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World J Gastroenterol 2006 February 7; 12(5): 776-779
World Journal of Gastroenterology ISSN 1007-9327

RAPID COMMUNICATION

Interleukin-1β gene polymorphism associated with hepatocellular carcinoma in hepatitis B virus infection

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Received: 2005-05-10 Accepted: 2005-08-26

Abstract

AIM: To examine the effect of interleukin-1-beta (IL-1β) promoter region C-511T and IL-1 receptor antagonist (IL-1RN) polymorphism among the patients with chronic hepatitis B virus (HBV) infection (HCC and non-HCC).

METHODS: Genomic DNA from 136 Thai patients with chronic HBV infection (HCC = 46 and non-HCC = 90) and 152 healthy individuals was genotyped for IL-1β gene polymorphism (-511) using polymerase chain reaction with sequence specific primers (PCR-SSP). The variable number of tandem repeats (VNTR) of IL-1RN gene was assessed by a PCR-based assay. The association between these genes and status of the disease was evaluated by χ^2 test.

RESULTS: IL-1B-511 genotype C/C was found to be significantly different in patients with HCC when compared with healthy individuals ($P = 0.036$, OR = 2.29, 95%CI = 1.05-4.97) and patients without HCC (P=0.036, OR = 2.52, 95%CI=1.05-6.04). Analysis of allele frequencies of IL-1B-511 showed that IL-1B-511 C allele was also significantly increased in patients with HCC, compared to that in healthy control ($P = 0.033$, OR = 1.72, 95%CI=1.04-2.84). However, no significant association in IL-1RN gene was found between the two groups.

CONCLUSION: IL-1B-511C allele, which may be associated with high IL-1B production in the liver, is a genetic marker for the development of HCC in chronic hepatitis B patients in Thai population.

Key words: Interleukin-1 beta gene; Polymorphism; Hepatocellular carcinoma; Hepatitis B

Hirankarn N, Kimkong I, Kummee P, Tangkijvanich P, Poovorawan Y. Interleukin-1β gene polymorphism associated with hepatocellular carcinoma in hepatitis B virus infection. *World J Gastroenterol* 2006; 12(5): 776-779

http://www.wjgnet.com/1007-9327/12/776.asp

INTRODUCTION

Hepatitis B virus (HBV) is the most common cause of acute and chronic liver disease worldwide, especially in Asia and Africa. It has been estimated that more than 350 million people worldwide, representing more than 5% of world population are carriers of HBV infection[1,2]. Approximately 250 000 deaths occur each year resulting from fulminant hepatic failure, cirrhosis, and hepatocellular carcinoma (HCC)[3]. Family studies in China provide some evidence that the host genetic factors influence viral persistence, as a higher concordance rate has been found for HBeAg persistence in identical twins compared with non-identical twins[4]. Thus, it is conceivable that genetic difference may affect the different outcomes of patients with HBV infection. Several genetic studies on the hosts have reported that human leukocyte antigen (HLA) genes[5-7] and various cytokine genes (TNF-α, IFN-γ, IL-12, IL-18, TGF-β, IL-10, IL-4) are associated with HBV susceptibility and/or HBV persistence or disease severity[8-11].

Interleukin-1 (IL-1) is a proinflammatory cytokine with multiple biological effects[12]. The IL-1 gene family (including IL-1A, IL-1B, and IL-1RN) on chromosome 2q13-21 encodes three proteins, which comprise the agonists IL-1α, IL-1β, and their naturally occurring inhibitor, IL-1 receptor antagonist (IL-1RN)[12,13]. Recently, allele 2 of IL-1RN intron 2 has been reported as a resistant marker of HBV infection, suggesting the role of IL-1 polymorphisms in the pathogenesis of developing chronic hepatitis B[14]. This allele is associated with enhanced IL-1β production *in vitro*[15] and *in vivo*[16]. Therefore, Zhang *et al*[14] hypothesized that high production of IL-1β may help

increase the production of other cytokines such as IL-2, IL-6, and TNF-α and trigger the complex immunological processes to eliminate the virus. Interestingly, besides its major role as a proinflammatory cytokine, IL-1β has been implicated as an important factor for tumor growth[17-19]. Several independent lines of evidence have also suggested that genetic polymorphisms within IL-1β gene are associated with gastric cancer and HCC in HCV infection[20-22].

The aim of the present study was to determine the genotype and allele frequencies of IL-1B-511 and IL-1RN VNTR polymorphisms among the Thai patients with chronic HBV infection (HCC and non-HCC) and healthy individuals to assess whether these genes are involved in chronic HBV susceptibility and/or HCC development.

MATERIALS AND METHODS

Subjects

One hundred and thirty-six Thai patients with chronic HBV infection were recruited into this study from Chulalongkorn Memorial Hospital. The diagnosis of chronic hepatitis B was established by seropositivity for HBsAg over a 6-month period and did not have any other type of liver diseases such as chronic hepatitis C or alcoholic liver disease. In addition, all the patients had elevated serum ALT and AST levels. Patients with chronic HBV infection were further divided into two groups: without ($n=90$) and with HCC ($n=46$) according to the absence or presence of concurrent HCC. Diagnosis of HCC was based on histopathology and/or a combination of mass lesion in the liver from hepatic imaging and serum alpha fetoprotein level > 400 ng/mL. Moreover, 152 ethnically and geographically matched controls from healthy blood donors of the Thai Red Cross Society were recruited.

Genotyping for SNPs of IL-1B and IL-1RN genes

Molecular genetic analysis was performed on genomic DNA obtained from peripheral blood leukocytes using standard salting-out method as previously described[23]. SNP at position -511 of IL-1B was genotyped by polymerase chain reaction (PCR) with sequence specific primer (PCR-SSP) (F-5' CTCATCTGGCATTGATCTGG-3' and R-5' GGTGCTGTTCTCTGCCTCGA-3')[24]. The PCR conditions were established as previously described[25].

The VNTR of IL-1RN gene was assessed by a PCR-based assay. Oligonucleotides F-5' CTCAGCAACACTCCTAT-3' and R-5' TCCTGGTCTGCAGGTAA-3' flanking this region were used as primers[24]. The PCR conditions were an initial denaturation at 94 °C for 2 min, followed by 35 cycles at 94 °C for 20, at 59 °C for 50 s, at 72 °C for 20 s, and a final extension at 72 °C for 7 min. Each allele was identified according to its size[24].

Statistical analysis

The association between these genes and disease status was evaluated by the statcalc from Epi info version 6 program[26] to calculate the odds ratio (OR) and 95% confidence interval (CI), Yates' corrected χ^2 and associated P values. $P<0.05$ was considered statistically significant. The groups were tested for conformity to the Hardy-Weinberg equilibrium by 2×2 χ^2 test comparing observed and expected numbers.

Table 1 IL-1β and IL-1RN polymorphisms in patients with HBV and healthy controls

Polymorphisms		Patients with HBV: Without HCC $n=90$ (%)	Patients with HBV: With HCC $n=46$ (%)	Healthy controls $n=152$ (%)
IL-1B-511				
	Genotype frequencies			
	C/C	17 (18.89)	17 (36.96)[1,2]	31 (20.39)
	C/T	51 (56.67)	21 (45.65)	79 (51.97)
	T/T	22 (24.44)	8 (17.39)	42 (27.63)
	Allele frequencies			
	C	85 (47.22)	55 (59.78)[3]	141 (46.38)
	T	95 (52.78)	37 (40.22)	163 (53.62)
IL-1RN				
	Genotype frequencies			
	1/1	74 (82.22)	38 (82.61)	121 (79.61)
	1/2	15 (16.67)	8 (17.39)	29 (19.08)
	2/2	1 (1.11)	0	1 (0.66)
	1/4	0	0	1 (0.66)
	Allele frequencies			
	1	163 (90.56)	84 (91.30)	272 (89.47)
	2	17 (9.44)	8 (8.70)	31 (10.20)
	4	0	0	1 (0.33)

[1]$P=0.036$ *vs* healthy controls, OR (95%CI) = 2.29 (1.05–4.97); [2]$P=0.036$ *vs* patients without HCC, OR (95%CI) = 2.52 (1.05–6.04); [3]$P=0.033$ *vs* healthy controls, OR (95%CI) = 1.72 (1.04–2.84).

RESULTS

The genotype and allele frequencies of IL-1B and IL-1RN in healthy control subjects and patients with chronic hepatitis B, including patients with and without HCC are shown in Table 1. All the three groups were in Hardy-Weinberg equilibrium with no significant χ^2 values compared to the observed and expected genotype frequencies of each of the tested polymorphisms. The heterozygous C/T of IL-1B was the most common genotype in all the three groups (51.97% in healthy controls, 45.65% in patients with HCC and 56.67% in patients without HCC). The homozygous T/T was the second most common genotype in healthy controls (27.63%) and patients without HCC (24.44%), followed by the C/C genotype that was found in 20.39% of healthy controls and in 18.89% of patients without HCC, respectively. In contrast to these two groups, the C/C was the second most common genotype in patients with HCC (36.96%), followed by the T/T genotype (17.39%). Comparison of IL-1B-511 genotype revealed that IL-1B-511 C/C genotype was significantly increased in patients with HCC compared to that in healthy controls ($P=0.036$, OR = 2.29, 95%CI = 1.05-4.97) and patients without HCC ($P=0.036$, OR = 2.52, 95%CI = 1.05-6.04). Analysis of allele frequencies of IL-1B-511 showed

that IL-1B-511 C allele was also significantly increased in patients with HCC, compared to that in the healthy controls ($P = 0.033$, OR = 1.72, 95%CI = 1.04-2.84). The effect of IL-1B-511 C allele was similar to autosomal recessive mode of inheritance. The presence of two C alleles (CC) was required to increase the likelihood of HCC development.

Four genotypes of IL-1RN (1/1, 1/2, 2/2, 1/4) were found in this study. The IL-1RN 1/1 genotype was the most common genotype in all the three groups (79.61% in healthy controls, 82.61% in patients with HCC and 82.22% in patients without HCC), followed by 1/2 genotype that was 19.08% in healthy controls, 17.39% in patients with HCC and 16.67% in patients without HCC, respectively. The 2/2 genotype was 0.66% in healthy control and 1.11% in patients without HCC, whereas the 1/4 genotype was 0.66% in healthy controls. There were no significant differences in genotype or allele frequencies of IL-1RN between patients with chronic hepatitis B and healthy controls.

DISCUSSION

The association between the development of chronic hepatitis B and the polymorphisms of IL-1B gene (-511C/T) and IL-1RN gene (VNTR at intron 2) was not observed in this study. However, the -511C allele of IL-1B gene was identified as a genetic marker for the development of HCC in patients with chronic HBV infection. The hypothesis regarding IL-1 genetic polymorphism and hepatocarcinogenesis is based on the assumption that carriers of these genotypes are associated with increased levels of IL-1B in the liver in response to HBV infection and hepatocyte damage that may finally lead to the development of HCC. This hypothesis is supported by the observation that IL-1B level is increased in the liver tissue surrounding the tumor tissue[27]. IL-1B is a proinflammatory cytokine as well as a tumor growth factor. There are several lines of evidence that support its role in tumor growth development. First, IL-1B can increase the production of prostaglandin E2 and hepatocyte growth factor[17]. Second, IL-1B can induce angiogenesis which is an important step in promoting tumor growth by either upregulating COX-2 or inducing nitric oxide[19] and vascular endothelial growth factor (VEGF)[28]. Third, IL-1B can also attenuate interferon-induced antiviral activity and STAT1 activation in the liver[29].

However, the IL-1B polymorphism in the promoter area in association with cancer remains controversial. Briefly, a number of studies mostly in the Caucasian population support that -511T in linkage disequilibrium with -31C is a risk haplotype for the development of gastric cancer[30-34]. There are more conflicting data regarding the effect of IL-1B-511/-31 haplotype on the risk of gastric cancer and HCV-related HCC in Asian population, while some studies support the result from the Caucasian group[16,21,35] and a number of studies reported that -511C/-31T is a risk haplotype for the development of cancer[22,36-40]. Interestingly, functional studies of IL-1B genotype seem to support that -511C/-31T haplotype is associated with high-production of IL-1B. First, the IL-1B -31 polymorphism involves a TATA sequence in the promoter and the -31T allele is associated with a five-fold elevated binding activity with the transcription initiation factor[30,31]. Second, mucosal IL-1B level is higher than IL-1B-31T level in *H pylori*-infected gastric cancer patients[40]. Although IL-1B -511T/-31C is associated with high level of IL-1B in the plasma[41], it is likely that gene expression in each organ is differently regulated and the assessment of IL-1B level in targeted organ is more reliable. The functional study in liver tissue is also required for the better understanding of the role of IL-1B genotype in chronic hepatitis and HCC development.

In conclusion, IL-1B-511C allele which may be associated with the high IL-1B production in the liver is a genetic marker for the development of HCC in chronic hepatitis B patients in Thai population.

ACKNOWLEDGMENTS

The authors greatly appreciate the participants and all the staff members who participated in chronic HBV study at King Chulalongkorn Memorial Hospital. Also, we would like to thank the National Blood Center for the recruitment of healthy controls and collection of research materials.

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S- Editor Wang XL and Guo SY **L- Editor** Elsevier HK **E- Editor** Cao L