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ORIGINAL ARTICLE

Interleukin-12B +1188A/C polymorphism contributes to increased hepatocellular carcinoma susceptibility: Evidence from a meta-analysis

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Summary
Background: Interleukin-12 (IL-12) is a multifunctional cytokine that induces interferon (IFN)-γ secretion and plays an important role in antitumor immunity. The IL-12B +1188A/C polymorphism was found to correlate with a decreased cytokine production and/or activity, which may lead to increased susceptibility to cancers including hepatocellular carcinoma (HCC). Previous epidemiological studies investigating the association between IL-12B +1188A/C polymorphism and HCC risk reported inconsistent results. We performed a meta-analysis to derive a precise estimation of the association.
Methods: All studies published up to July 2014 on the association between IL-12B +1188A/C polymorphism and HCC risk were identified by searching electronic databases including PubMed, Embase, Cochrane library, and Chinese Biomedical Literature database (CBM). Data were extracted by two independent authors and the odds ratios (ORs) together with corresponding 95% confidence intervals (CIs) were used to assess the association between IL-12B +1188A/C polymorphism and HCC risk.
Results: Five studies with 1864 cases and 2077 controls were included in the meta-analysis. We observed that the IL-12B +1188A/C polymorphism was significantly correlated with increased HCC risk when all studies were pooled into the meta-analysis (CC vs. AA: OR = 1.306, 95% CI

Abbreviations: HCC, Hepatocellular carcinoma; IL-12, Interleukin-12; HWE, Hardy—Weinberg equilibrium; SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval.

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1.063—1.606, $P = 0.011$; AC vs. AA: OR = 1.193, 95% CI 1.014—1.405, $P = 0.034$; CC + AC vs. AA: OR = 1.260, 95% CI 1.098—1.445, $P = 0.001$). In subgroup analyses by ethnicity, source of control, and study quality, significant increased HCC risk was found in Asians, hospital-based studies, and high quality studies.

Conclusions: The present meta-analysis suggests that the IL-12B +1188A/C polymorphism is a low-penetrant risk factor for HCC development, especially among Asians. Further large and well-designed studies are needed to confirm this association.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers and the third leading cause of cancer-related deaths worldwide [1,2]. HCC shows substantial geographical variation, with a high prevalence rate in Eastern and South-eastern Asia, sub-Saharan Africa, and Melanesia [1]. Although the management of HCC has significantly improved during the last few years, the precise molecular mechanism involved in hepatic carcinogenesis remains unclear [3]. Previous epidemiological studies have established that chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), liver cirrhosis, habitual alcohol abuse, and exposure to aflatoxin B1 were major risk factors for HCC development [4—6]. However, most subjects with these known environmental risk factors never develop HCC and many HCC cases occur among individuals without these risk factors, suggesting that other factors such as genetic factor also play an important role in hepatic carcinogenesis.

Interleukin-12 (IL-12) is an important pro-inflammatory heterodimeric cytokine composed of two disulfide-linked subunits (p. 35 and p. 40) encoded by the IL-12A and IL-12B genes, respectively [7,8]. The cytokine plays a central role in promoting Th1 immune response and inducing the differentiation of natural killer cells and $CD4^+$ T cells toward IFN-γ-secreting cells [9,10]. In addition, IL-12 has the potent property of angiogenesis inhibition through induction of antiangiogenic factors including IFN-γ-inducible protein-10 (IP-10) and Mig [9]. Due to the immunomodulating and antiangiogenic activities, IL-12 has been regarded as one of the most feasible cytokines to be applied to immunotherapy of neoplasms. Clinical studies showed that there was a correlation between the levels of serum IL-12 and disease severity in patients with gastric cancer [11]. Meanwhile, in animal model systems, IL-12 gene transfected into tumor cells enhanced both specific and nonspecific antitumor immune responses, which indicated if IL-12 gene were transferred into dendritic cells, it should induce highly effective antitumor immune responses [12,13]. The gene encoding IL-12B is located on chromosome 5q31—33 in humans. It was reported that a single nucleotide change from ±1188A to ±1188 C in the 3′ untranslated region (UTR) of the IL-12B gene (rs3212227) influences IL-12 production or protein expression [14,15]. The wild type ±1188AA genotype was associated with relatively higher expression of IL-12 cytokine than the AC and the CC genotypes in EBV-transformed human cell lines [16]. Moreover, IL-12B mRNA from the ±1188A allele was more stable than that from the ±1188 C allele [17].

Based on the important biological function of IL-12B +1188A/C polymorphism, several molecular epidemiological studies have been performed to investigate the effect of IL-12B +1188A/C polymorphism on HCC risk, but the results were inconsistent [7,18—21]. Some studies reported that the IL-12B +1188A/C polymorphism was associated with an increased susceptibility to HCC [20,21]. However, other studies have failed to confirm such an association [7,18,19]. For genetic association studies investigating candidate polymorphisms and disease risk, sample size is an important influence factor for study accuracy [22]. Small sample size might have insufficient power to detect a true association of modest effect, especially for the complex multifactorial diseases such as HCC [3]. While pooling data from all eligible studies by meta-analysis has the advantage of increasing statistical power and reducing random error and could obtain precise estimates for some potential genetic associations [23]. Therefore, in this study, we conducted a quantitative meta-analysis including all eligible studies to investigate the association between IL-12B +1188A/C polymorphism and HCC risk.

Materials and methods

Literature search

A comprehensive literature search in Pubmed, Embase, Cochrane library, and CBM was conducted using the following combined keywords.

''IL-12'', ''interleukin-12'', ''polymorphism'', ''genetics'', ''liver cancer'', ''hepatocellular carcinoma'' and ''HCC''. The latest search was done in July 2014. There was no restriction on sample size, time period, population, language, or type of report. Additional studies were identified by a hand search of the references of original studies. We also used the ''Related Articles'' function of each research article in PubMed to search potentially relevant articles. If more than one article was published using the same dataset, only the study with the largest sample size was included.

Inclusion criteria

Studies included in the meta-analysis were required to meet the following criteria: