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Original scientific paper

CHARACTERISATION OF B KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTOR GENES AND TELOMERIC AND CENTROMERIC MOTIFS IN HEMATOPOIETIC STEM CELL TRANSPLANTATION DONORS IN VOJVODINA, SERBIA

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The outcome of HSCT is strongly influenced by the genetic similarity or identity in the HLA genes that affects the incidence of graft-versus-host disease (GvHD). Successful allogeneic HSCT, however, depends also on T-cell mediated graft-versus-leukemia (GvL) effect, in which donor-derived T cells and natural killer (NK) cells kill these malignant cells in the patient, therefore playing a crucial role in relapse prevention. The aim of this study was to make the predictive analysis of the structure and distribution of B KIR alleles and centromeric and telomeric KIR genotypes in HSCT donors in Vojvodina with regard to their contribution to protection from relapse. A total of 124 first-degree relatives of patients with hematological malignancies were examined for the presence or absence of 15 KIR genes by using of PCR-SSO technique with Luminex xMap technology. The percentage of individuals carrying each KIR gene, centromeric and telomeric KIR haplotypes and genotypes was determined by direct counting. Sixty two percent of the HSCT donors in Vojvodina carry A KIR haplotype, while nearly 38% carry B KIR

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haplotype. The distribution of B KIR genes showed that among 124 studied HSCT donors, 31(25%) do not carry none of the KIR genes belonging to B group, 71.77% of donors have two or more B KIR genes, 61.29% of them carry KIR 2DL2 and 2DS2 or more B KIR genes. The analysis of centromeric and telomeric KIR genotypes, showed that Cen-A1/Tel-A1 genotype had a highest frequency of 51.47% and Cen-B2/Tel-B1 the lowest frequency of 1.30%. The usage of donor KIR B gene content and centromeric and telomeric KIR gene structure could be used in development of a simple algorithm to identify donors who will provide the most protection against the relapse in related HSC transplants.

Key words: B KIR gene content, KIR motifs

INTRODUCTION

Natural killer (NK) cells, which comprise 10–15% of all circulating lymphocytes, act as central components of the innate immune response, providing immediate defense against infectious agents and cancer. They also contribute to placentation and the success of reproduction (PYO *et al*., 2010; NEMAT-GORGANI *et al*., 2014; ASHOURI *et al*., 2009). NK cells exert their functional effects by physically interacting with other types of cell, engagements that can lead to the killing of cells damaged by infection or malignancy, and to the secretion of cytokines that recruit other inflammatory immune system cells (PARHAM *et al*., 2012; MIDDLETON and GONZALES, 2010). As part of the mechanisms directing their effector functions, these cells utilize a number stimulatory and inhibitory receptors that in humans react with major histocompatibility complex (MHC) class I antigens (HLA-A, B, and C ligands) expressed by host cells. Of particular interest here is the diverse family of killer-cell immunoglobulin-like receptors (KIR) that recognize four mutually exclusive epitopes of the highly polymorphic HLA-A, HLA-B and HLA-C molecules. These epitopes comprise the A3/11 epitope carried by HLA-A*03 and HLA-A*11 allotypes, the Bw4 epitope carried by around one third of HLA-A and HLA-B allotypes, the C2 epitope carried by the subset of HLA-C allotypes having lysine at position 80, and the C1 epitope carried by the complementary subset of HLA-C allotypes that have asparagine at position 80 (NEMAT-GORGANI *et al*., 2014; HOU *et al*., 2012).

Currently, 15 different KIR loci (*KIR2DL1, KIR2DL2/KIR2DL3, KIR2DL4, KIR2DL5A, KIR2DL5B, KIR2DS1–5, KIR3DL1/KIR3DS1, KIR3DL2–3,* and two pseudogenes, *KIR2DP1* and *KIR3DP1*), have been identified (http://www.ebi.ac.uk/ipd/ kir/). Selected combinations of these genes are encoded on haplotypes within a 100- to 200-kb region of the Leucocyte Receptor Complex (LRC) located on human chromosome 19q13.4 (PYO *et al*., 2010; NEMAT-GORGANI *et al*., 2014; ASHOURI *et al*., 2009; PARHAM *et al*., 2012). Allogeneic hematopoietic stem cell transplantation (HSCT) is an established curative treatment for many hematological malignancies. The outcome of HSCT is strongly influenced by the genetic differences between donor/recipient pairs (WARREN *et al.*, 2012). Genetic similarity or identity in the HLA genes in the major histocompatibility complex on chromosome 6, affects the incidence of graft-versus-host disease (GvHD), the major complication of HSCT. Successful allogeneic HSCT, however, depends also on T-cell mediated graft-versus-leukemia (GvL) effect, in which donor-derived T cells clear the remaining leukemic cells in patient. In addition to alloreactive T cells, donor-derived natural killer (NK) cells, are able to kill these malignant or virus-infected cells in the patient. NK cells might therefore have a crucial role in relapse prevention by destroying remaining acute myeloblastic leukemia cells (WARREN *et al.*, 2012; FOLEY *et al*., 2014; VELARDI, 2008a).

KIR genes can be divided into haplotypes A and B according to the gene content. KIR haplotypes A have simple, fixed gene numbers and haplotypes B have a more variable gene content with additional activating KIR genes. The position of each KIR gene is fixed, and centromeric (Cen) or telomeric (Tel) motifs can be defined for each haplotype, i.e. Cen-A, Tel-A, Cen-B and Tel-B. In HSCT, recent data have demonstrated that both Cen-B and Tel-B motifs strongly contribute to protection from relapse and improve survival (STERN *et al.,* 2011). Compared with A haplotype motifs, centromeric and telomeric B motifs both contributed to protection from relapse and improved survival, but Cen-B homozygosity had the strongest independent effect. With Cen-B/B homozygous donors the cumulative incidence of relapse was 15.4% compared with 36.5% for Cen-A/A donors (COOLEY *et al*., 2010).The aim of this study was to make the predictive analysis of the structure and distribution of B KIR alleles and A/B KIR haplotypes in HSCT donors in Vojvodina with regard to their contribution to protection from relapse.

MATERIAL AND METHODS

Subjects

A total of 124 first-degree relatives [median age: 30 (1-60) years; male/female: 64/60] from 95 families with hematological malignant diseases were included in the study. The study protocol was approved by the Ethics Committee of the Clinical Center of Vojvodina. Donors were interviewed and an informed consent was received from all participants.

DNA purification

Genomic DNA was extracted from peripheral blood samples using silica-based method by either QIAamp blood mini kit (Qiagen GmbH, Hilden, Germany) or the GeneJET Genomic DNA Purification Kit (Thermo Fisher Scientific Inc., Vilnius, Lithuania). The quality and quantity of DNA samples were determined by UV spectrophotometry, and the concentration was adjusted to 100 ng/μl.

KIR genotyping and haplotype group assignment

The presence or absence of 15 KIR genes (*KIR3DL3, KIR2DS2, KIR2DL2, KIR2DL3, KIR2DL5, KIR2DS3/2DS5, KIR2DP1, KIR2DL1, KIR3DP1, KIR2DL4, KIR3DL1, KIR3DS1, KIR2DS1, KIR2DS4* and *KIR3DL2*) was determined by the use of reverse sequence-specific oligonucleotide technique (Immucor Transplant Diagnostics, Inc., Stamford, Connecticut) with Luminex xMap technology (Luminex Corp., Austin, TX). Donors were assigned the A/B, B/B or A/A genotype by their KIR gene content. Individuals having only genes of the group A KIR haplotypes (*KIR3DL3-2DL3-2DL1-2DP1-3DP1-2DL4-3DL1-2DS4-3DL2*) were considered to be homozygous for the A haplotype and assigned the KIR genotype AA. Individuals lacking any of the four A haplotype associated genes (*KIR2DL1, 2DL3, 3DL1* and *2DS4*) that have a known function and vary among individuals in their existence were regarded to be homozygous for group B haplotypes and assigned the KIR genotype BB. All other individuals were regarded to be heterozygous for A and B haplotypes and assigned the KIR genotype AB.

Genotypes for the centromeric (Cen) and telomeric (Tel) parts of the KIR locus were assigned according to the presence or absence of one or more B haplotype-defining KIR genes: Cen-A1, Cen-B1, Cen-B2, Tel-A1 and Tel-B1. As examples, Cen-A1 is comprised of *KIR3DL3— KIR2DL3— KIR2DP1—KIR2DL1—KIR3DP1* in this gene order while Tel-A1 includes *KIR2DL4— KIR3DL1—KIR2DS4—KIR3DL2* (MOESTA and PARHAM, 2012) (Table 1).We defined

the KIR B–content score for each donor's KIR genotype as the number of centromeric and telomeric gene-content motifs containing B haplotype–defining genes. A calculator for classification of the donor KIR B status (best, better, neutral) we found at http://www.ebi.ac.uk/ipd/kir/.

Table 1.Genes carried by centromeric and telomeric KIR haplotypes

			Centromeric region								Telomeric region						
Hap.	Cen.	Tel.	3DL3	2DS2	2DL2/3	2DL5B	2DS3/5	2DP1	2DL1	3DP1	2DL4	3DL1/S1	2DL5A	2DS3/5	2DS1	2DS4	3DL2
A	Cen-A	Tel-A	■		2DL3			■		■	■	■				■	■
B	Cen-B	Tel-B	■	2DS2	2DL2			■		■	■	■	■	■	■		■
	Cen-B	Tel-B	■	2DS2	2DL2	■	■	■		■	■	■	■	■	■		■
	Cen-B	Tel-A	■	2DS2	2DL2	■	■	■		■	■	■				■	■
	Cen-A	Tel-B	■		2DL3			■		■	■	■	■	■	■		■

■ =Presence of KIR gene

□ =Absence of KIR gene

(MOESTA and PARHAM, 2012)

Statistics

The percentage of individuals carrying each KIR gene, centromeric and telomeric KIR haplotypes and genotypes was determined by direct counting (individuals positive for the gene divided by the individuals tested per population×100). Frequencies of A and B haplotypes were calculated using the following formula: group A=2nAA+nAB/2N and group B=2nBB+nAB/2N, where nAA, nAB, and nBB were the numbers of AA, AB, and BB genotypes and N was the total number of individuals tested.

RESULTS

KIR gene frequency distribution

All 15 known KIR genes were detected in HSCT donors analyzed in this study, and two of four framework KIR genes (*3DL3* and *3DP1*) were detected in all 124 individuals analyzed, where the gene frequency was 1. *KIR 3DL2*, *2DL4*, *2DL1* and *3DL1* genes were common with gene frequency of 0.983, 0.967, 0.959, and 0.935, respectively. *KIR 2DP1*, *2DS4*, *2DL3*, *2DS2* and *2DL2* genes were less common with frequencies of 0.951, 0.903, 0.854, 0.637 and 0.629, respectively. The *KIR 2DS3* and *2DS5* gene frequencies were the lowest at 0.354 and 0.225, respectively (Table 2).

Table 2. The distribution of the frequencies of KIR genes in related HSCT donors in Vojvodina

KIR gene n=124	Gene frequencies
2DL1	0.959
2DL2	0.629
2DL3	0.854
2DL4	0.967
2DL5	0.516
3DL1	0.935
3DL2	0.983
3DL3	1.000
2DS1	0.379
2DS2	0.637
2DS3	0.354
2DS4	0.903
2DS5	0.225
3DS1	0.362
2DP1	0.951
3DP1	1.000

KIR genotype and haplotype frequencies

Overall, the A haplotype associated KIR genes occurred more frequently than the B haplotype associated KIR genes, where 62% of the HSCT donors on Vojvodina carry A KIR haplotype, while nearly 38% of donors carry B KIR haplotype. The analysis of the A/A, A/B and B/B KIR genotype distribution revealed that only one HSCT donor (0.80%) carry all of the KIR genes belonging to B group without presence any of A group KIR genes, frequency of A/A KIR genotype is 25%, while the most common is the A/B genotype with a frequency of 74.1%.The B KIR gene content in related HSCT donors is presented in Table 3. The distribution of B KIR genes showed that among 124 studied HSCT donors, 31(25%) do not carry none of the KIR genes belonging to B group, while 71.77% of donors have two or more B KIR genes and 61.29% of donors carry *KIR 2DL2* and *2DS2* or more B KIR genes.

Centromeric and telomeric KIR haplotypes and genotypes distribution

The distribution of telomeric and centromeric KIR haplotypes revealed that nearly 80% of HSCT donors in Vojvodina carried *KIR2DL4-3DL1-2DS4-3DL2* gene cluster and 60.5% of donors carried KIR *3DL3-2DL3-2DP1-2DL1-3DP1* gene cluster, respectively. Among all existing centromeric KIR haplotypes, Cen-B2 was present in the lowest frequency among HSCT donors of 13.7% (Table 4). The analysis of centromeric and telomeric KIR genotypes among studied donors showed that A haplotype genes of the centromeric region in combination with Tel-A of the telomeric region (Cen-A1/Tel-A1) had a highest frequency of 51.47%.The lowest frequency was observed for Cen-B2/Tel-B1 KIR genotype with frequency of 1.30% (Table 5).

Table 3. B KIR gene content in related HSCT donors in Vojvodina

2DL2	2DL5	2DS1	2DS2	2DS3	2DS5	3DS1	No.	%
							31	25.0
■			■				24	19.3
■	■	■	■	■			15	12.0
■	■		■	■			15	12.0
■	■	■	■	■	■	■	8	6.45
■	■	■	■		■	■	7	5.64
	■	■			■		7	5.64
■	■		■	■		■	3	2.41
■	■	■	■		■		2	1.61
	■	■	■		■	■	2	1.61
		■					2	1.61
						■	1	0.80
	■	■				■	1	0.80
■	■						1	0.80
	■	■		■	■	■	1	0.80
			■				1	0.80
■	■	■			■	■	1	0.80
■			■	■			1	0.80
■	■	■	■	■			1	0.80
Total							124	100

■ =Presence of KIR gene

□ =Absence of KIR gene

Table 4. Distribution of centromeric and telomeric KIR haplotypes in related HSCT donors in Vojvodina

Cen A1	Cen B1	Cen B2	Tel A1	Tel B1
60.5%	25.8%	13.7%	79.44%	20.56%

Table 5. Distribution of centromeric and telomeric KIR genotypes in related HSCT donors in Vojvodina

CenA1/TelA1	CenA1/TelB1	CenB1/TelA1	CenB1/TelB1	CenB2/TelA1	CenB2/TelB1
51.47%	8.06%	15.62%	10.68%	12.87%	1.30%

Assignments the donors to one of 3 groups based on KIR B-content

We determined KIR B-content scores for all donors according to the system proposed by Cooley et al. that is available at (www.ebi.ac.uk/ipd/kir/donor_b_content.html). These results were condensed according to the Donor KIR B-content group calculator (neutral = score of 0, better = score of 1 or 2, best = score of 3 or 4). Seventy-four (59.67%) donors had a neutral score, 33 (26.63%) had a score of 1/2, and 17 (13.70%) had a score of 3/4, respectively.

DISCUSSION

Diversity in human *KIR* genotype is sum from three components: haplotypic gene content, allelic polymorphism and the combination of maternal and paternal haplotypes. The combined effects of these three components are such that unrelated individuals usually differ in *KIR* genotype and ethnic populations have widely differing *KIR* genotype frequencies. Overall, the frequencies of the inhibitory KIR genes were higher and more homogeneous among worldwide populations than for the activating genes and KIR gene frequencies in the studied HSCT donors are in agreement with the predominantly European populations (KAMENARIĆ BUREK *et al.*,2013; DJULEJIĆ *et al*.,2010; BONTADINI *et al*., 2006; GUINAN *et al.*,2010).

Since the patients transplanted from donors homozygous for KIR haplotype A had a greater risk of developing grade II–IV acute GVHD compared with those transplanted from a donor carrying at least one B haplotype (COOLEY *et al*., 2010) it is developed an interesting and innovative algorithm based on the number of donor KIR haplotype B motifs (score from 0 to 4). Donor high KIR B-content score is in association with better probability of event free survival (EFS) and lower relapse risk (COOLEY *et al*., 2010; LITERA *et al*., 2011; OEVERMANN *et al*., 2014). Our result showed that although 0.80% donors carry BB KIR genotype, 74.1% of them carry A/B genotype with relively very high percentage of donors carrying at least *KIR2DL2* and *2DS2*, that are in association with statistically significant longer relapse-free survival (P = 0.015) in the patients with AML whose donors have *KIR2DL2* or *KIR2DS2* (IMPOLA *et al*., 2014). Nearly 27% of donors have better score and nearly 14%, the best B KIR score, respectively.

Since the best outcome is observed for patients transplanted from donors with KIR B–content score 2 or greater (COOLEY *et al*., 2010; LITERA *et al*., 2011) and that B haplotype genes of the centromeric region had a stronger effect in improving the outcome of transplantation than those of the telomeric region (COOLEY *et al*., 2010) our results showed that among all studied HSCT donor, 13.99% were Cen-B/B homozygous. When the number of activating KIR genes present in the donors was taken into account, where grafts from the donors carrying ≥ 3 activating KIR genes provide significant protection from transplant related mortality (TRM) and significantly better EFS compared with A haplotype donors (TRM: 12 vs. 67%, $p<0.003$) (EFS: 71 vs. 33%, $p=0.02$) (VELARDI *et al*., 2008b), our results showed that 39 (31.45%) of donors carried ≥ 3 activating KIR genes.

CONCLUSION

In conclusion, an accurate evaluation of the complexity of the KIR gene system, together with adopting the practice of usage of donor KIR B gene content and centromeric and telomeric KIR gene structure could be used in development of a simple algorithm to identify donors who will provide the most protection against the relapse in related HSC transplants.

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KARAKTERIZACIJA GENA IMUNOGLOBULINU SLIČNIH RECEPTORA ĆELIJA PRIRODNIH UBICA I TELOMERNIH I CENTROMERNIH MOTIVA KOD DONORA MATIČNIH ĆELIJA HEMATOPOEEZE U VOJVODINI, SRBIJI

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Izvod

Ishod transplantacije metičnih ćelija hematopoeze (TMĆH) zavisi od stepena podudarnosti u HLA genima koji utiče na incidencu bolesti kalem protiv domaćina (GvHD). Uspeh alogene TMĆH zavisi i od T-ćelijama posredovanog graft-vs-leukemiju (GvL) efekta, gde T ćelije i ćelije prirodne ubice (NK) donora ubijaju maligne ćelija pacijenta, zbog čega imaju ključnu ulogu u prevenciji recidiva. Cilj ove studije je da se napravi prediktivna analiza za izbor najpogodnijeg donora MĆH u Vojvodini na osnovu distribucije B KIR alela i centromernih i telomernih KIR motiva sa ciljem zaštite od recidiva bolesti. Sto dvadeset i četiri donora u prvom stepenu srodstva sa bolesnicima sa hematološkim malignitetima ispitano je na prisustvo ili odsustvo 15 KIR gena upotrebom PCR-SSO tehnike. Zastupljenost osoba nosioca KIR gena, centromernih i telomernih KIR haplotipova i genotipova je određen direktnim brojanjem. Šezdeset dva posto donora MĆH u Vojvodini poseduje A KIR haplotip, dok skoro 38% poseduje B KIR haplotip. Distribucija KIR B gena je pokazala da od 124 ispitivana donora, 31 (25%) ne poseduju KIR gene grupe B, 71.77% donora ima dva ili više B KIR gena, 61.29% njih poseduju KIR 2DL2 i 2DS2 ili više B KIR gena. Analiza centromernih i telomernih KIR genotipova, pokazala je da Cen-A1 / Tel-A1 genotip ima najveću učestalost 51.47% a Cen-B2 / Tel-B1 najnižu frekvenciju od 1.30%. Analiza sadržaja B KIR gena u donora MĆH i centromernih i telomernih KIR motiva može da posluži za izradu algoritma za identifikaciju najpogodnijeg donora za transplantaciju MĆH uz maksimalnu zaštitu protiv recidiva bolesti.

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