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IFN-γ (+874) and not *TNF-α* (−308) is associated with HBV-HCC risk in India

Roli Saxena · Yogesh Kumar Chawla · Indu Verma · Jyotdeep Kaur

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Abstract Tumor necrosis factor (TNF)-α and interferon (IFN)-γ, the pro-inflammatory Th1 cytokines are the indispensable coordinators of the inflammatory responses involved in hepatitis B virus (HBV) pathogenesis. This study attempted to evaluate any possible association among *TNF-α* (−308G>A) and *IFN-γ* (+874T/A) genotypes, the spontaneous blood and mRNA levels and expression of their major signal transducers, namely STAT1 and NF-κB with hepatitis B virus-induced hepatocellular carcinoma (HCC) susceptibility in India. For this, 398 subjects (146 controls, 68 inactive-HBV-carriers, 64 chronic-active HBV patients, 61 HBV-cirrhotics, and 59 HBV-HCC subjects) were enrolled. Polymerase chain reaction–restriction fragment length polymorphism, allele-specific PCR, enzyme-linked immunosorbent assay, reverse transcriptase-PCR, and Western blot analysis were done for assessing polymorphism, blood levels, mRNA expression, and protein expression of signal transducers, respectively, of TNF-α and IFN-γ. The study revealed no significant association of *TNF-α* (−308) GA genotype, while a significant negative association of *IFN-γ* (+874) TA and AA genotypes, in HBV-HCC risk. Moreover, blood levels of TNF-α were significantly elevated as disease progresses to HCC, while IFN-γ levels were raised in HCC patients only. Besides, *IFN-γ* mRNA levels were significantly elevated in cirrhotics, with no change observed in *TNF-α* transcript levels. Moreover, NF-κB expression also consistently increased during HCC progression. These observations suggest a vital negative association of *IFN-γ* (+874) with HBV-HCC risk, with no significant association evident in *TNF-α* (−308). However, the TNF-α and IFN-γ levels markedly increased in HCC development.

Keywords TNF-α · IFN-γ · HBV · HCC

R. Saxena · I. Verma · J. Kaur (✉)
Department of Biochemistry, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India
e-mail: jyotdeep2001@yahoo.co.in

Y. K. Chawla
Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

Introduction

Hepatitis B virus (HBV) infection is the primary causative factor of hepatocellular carcinoma (HCC), infecting about 2 billion people, with more than 350 million people suffering from chronic HBV infection worldwide [1]. Studies have revealed that cytokines play an important role in host defense against HBV infection, directly by inhibiting the viral replication and indirectly by determining the predominant pattern of the host immune response. Moreover, the host immune response is regulated by the genetic background, including variations associated with single-nucleotide polymorphisms (SNPs) within the promoter region of cytokine genes. These genetic mutations in certain cytokine genes can result in the altered levels of the respective protein production, which modulates the outcome of chronic viral hepatitis. Consistent to this, in our previous study, we observed a significant positive association of interleukin-1 receptor antagonist (*IL-1RN*) 1/2 genotype with HBV-HCC development, among controls and carriers. Besides, its 2/2 genotype acted as a potential risk factor for hepatitis and subsequent cirrhosis development, among the same groups. Moreover, proinflammatory IL-1B levels significantly and steadily elevated with the disease progression to HCC, as compared to controls in Indian population [2]. Further data from the animal models