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Distribution of HLA Tissue Groups in Patients with Gastric Cancer

Mide Kanserli Hastalarda HLA Doku Grupları Dağılımı

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Abstract

Objective: Gastric cancer is an important disease that is seen all over the world and that threats public health. At the same time, gastric cancer is a heterogeneous disorder with multifactorial etiologies. Recent studies have shown a significant association between HLA antigens and gastric adenocarcinoma. The aim of the present study was to determine the distribution of HLA class I (HLA-A, B and C) and class II (HLA-DR, DQ and DP) antigens in Turkish patients with gastric adenocarcinoma.

Materials and Methods: HLA alleles or HLA haplotypes associated with gastric cancer were established in the Turkish population using PSR-SSP analysis in 71 unrelated patients with gastric cancer and in 82 unrelated healthy controls. The statistical significance of differences in allele frequencies between patients and controls was measured by the Chi-square test with Yates's correction.

Results: The study revealed that the HLA-Cw5 antigen is more prevalent in patients with gastric cancer (p=0.042) and that the HLA-DRB1*15 antigen is more prevelent in the control group (p=0.021).

Conclusion: It is probable that HLA-Cw5 is a risk factor for gastric cancer whereas HLA-DRB1*15 plays a protective role for this disease. The results show that different loci on HLA may control resistance to or tendency for any disease in different societies; each society should determine its own tissue group.

Key Words: Gastric cancer, HLA antigens, HLA-Cw5, HLA-DRB1*15

Özet

Amaç: Mide kanseri tüm dünyada sık görülen ve toplum sağlığını tehdit eden önemli bir hastalıktır. Aynı zamanda mide kanseri multifaktöriyel etyolojiye sahip heterojen bir hastalıktır. Son zamanlarda yapılan çalışmalar HLA antijenleri ile mide adenokanserleri arasında önemli bir ilişki olduğunu gösterdi. Bu çalışmanın amacı, mide adenokanserli Türk hastalarda HLA sınıf I (HLA-A, B ve C) ve sınıf II (HLA-DR, DQ ve DP) antijenlerinlerinin dağılımını belirlemekti.

Gereç ve Yöntem: 82 akraba olmayan sağlıklı kontrollerde ve 71 akraba olmayan mide kanserli hastalarda PSR-SSP analizi kullanılarak Türk populasyonunda HLA allelleri veya HLA haplotipleri ile mide kanseri arasındaki ilişki belirlendi. Hasta ve kontroller arasında alel sıklığındaki istatistiksel anlamlı farklılıklar Yates düzeltmeli ki-kare testi ile hesaplandı.

Bulgular: Çalışma, kontrol grubunda ise HLA-DRB1*15 antijeninin (p=0.021), mide kanserli hastalarda ise HLA-Cw5'in (p=0.042) istatistiksel olarak anlamlı olacağını ortaya çıkardı.

Sonuç: Muhtemel ki, HLA-Cw5 mide kanseri için mide kanseri için bir risk faktörü, HLA-DRB1*15 ise mide kanserine karşı koruyucu rol oynamaktadır. HLA üzerindeki farklı lokusların mide kanserine direnci veya yatkınlığı kontrol edebileceği kanısına varıldı. HLA antijenleri herhangi bir hastalıkta farklı toplumlarda farklı şekilde eksprese olacağından her toplum kendi doku grubunu belirlemelidir.

Anahtar Kelimeler: HLA antijenleri, HLA-Cw5, HLA-DRB1*15, Mide kanseri

Introduction

Gastric adenocarcinoma is one of the most frequently occurring malignant diseases in the world, particularly in Japan [1, 2]. The control of gastric cancer at advanced stages still remains difficult, despite various treatments such as gastrectomy with extensive lymphadenectomy [3] and surgery combined with chemotherapy [4]. Therefore, further exploration of etiologies and biological features of gastric cancer is mandatory to improve its diagnosis and management. Although a large number of risk factors have been associated with gastric adenocarcinoma, a definite etiology for the majority of gastric adenocarcinomas is still unknown [5]. Certain associations have been demonstrated, but a well-delineated working model of gastric cancer development has not been formulated. This disease is a complex trait that involves multiple factors, including environmental and genetic interactions [6]. However, it has been unclear whether the genetic factors are correlated with the progression of gastric cancer. Because of the pivotal roles played by the products of the MHC genes in the immune system, it is not surprising that these genes have an important influence on immune disorders [7]. HLA antigens are cell surface proteins that bind to the antigen-specific T-cell receptor, forming an important signaling event for the cell and inducing or suppressing the immune response. There are two classes of HLA genes: HLA class I (HLA-A) and HLA class II (HLA-DR, HLA-DQ and HLA-DP). All of these genes are highly polymorphic, with variant alleles of putative functional significance [8]. Class I molecules are composed of an MHC-encoded heavy chain associated with $ß_2$-microglubulin. Present on virtually all nucleated cells and platelets, they present antigens to $CD8^+$ T cells, mainly of the cytotoxic phenotype. Class II molecules, also composed of two chains, coded for by A and B genes, respectively, are present on B cells, dendritic cells, activated T cells, and macrophages. They present peptides to $CD4^+$ T cells, mainly of the "helper" function. An important "business end" of both class I and II molecules is the peptide binding groove that presents the (processed) antigen to the T cell [9]. It is suggested that the HLA system or the MHC may play some role in the survival of cancer patients. Additionally, there have been some reports that certain HLA types are associated with the

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prognosis of malignant dissease, e.g., HLA-B8 antigen for Hodgkin's disease [10], HLA-A9 antigen for acute lymphoblastic leukemia [11], and HLA-DRB1*0901 antigen for esophageal carcinoma [12].

Recently, it was reported that HLA class I and class II genes are associated with gastric cancer in different populations [13-16]. In the Turkish population, no report has described associations between HLA and gastric cancer by using polymerase chain reaction (PCR) techniques. The present study was directed at DNA typing of HLA class I and class II genes and haplotype analysis of patients and controls to elucidate the HLA alleles or HLA haplotypes associated with gastric cancer in the Turkish population.

Materials and Methods

Subjects

Seventy-one patients with gastric adenocarcinoma (23 women and 48 men) were studied. Their ages ranged from 29 to 87 years old, with a mean age of 58.97±12.92 at the time of diagnosis. All patients were referred for investigation to the Department of Internal Medicine, the Research Hospital of Ataturk University, Erzurum, Turkey. The criteria for the diagnosis of gastric carcinoma were based on endoscopic findings and histopathological conformation of the tissue obtained by endoscopic biopsy.

The control group consisted of 82 individuals (31 women and 51 men) of Turkish origin. Their ages ranged from 28 to 74 years old, with a mean age of 48.91±10.32, and they were selected from among healthy bone marrow or kidney donors. These studies were performed according to the principles of the Declaration of Helsinki.

DNA extraction and HLA genotyping

EDTA blood was used to prepare DNA from peripheral blood cells using the Sigma GenElute Kit according to the manufacturer's instructions.

Low-resolution typing for the HLA-A,-B,-C and HLA-DR/DQ was performed by means of the PCR-SSP (sequence-specific primers) method using SSP HLA class I generic DNA Typing Tray, Lot 002 and using SSP HLA class II generic DNA Typing Tray, Lot 004 (One Lambda, Canoga Park, CA, USA) according to the manufacturer's instructions.

Statistical analysis

The statistical significance of differences in allele frequencies between patients and controls was measured by the Chi-square test with Yates's correction. The level of significance was $p<0.05$. The degree of association was calculated using the OR (odds ratio). All statistical calculations were performed using the SPSS 11.5 program for Windows software.

Results

The frequencies of HLA class I (HLA-A, B and C) and class II (HLA-DR, DQ and DP) antigens were analyzed in 71 patients with gastric cancer and 82 unrelated healthy controls. Tables 1 and 2 show the frequencies of HLA-C and HLA-DRB1 alleles.

As shown in Table 1, a positive association between HLA-C alleles and gastric cancer was observed for HLA-C*5 (phenotype frequency in the patients versus that in the controls, 9.85% vs. 1.21%, OR 8.859, P = 0.042, 95% confidence interval 1.063-73.866). However, the HLA-DRB1*15 allele was less frequently found in patients with gastric cancer than controls (5.63% vs. 19.51%, OR 0.246, P=0.021, 95% confidence interval 0.078-0.776) (Table 2).

No statistically significant difference in the frequencies of HLA-A, -B and -DQ alleles was found between patients with gastric cancer and the normal controls (data not shown).

Discussion

Although environmental factors play a major role in the development of gastric cancer, different host factors may also influence patients' susceptibility to gastric cancer. In this study, we evaluated class I and class II HLA in a Turkish population admitted to the Research Hospital of Ataturk University of Erzurum. Although this study is probably the first study of HLA typing for HLA class I and HLA class II regions of gastric cancer in the Turkish population using the DNA typing method, we found statistically significant associations

Table 1. Frequencies of the HLA-C alleles in Turkish gastric cancer patients and controls

HLA	Patients	Controls	P	OR	CI (%95)
Cw*1	2 (2.81%)	3 (3.65)	1.000	0.763	0.124-4.702
Cw*2	4 (5.63%)	8 (9.75%)	0.519	0.552	0.159-1.918
Cw*3	9 (12.67%)	9 (10.97%)	0.941	1.177	0.440-3.150
Cw*4	32 (45.07%)	34 (41.46%)	0.775	1.158	0.610-2.200
Cw*5	7 (9.85%)	1 (1.21%)	0.042	8.859	1.063-73.866
Cw*6	8 (11.26 %)	18 (21.95%)	0.124	0.451	0.183-1.113
Cw*7	17 (23.94%)	24 (29.26%)	0.576	0.761	0.369-1.568
Cw*8	3 (4.22 %)	2 (2.43%)	0.870	1.765	0.286-10.872
Cw*9	0	0	-	-	-
Cw*10	0	0	-	-	-
Cw*17	1 (1.40%)	1 (1.21%)	1.000	1.157	0.071-18.843

Table 2. Frequencies of the HLA-DRB1 alleles in Turkish gastric cancer patients and controls

HLA	Patients	Controls	P	OR	CI (%95)
DRB1*01	2 (2.81%)	7 (8.53%)	0.248	0.311	0.062-1.546
DRB1*04	20 (28.16%)	29 (35.36%)	0.437	0.717	0.360-1.425
DRB1*07	12 (16.90%)	10 (12.19%)	0.551	1.464	0.591-3.627
DRB1*08	0	1 (1.21%)	1.000	-	-
DRB1*09	1 (1.40%)	0	0.942	-	-
DRB1*10	0	3 (3.65%)	0.297	-	-
DRB1*11	27 (38.02%)	28 (34.14%)	0.741	1.183	0.611-2.294
DRB1*12	1 (1.40%)	3 (3.65%)	0.717	0.376	0.038-3.700
DRB1*13	25 (35.21%)	19 (23.17%)	0.144	1.802	0.888-3.656
DRB1*14	7 (9.85%)	7 (8.53%)	0.999	1.172	0.390-3.519
DRB1*15	4 (5.63%)	16 (19.51%)	0.021	0.246	0.078-0.776
DRB1*16	7 (9.85%)	5 (6.09%)	0.574	1.684	0.510-5.562
DRB1*17	14 (19.71%)	20 (24.39%)	0.618	0.761	0.352-1.648
DRB1*18	1 (1.40%)	0	0.942	-	-

for HLA-Cw*5 in patients with gastric cancer and for HLA-DRB1*15 in controls. Our results present evidence that HLA-Cw*5 and HLA-DRB1*15 play different roles in the development of gastric cancer; HLA-Cw*5 may be predispositional (OR=8.859, P=0.042), whereas HLA-DRB1*15 may be protective (OR=0.246, P=0.021). Furthermore, for the first time, we report that these two genotypes may be effective in Turkish patients with gastric cancer.

Several studies have reported an association of gastric cancer with HLA in different ethnic groups [14-19]. Lee et al. [16] and Magnusson et al. [17] have reported that HLA-DQB1*0301 and HLA-DRB1*1601 are the principal susceptibility alleles for gastric cancer in different populations of caucasians. Wu MS et al. have determined that HLA-DQB1*0602 may be predispositional and that HLA-DQB1* may be protective for gastric cancer in the Taiwanese population [14]. Ohmori et al. have found slightly different frequencies of HLA-DRB1*0101, DQA1*0104 and DQB1*05031 between gastric cancer patients and controls among Japanese patients [18]. Moreover, the positive association of HLA-DR3 in gastric cancer patients from Andhra Pradesh, India was reported by Jayanthi [19]. On the other hand, many studies have determined only a poor association or no significant association between HLA and gastric cancer [20, 21]. We also have demonstrated that there are no significant differences between frequencies of HLA-A, -B, -DQ and gastric cancer in the Turkish population (data not shown).

The mechanism of association between the HLA-Cw*5 and gastric adenocarcinoma was not clear. Probable different explanations may be caused in part by differences in methodology of HLA typing and ethnic background. The genotype aspect of HLA may vary among different ethnic populations. On the other hand, many studies have revealed that HLA alleles associate with the development of gastric cancer and infection by Helicobacter pylori [15-17, 22].

In conclusion, in this study, there was a high prevalence of HLA-Cw5 antigen in patients with gastric cancer, and HLA-DRB1*15 antigen was was found to be highly associated with the control group. It is probable that HLA-Cw5 is a risk factor for gastric cancer, whereas HLA-DRB1*15 plays a protective role for this disease. The results show that different loci on HLA may control resistance to or tendency for any disease in different societies; each society should determine its own tissue group. We believe that further evaluations of the genetic risk of gastric adenocarcinoma are necessary.

Conflict interest statement: The authors declare that they have no conflict of interest to the publication of this article.

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