver diseases. The meta –analysis of sun *et al*[216] indicated that there is no significant correlation between elevated risk of HBV-infected HCC and IFN-γ +874A/T polymorphism[215]. Gene polymorphisms in Type III IFNs were mainly focused on the response to IFN therapy, as there is not many specific studies focus on the effect of this polymorphism on the chronic hepatitis infections and its progression to HCC.

**OTHER CYTOKINE GENE POLYMORPHISMS**

***IL-2 gene polymorphisms***

IL-2 is a cytokine produced by the activated CD4+ and CD8+T-cells and DCs. IL-2 plays a central role in the immune response and its regulation as it stimulates the proliferation and differentiation of NKs. Moreover, it stimulates the production of TGF-α and IFN-γ[13,217]. IL-2 has been reported to be a suspected player in the inhibition of the carcinogenesis and the immune response against tumors, therefore it was suggested to be a candidate for cancer immunotherapy[217]. IL-2 gene has five exons with five introns and it is located on chromosome 4q26-q27. IL-2 gene polymorphisms have been found to affect the levels of secreted IL-2 and those polymorphisms have been reported to be associated with a wide range of cancers[218-221]. HCC risk and IL-2 gene polymorphisms has been scarcely studied. IL-2+114T/G has been studied by Peng *et al*[14], they documented the increased association between IL-2+114GG genotype, IL-2+114G allele and HBV-related HCC[13,222].

***IL-27 gene polymorphisms***

IL-27 is a cytokine of the IL-12 family. IL-27 is secreted after APCs activation, which lead the induction of Th1 response and IFN-γ secretion. Recent reports suggested that IL-27 induce CTLs response which impair cancer progression and induce IFN-γ inducible protein-10 (IP-10) which impair the angiogenesis process[223-225]. IL-27 gene consists of five exons and it is located on chromosome 16p11. There are few studies on the IL-27 gene polymorphism and the hepatitis-related HCC risk. Ali *et al*[226] reported that IL-27 (−964A/G, 2905T/G and 4730T/C) gene may not contribute to HBV infection. Peng *et al*[14] Studied the association between HBV-related HCC and IL-27-954A/G and IL-27 2905T/G, they found that there is no association between the hepatitis-related HCC and IL-27 gene polymorphism.

***IL-4 gene polymorphisms***

IL-4 is chiefly Th2 pleiotropic cytokine which is produced by a variety of cells as mast cells, basophils and eosinophils. IL-4 gene is located on chromosome 5q31 and the gene was reported to have polymorphisms as 2590C/T (rs2243250), 2979G/T (rs2227284), 233C/T (rs2070874), and +3437C/G (rs2227282) [227,228]. Few studies have been conducted on the role of IL-4 gene polymorphisms in the HCC. In meta –analysis of Lu *et al*[227], IL-4 gene polymorphisms may have a role in hepatitis-related HCC as 2590C/T and 233C/T which are linked with increased risk for HBV-related HCC and IL-4-590C/T which has been described to be associated with HBV progression to cirrhosis[4] and HBV-related HCC[228].

***IL-12 gene polymorphisms***

IL-12 is Th1 cytokine produced by APCs. It activates NKs and CTLs in addition to the induction of IFN-γ production. The critical role of IL-12 in Th1 immune response suggest that IL-12 may have a role in the immune response against cancer cells[7,13]. IL-12 gene polymorphisms are still unknown for its role in hepatitis-related HCC. While some studies reported that IL12B rs3212227A/C and IL12A rs2243115 T/G have been reported to have no role in HBV-related HCC[7,100], Sexena *et al*[4] reported that IL12B rs3212227A/C has a suspicious role in HCC, which may have attributed to the ethnic variations. On the other hand, Liu *et al*[7] reported that IL12A rs568408 G/A may be a genetic element in HBV-related HCC.

**CONCLUSION**

Several association studies have been performed on cytokine gene polymorphism and hepatitis related HCC. They vary considerably between different populations studied. Due to differences in sample size, the ethnicity of the study population, the disease stage, and even the genotyping method, it is difficult to conclude definite associations based on the available data. Moreover, a thorough understanding of host-virus interactions, which may or may not end up with HCC is still in progress. Several important biological and clinical pertinent questions and their correlation with documented cytokine gene polymorphisms still need to be addressed. This is of maximum importance not only for a better understanding of liver malignancy but also for global viral hepatitis immunobiology. Thus, an integrated work, including larger set of individual s in various sets of populations is required.

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**Figure 1 Multiple etiologies of** **hepatocellular carcinoma.** HCC: Hepatocellular carcinoma.

**Table 1 Associations between cytokine gene polymorphisms and hepatocellular carcinoma**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Cytokine Gene | Polymorphism | Risk factor  (Reference) | Protective factor  (Reference) | No association with HCC (Reference) |
| IL-1β | -511T/C | Hirankarn *et al*[73] 2006  Wang *et al*[75] 2003  Tanaka *et al*[76] 2003 |  |  |
| -31C/T | Wang *et al*[75] 2003 |  |  |
| IL-1RN | Intron 286 bp  Allele 2 VNTR | Chen *et al*[65] 2005  Saxena *et al*[74] 2013 | Zhang *et al*[71] 2004 | Wang *et al*[75] 2003 |
| TNF-α | -1031T/C |  |  | Wei *et al*[87] 2011 |
| -863C/A | Wei *et al*[87] 2011 |  |  |
| -857C/T |  |  | Wei *et al*[87] 2011 |
| -308G/A | Akkız *et al*[78] 2009  Shin *et al*[2] 2015  Jeng *et al*[79] 2009  Talaat *et al*[80] 2012  Wei *et al*[87] 201 1 | Wilson *et al*[71] 1992  Yang *et al*[70] 2009 |  |
| -238G/A | Wei *et al*[87] 2011 |  |  |
| IL-6 | -597G/A |  |  | Tang *et al*[1] 2014  Saxena *et al*[103] 2014  Chang *et al*[104] 2015 |
| -572G/C | Park *et al*[105] 2003 |  | Tang *et al*[1] 2014  Saxena *et al*[103] 2014  Chang *et al*[104] 2015 |
| -174G/C | Ognjanovic *et al*[11] 2009 | Falleti *et al*[101] 2010  Terry *et al*[102]2000  Giannitrapani *et al*[27] 2011 | Nieters *et al*[100] 2005 |
| IL-10 | -1082G/A | Migita *et al*[119] 2005  Tseng *et al*[120] 2006  Saxena *et al*[103] 2014 |  | Bouzgarrou *et al*[121] 2009 |
| -819T/C | Migita *et al*[119] 2005  Tseng *et al*[120]2006  Saxena *et al*[103] 2014 |  | Bouzgarrou *et al*[121] 2009 |
| TGF-β1 | -509C/T | Grainger *et al*[148]1999  Ma *et al*[5] 2015 | Zhong-heng *et al*[153] 2012  Qi *et al*[140] 2009 | Wang *et al*[131] 2005  Shi *et al*[151] 2012 |
| +869T/C |  | Ben-Ari *et al*[145] 2003  Ribeiro *et al*[46] 2007  Migita *et al*[119] 2005  Xin *et al*[147] 2012 |  |
| IL-18 | -607A/C | Karra *et al*[175] 2015  Bouzgarrou *et al*[167] 2008 | Zhang *et al*[177] 2005  Hirankarn *et al*[73] 2006 |  |
| -137C/G | Zhang *et al*[177] 2005  Hirankarn *et al*[73] 2006 |  |  |
| 148G/C | Kim *et al*[178] 2009 |  |  |
| IL-16 | rs11556218T/G | Li *et al*[20] 2011 |  |  |
| rs4072111C/T | Li *et al*[20] 2011 |  |  |
| rs4778889 | Romani *et al*[196] 2014 |  |  |
| IL-13 | rs20541G/A | Deng *et al*[201] 2015 |  |  |
| IFN-γ | +874T/A | Nieters *et al*[100] 2005 | Dai *et al*[212] 2006  Bouzgarrou *et al*[121] 2009 | Barrett *et al*[213] 2003  Abbas *et al*[214] 2005 |
| IL-2 | +114 T/G | Peng *et al*[13] 2014  Wang *et al*[222] 2015 |  |  |
| IL-27 | -954A/G  2905T/G |  |  | Peng *et al*[14] 2013 |
| IL-4 | 2590C/T  233C/T | Lu *et al*[227] 2014  Wu *et al*[228] 2015 |  |  |
| IL-12A/  IL-12B | rs3212227A/C | Saxena *et al*[4] 2014b |  |  |
| rs2243115T/G |  |  | Nieters *et al*[100] 2005  Liu *et al*[7] 2011 |
| rs568408G/A | Liu *et al*[7] 2011 |  |  |
| IL-21 | rs13143866  rs2221903 | Yao *et al*[228] 2015 |  |  |
| rs907715 |  | Yao *et al*[228] 2015 |  |
| IL-17A/IL-17F | rs4711998  rs2275913  rs763780 |  | Xi *et al*[229] 2015 |  |