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CHARACTERIZATION OF MINOR HISTOCOMPATIBILITY ANTIGENS AND THEIR ROLE IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: SINGLE CENTER EXPERIENCE IN TURKIYE

MİNÖR DOKU UYGUNLUK ANTİJENLERİNİN KARAKTERİZASYONU VE ALLOJENİK HEMATOPOETİK KÖK HÜCRE NAKLİNDEKİ ROLÜ: TÜRKİYE'DE TEK MERKEZ DENEYİMİ

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ABSTRACT

Objective: The minor histocompatibility antigens (mHAgs) are the epitopes composed of polymorphic essential peptides, and they create T cell response limited to a variety of class I and II HLA alleles. In recent years, there has been extensive research on the distribution of polymorphic regions in different populations. The incompatibility between recipient and donor, may initiate a strong cellular immune response despite HLA full-matched transplantation. We determined the frequency of minor antigens among hematopoietic stem cell transplantation (HSCT) recipients who underwent transplantation for various hematological diseases.
Material and Methods: The study population included 200 healthy individuals, 150 HLA-typed patients who were candidates for allogeneic HSCT, and 20 recipients/donors with allogeneic transplants. Minor HAgs identified by using polymerase chain reaction (PCR) and sequence specific primer (SSP) methods.
Results: When the allele frequencies and genotypes of the patients were compared with those of the healthy group, the difference was not significant regarding to immunogenic or non-immunogenic allele frequencies. The individuals with immunogenic homozygous H allele (HH genotype) were a few more in the healthy group, and this difference proved to be statistically significant. In fact, our study population Insufficient though the number was, based on the data received from 20 transplant patients and donors, GvHD was observed in 5 of 10 patients who had minor incompatibility.
Conclusion: We assume that determining the mHAg frequencies in the healthy Turkish population and in patients with malignant hematological diseases will likely contribute to the understanding of the immune response.
Keywords: Minor Histocompatibility Antigens, Allogeneic Hematopoietic Stem Cell Transplantation, Graft-versus-host disease.

ÖZ

Amaç: Minör doku uygunluk antijenleri (mHAg), polimorfik esansiyel peptitlerden oluşan epitoplar olup sınıf I ve II insan lökosit antijeni (HLA) alel çeşitleri ile sınırlı olan bir T hücresi yanıtı ortaya çıkarırlar. Son yıllarda, farklı popülasyonlarda polimorfik bölgelerin dağılımı hakkında kapsamlı araştırmalar yapılmıştır. Alıcı ve verici arasındaki mHAg uyumsuzluğu, HLA tam uyumlu transplantasyona rağmen güçlü bir hücresel immün yanıtı başlatabilir. Çalışmamızda çeşitli hematolojik hastalıklar nedeniyle allojeneik hematopoietik kök hücre nakli (AHKN) yapılan hastalarda mHAg sıklığının belirlenmesi amaçlanmıştır.
Gereç ve Yöntem: Çalışma popülasyonu 200 sağlıklı bireyi, AHKN adayları olarak HLA'sı tiplendirilmiş olan 150 hastayı ve 20 AHKN alıcısı/donörünü içermektedir. mHAg'lar, polimeraz zincir reaksiyonu (PZR) ve diziye özgü primer (SSP) yöntemleri kullanılarak belirlendi.
Bulgular: Hastaların alel frekansları ve genotipleri sağlıklı grup ile karşılaştırıldığında, immünojenik veya immünojenik olmayan alel frekansları açısından fark anlamlı değildi. Sağlıklı grupta immünojenik homozigot H aleli (HH genotipi) olan bireyler daha azdı ve bu fark istatistiksel olarak anlamlıydı. Çalışma popülasyonumuz küçük olmasına rağmen, 20 transplant hastasından ve donöründen alınan verilere göre, 10 hastanın %50'sinin minör uyumsuzluk kaynaklı Graft versus host hastalığı (GVHH) olduğu gözlendi.
Sonuç: Sağlıklı Türk popülasyonunda ve malign hematolojik hastalığı olan hastalarda mHAg frekanslarının belirlenmesinin immün yanıtın anlaşılmasına katkı sağlayacağını düşünmekteyiz.
Anahtar Kelimeler: Minör Doku Uygunluk Antijenleri, Allojenik Hematopoietik Kök Hücre Nakli, Graft-versus-host hastalığı

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (AHSCT) is a potentially curative therapy for many malignant and nonmalignant hematologic diseases. Recipient donor Human Leukocyte Antigen (HLA) mismatch for major histocompatibility antigens encoded on the short arm of chromosome 6 is the most important risk factor for graft-versus-host disease (GVHD) (1, 2). Recipient donor HLA mismatch for minor histocompatibility antigens (mHAgs) encoded by sex-linked or autosomal loci also contributes to the risk of GVHD (3-6). The impact of mismatches of mHAgs on the development of GVHD is the best studied in pairs of siblings who are HLA identical. A mHAg is of clinical interest only if it is immunogenic and when it has a moderately increased frequency distribution in the population. The HA-1 antigen fulfills two of the conditions required for the induction of GVHD: it is immunogenic and has a moderate (69%) phenotypic frequency. The tissue distribution of mHAgs might explain its correlation with GVHD. The H-Y and HA-3 antigens occur on hematopoietic and nonhematopoietic cells. HA-1 and HA-2 are expressed only on cells derived from hematopoietic precursors, including dendritic cells and epidermal Langerhans' cells (7,8). Since the chief function of the latter cells is to present antigens to T cells, they are plausible candidates for eliciting a graft-versus-host reaction from donor T cells. HA-1 and HA-2 are encoded by biallelic loci, along with immunogenic variants, HA-1H and HA-2V, which are expressed along with HLA-A2 antigens and induce strong HLA-A2-restricted alloreactive T-cell responses, and non-immunogenic counterparts, HA-1R and HA-2M, which represent functional null alleles that are poorly presented by HLA class I molecules. HA-1 and HA-2 are potential targets of selective graft-versus-leukemia and graft-versus-tumor reactivity after HSCT. It was recently reported that mismatches for two HLA*02:01-restricted mHAgs: HA-1 and HA-8 increased the incidence of severe acute GVHD (aGVHD) when the donor had A/A genotype in rs231775 of CTLA4 gene (9). The information of mHA genotyping is useful for selection of therapeutic targets in the post-transplant immunotherapy.

In this study, we aimed to determine the frequency of mHAs in the healthy population and to find out the relationship between mHAs and hematopoietic malignant diseases. In addition we investigated whether or not mismatching of mHAs contributes to acute GVHD (grade II or higher) in recipients of HLA-identical bone marrow.

MATERIAL AND METHODS

We have 200 healthy people, 150 patients with various malignant hematologic disorders, 20 recipients of HSCT and their sibling donors, who were HLA identical, at Istanbul University, Istanbul Faculty of Medicine, Adult Bone Marrow Transplantation Unit. The donor–recipient pairs were selected on the basis of the presence of HLA-A2, which is the HLA restriction molecule for mHAg HA-1. The recipients underwent HSCT for acute lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, or aplastic anemia. None of the recipients received T cell depleted bone marrow. As prophylaxis against GVHD, they received cyclosporine and short course methotrexate. In the assessment of GVHD, a grade of 0 or I was considered to indicate the absence of such disease, and a grade of II or higher its presence.

The project was approved by the Ethical Committee of the Istanbul Faculty of Medicine (2019/983).

Blood samples were obtained from the patients and their sibling donors before HSCT. The search for and selection of an HLA-identical sibling donor were based on HLA typing for the HLA-A, B, and DR antigens of the patients' families. HA-1 allele polymerase chain reaction (PCR) and sequence specific primer (SSP) methods were employed (PCR-SSP kit, One Lambda Inc). The domains described by two alleles of HA-1 can be seen in Table 1. The amplified PCR products were analyzed through 2% gel electrophoresis and were visualized in UV transilluminator following ethidium bromide staining.

Table 1: Primer Recognition Sites

Alleles	5' Recognition Sites	3' Recognition Sites	Size
HA-1H (Histidine)	345ACACT349	500CTGCA504	190bp
HA-1R (Arginin)	345ACACT349	500TTGCG504	190bp

Evaluation and Interpretation of the Data

The mHA alleles were tested for Hardy–Weinberg equilibrium. was tested. The Fisher's Exact test and the Chi Square test were conducted through SPSS program. The results were evaluated in terms of allele frequencies, Odds ratio, 95 % Confidence Interval, and p value.

RESULTS

We typed 20 pairs of HSCT donors and recipients who were HLA identical for HLA-A2. The results were then evaluated to determine whether they were correlated with the development of GVHD after HSCT. Allelic variant distribution was similar between recipients and donors whereas frequencies for RR, HH and HR genotypes were found as 35%, 10% and 55% respectively (Table 2). Ten patients were mHAg mismatched and one of them developed acute GVHD. Among 200 healthy individuals 45.7% had H allele and 54.2% the R allele matching Hardy-Weinberg Equilibrium (HWE) (Table 3). Upon allelic variant distribution, genotype frequencies were as follows; RR with 26.5%, HH with 8% and HR with 55.5%. The allelic frequency for H allele and R allele was 43.3%, and 56.6% respectively in the study group encompassing the cases with malignant hematological diseases (Table 3). The genotype frequencies of the healthy group and the patients can be seen in Figure 1. HH genotype were found to be higher frequency in the healthy group,

Table 2: The HA1 genotypes and GVHD conditions of the recipients and donors

Control No:	Sex Recipient/ Donor	aGVHD	cGVHD	Minor HA1 Recipient	Minor HA1 Donor
1	E/K	-	-	HR	HR
2	E/E	+	-	HR	HR
3	E/E	-	-	RR	RR
4	E/E	-	-	HH	HR
5	E/E	Early ex		HR	HR
6	E/K	-	Ex-not assessed	RR	HR
7	K/E	-	Ex- not assessed	RR	RR
8	E/E	+	+	HR	RR
9	E/E	-	-	HR	RR
10	K/K	-	-	RR	RR
11	E/K	+	Ex- not assessed	RR	HH
12	E/E	+	+	RR	HR
13	E/E	+	+	HR	HR
14	K/K	-	Recurrence	RR	HR
15	K/K	+	+	HH	RR
16	E/E	-	-	HR	RR
17	K/E	-	+	HR	HR
18	K/E	-	-	HR	HR
19	K/K	-	+	HR	HH
20	E/K	+	Ex- not assessed	HR	HR

Table 3: The HA1 allele frequencies of the healthy and patient groups

mHAg allele	Healthy Group (n:400) (n / %)	Patients Group (n:300) (n / %)
HA1-H	183 / 45.7	130 / 43.3
HA1-R	217 / 54.2	170 / 56.6

compared with the patients (11.7%-18% $p \leq 0.05$, 95%CI=0.289-1.023). The HR genotype was a little more in the patient group, no statistical significance was observed (65.3%-55.5% p=0.06).

DISCUSSION

Previously mHAgs were identified through in vitro proliferation of specific cytotoxic T lymphocytes (CTL) in patients who developed GVHD and then cloning these cells. Since 1998, when DNA based methods were first used, PCR-Restriction fragment length polymorphism (RFLP) and allele specific primers as well as PCR amplification methods have come into use (10-12). mHAgs are polymorphic in structure, and they are immunogenic for T cells, thus capable of initiating reactions related to the graft. Early studies on this issue included the presence of H-Y-related CTL and immune reactions through mHAgs in patients who received hematopoietic stem cell transplant (HSCT) from HLA compatible siblings. Goulmy and colleagues studied 5 mHAgs that were not related to the gender chromosome and showed that the HA-1 difference between HLA compatible recipient and donor had an effect on the development of II-IV grade aGVHD (12). Although it is quite difficult to distinguish GVHD from GVL/T (graft and leukemia/tumor), regulation of GVL effect is one of the main problems in allogeneic.

While stem cell transplantation suppresses GVHD, it is necessary to simultaneously stimulate GVL/T.

Accordingly, it may be of use to stimulate the CTLs against mAHgs like HA-1 (13). Donor T cells, held responsible for the anti-leukemic effect of donor leukocyte infusion performed on patients with recurrent leukemia after stem cell transplant, identify the HA-1 and HA-2 minor antigens in malign cells and become reactive. Donor based T cells are capable of eliminating hematological malignancies by specifically focusing on the minor antigens on the hematopoietic cells (14-16)

One important goal of our study was to determine the allele and genotype frequencies of the healthy population. In control group, the HA-1H allele frequency was 45.7%, and the HA-1R allele frequency was 54.2%, being in the healthy group. In the study conducted by Kotzampasaki and colleagues in Greece, 49 healthy bone marrow donors had the same alleles in frequencies of 29% and 70% respectively (14). A research conducted by Goulmy and colleagues studied 2262 subjects from 6 different ethnic groups in 16 countries in 5 different continents by making 10 different minor antigen genotype classifications. They found that the HA-1H and HA-1R were 47.6 % and 52.4 % respectively in East Asian populations; they were found to be 47.8 % and 52.2 % in African Americans, and 35.9 % and 64.1 % in Caucasian (14). As this study suggests, HA-1 antigen genotypes frequencies vary in different races. Some of the differences in this study have a geographical basis, whereas others are distributed randomly. In the future, the importance of these population studies will be understood with respect to potential clinical practices of minor H antigens as an immunotherapeutic tool after HSCT. In HLA-matched unrelated transplants, the application of adaptive cellular or vaccination treatments specific to the Minor H antigen based on ethnicity will enhance the T cell-related GvT response.

The allele frequencies and genotypes of 150 patients with a variety of hematological malignancies were compared with those of the healthy group, and it was found that there was no significant difference between the two groups either in immunogenic or in non-immunogenic allele frequencies. The individuals having immunogenic homozygous H allele (HH genotype) in their genotype frequencies were a few more in the healthy group, and this difference proved to be statistically significant. Although those having the immunogenic heterozygote H allele (HR genotype) were a few more in the patient group, no sta-

tistical significance was observed. The HA-1H allele frequency was found to be 37.5% in HSCT recipients and donors. Terlizzi and colleagues conducted a study on 200 healthy individuals in northern Italy and found that the HA-1H and HA-1R allele frequencies were 29.3% and 70.7%. The same study revealed that 100 hundred patients with hematological malignancies and solid tumors had similar allele frequencies, and that there was no relationship between the frequencies and occurrence of cancer (7). mHAgs play a central role in both GVL and GVHD. Their discovery and characterization are crucial in developing strategies to improve HSCT outcomes (17).

It is known that recipient-donor minor antigen mismatch in bone marrow transplantations reduces the chance of survival after transplantation and increases acute or chronic GVHD (cGVHD). In this study, there was minor antigen incompatibility in 10 patients (10%) and acute/chronic GVHD in 5 patients. It is known that in HLA compatible HSCT series, aGVHD of 19% to 66% is observed (8, 18-19). As far as the 20 transplant recipients and donors are concerned, though the number is low, the finding of GVHD in 50% of 10 patients with minor incompatibility is consistent with other studies in the literature (20-22).

HA-2 (rs61739531) is expressed in cells of hematopoietic origin 71 where there is evidence for GVL in AML with low risk of GVHD. Similarly, other ubiquitously expressed mHAgs are associated with GVL in chronic myelogenous leukemia without evidence of GVHD, suggesting complex alloreactivities from antigen processing, presentation, and costimulation (23).

Minor HAgs arise from the fraction of self-peptides presented conventionally on MHC molecules that happen to be allelically variant (6). Their antigenicity is revealed in transplantation settings because such variant peptides are perceived as foreign to a host's T cells. With the advances in genome wide sequencing and T cell-epitope identification technologies, the number of molecularly identified mHAgs has increased exponentially (24-26). Immunodominant mHAgs have attracted attention as immunotherapeutic targets for hematologic malignancies (10-12).

In conclusion, the uses of mHAg identification include the understanding of immune response against mHAgs, detection of the GVHD risk, recognition of the GVL effect likelihood, selection of the most suitable donor, and determination of the likelihood of adaptive immunotherapy in malignant hematological diseases.

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