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ORIGINAL ARTICLE

Autoimmune hepatitis association with single nucleotide polymorphism of interleukin-2, but not interferon-gamma

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KEYWORDS
Autoimmune hepatitis;
Cytokine;
Interleukin-2;
Interferon-gamma;
Single nucleotide polymorphism

Summary
Background: Autoimmune hepatitis (AIH) is a chronic inflammation in hepatocellular tissues associated with circulating autoantibodies. Imbalance in T-cells population and dysregulation in several cytokine profiles has been implicated in pathogenesis of AIH. This study was performed to assess potential association of AIH with interleukin-2 (IL-2) and interferon-gamma (IFN-γ) genes single nucleotide polymorphisms (SNPs).
Methods: Fifty-six patients with AIH and 139 healthy individuals were enrolled in this study. *IL-2* and *IFN-γ* typing was performed, using polymerase chain reaction with sequence-specific primers (PCR-SSP) assay. The frequencies of alleles, genotypes and haplotypes in AIH patients were compared to healthy controls.

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Results: *IL-2* T allele at position +166 (rs2069763) showed significant higher frequency in AIH group (36%), compared to the controls (21%) (OR = 2.06; 95% CI, 1.24—3.43, *P*-value < 0.01). The frequency of *IL-2* TT genotype at +166 position was also associated with AIH (OR = 18.68, 95% CI 3.74—126.04, *P*-value < 0.01). G/T alleles of *IL-2* at −330 (rs2069762) and A/T alleles on UTR +5644 position at *IFN-γ* and their subsequent haplotypes, did not show significant association with AIH.
Conclusions: This study identified *IL-2* T allele at +166 position and TT genotype as susceptibility gene in AIH which would provide better understandings into the mechanisms of AIH and potential immune modulation therapies.
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Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease, characterized by liver transaminase elevation, interface hepatitis histologic pattern, high serum gammaglobulins and presence of circulating autoantibodies toward liver antigens, while any other description for liver cell injury is ruled out [1,2]. The disease presents with female predominance and is considered rare in childhood, though it may occur in very young children [3]. The presence of specific antibodies such as antinuclear antibodies (ANA), smooth muscle antibody (SMA) and antibodies to liver/kidney microsome type 1 (anti-LKM1), are important for confirming the diagnosis of AIH [4]. Based on disease occurrence and development, AIH can be categorized into two types: type 1, presence of ANA and/or SMA, and type 2, presence of anti-LKM1 [5]. The main process involving the failure of self-tolerance in AIH is not yet thoroughly understood, however the pathogenic effects of Th1 cells and the protective contributions of Th2 cells have been known as a hallmark feature in most autoimmune based diseases [6]. Under normal physiological conditions, Th1 and Th2 cells, along with their associated cytokines, can cross-regulate each other [7]. Therefore, a change in balance and function of these groups of immune cells can trigger an autoimmune response. In pathogenesis of AIH, Th1/Th2 imbalanced responses in the liver have long been proposed to correlate with extended inflammation and subsequent liver fibrosis [8].

Th1 cells are principally responsible for cellular immunity against intracellular antigens and are characterized by their secretion of interferon gamma (IFN-γ) and interleukin-2 (IL-2) and tumor necrosis factor-beta (TNF-β), while, Th2 cells are characterized by the production of IL-4, IL-5 and IL-13 [9].

IL-2 as a pro-inflammatory cytokine which enhances the function of natural killer cells and stimulate the immune system as a therapeutic agent, effectively participates in the activation of T-cells to produce TNF-α and IFN-γ [10].

Since cytokines have crucial functions in development, differentiation and regulation of immune cells, dysregulation of cytokines production or action is thought to have a central role in development of autoimmune process in AIH [11].

As the presence of cytokine gene polymorphisms may affect the cytokine levels in AIH and to clear our view of the pathogenesis, this study was designed to observe single nucleotide polymorphisms (SNPs) of the pro-inflammatory cytokines IL-2 and IFN-γ genes and their probable association with AIH in pediatric patients.

Patients and methods

Subjects

The study group was consisted of 56 AIH patients and 139 healthy controls, from Iranian ethnic group. Patients were selected by simple random selection method from the population of AIH-diagnosed patients referred to the Children's Medical Center, the main referral center for pediatric patients in Tehran, Iran. Healthy controls were randomly selected from blood donors at Iranian Blood Transfusion Organization.

Informed written consent was obtained from all participants; and study was approved by Ethical Committee of Tehran University of Medical Sciences.

DNA sampling and analysis

DNA was extracted from whole blood sample by a simple Salting Out method. Cytokine typing was performed by polymerase chain reaction with sequence-specific primers (PCR-SSP) assay and cytokine gene polymorphism kit was obtained from Heidelberg University, Heidelberg, Germany.

A thermal cycler Techne Flexigene apparatus was used to carry out the amplification (Rosche, Cambridge, UK). PCR products were visualized by 2% agarose gel and after exposure to a UV transilluminator, a picture was taken for interpretation and documentation. For each primer, one control sample, either a β-globin gene with 89-bp or a CRP gene with 440-bp was utilized. IL-2 and IFN-γ genes and their polymorphisms were studied: *IL-2* G/T allele polymorphisms at two positions −330 (rs2069762) and +166 (rs2069763) and *IFN-γ* A/T alleles on UTR +5644 position.

Statistical analysis

Allelic and genotype frequencies were counted in patients and controls by direct gene counting. Frequencies in patients and controls were compared using chi-square test. The *P*-values and 95% confidence intervals (CI) were calculated for odds ratio (OR) of alleles and genotypes. *P*-value of less than 0.05 was considered as level of significance.

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