KIR-HLA-A and B alleles of the Bw4 epitope against HIV infection in discordant heterosexual couples in Chaco Argentina

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Summary

Activating and inhibitory killer immunoglobulin-like receptors (KIR) and their ligands HLA-Bw4 (loci A and B) were studied by way of establishing whether they can contribute to protection against HIV-1 infection in highly exposed and persistently seronegative (HESN) patients. Twenty-three HIV-1 serodiscordant heterosexual couples, 100 HIV-1$^+$ patients and 200 healthy individuals were included in this retrospective case–control study. HLA typing was performed by means of PCR followed by sequence-specific oligonucleotide probe reverse hybridization. KIR3DL1 and KIR3DS1 were studied by PCR sequence-specific primers. The frequency of KIR3DS1(3DS1/3DL1)-Bw4 combination was significantly higher in HESN patients versus the discordant couples ($P = 0{\cdot}0003$) and HIV-1$^+$ patients ($P = 0{\cdot}0001$). Conversely, the KIR3DL1/KIR3DL1 homozygosity was significantly decreased in HESN patients versus the discordant couples ($P = 0{\cdot}00003$), and HIV-1$^+$ patients ($P = 0{\cdot}00066$). The frequency of HLA-A*32 and HLA-B*44 was higher in HESN versus their discordant couples ($P = 0{\cdot}009$; $P = 0{\cdot}049$), and HIV-1$^+$ patients ($P = 0{\cdot}00002$; $P = 0{\cdot}0001$). This had greater significance in combination with KIR3DS1 (3DS1/3DL1). KIR3DS1(3DS1/3DL1) could have a greater effect on protection against HIV-1 infection in HESN patients when bound to a specific HLA allele, in this case HLA-A*32 and HLA-B*44, both Bw4 alleles. The differences probably arise both in the HLA alleles and in the subtypes of KIR receptors depending on the ethnic group studied.

Keywords: HIV-1; HLA, human leucocyte antigen; killer immunoglobulin-like receptor; KIR3DL1; KIR3DS1.

Introduction

In the last decade, numerous studies have examined the importance of killer immunoglobulin-like receptors (KIR) on natural killer (NK) cells and their HLA class I ligands. The regulation of activity on these cells is under the control of a range of activating and inhibitory receptors that work in concert to identify and destroy aberrant target cells. Inhibitory receptors have long cytoplasmic tails comprising immune-receptor tyrosine-based inhibitory motifs that translate inhibitory signals whereas the activating KIR do not have signalling motifs, but can associate with an adaptor through a positively charged residue in their transmembrane region. The adaptor molecules have immune-receptor tyrosine-based activation motifs that translate an activating signal when the receptor binds to their respective ligands.[1,2] Several KIR and HLA interactions have been described. KIR and HLA loci are both highly polymorphic. The pairs of HLA class I ligands and the KIR that can be used to regulate the NK cell responses vary between individuals within a population, and are dependent upon the combination of KIR and HLA class I genes that each person inherits.[3–5]

The activating NK cell receptor KIR3DS1 (KIR3 immunoglobulin-domain where 'S' stands for short cytoplasmic tail and '1' is the particular gene) and the

inhibitory receptor KIR3DL1 (KIR3 immunoglobulin-domain where 'S' stands for long cytoplasmic tail and '1' is the particular gene) segregate as alleles of the same locus and share about 97% sequence similarity in their extracellular domain, suggesting that they may bind similar ligands.[5,6]

The KIR3DL1 receptor binds the HLA-Bw4-80I allotypes with higher affinity.[6] Carr *et al.*[7] showed that KIR3DS1 receptors do recognize HLA-Bw4 ligands, this may be peptide dependent and although there is no direct evidence, genetic epidemiological data strongly support such an interaction.

Bw4 epitopes of the HLA-B comprise B*13, B*27, B*37, B*38, B*44, B*47, B*49, B*51, B*52, B*53, B*57, B*58, B*59, B*1513 alleles and HLA-A comprise A*24, A*23, A*25, A*32;[6–8] see also the website http://hla.alleles.org/antigens.

KIR3DS1 showed strong inhibition of HIV-1 replication in target cells that expressed HLA-Bw4-80I compared with those that did not show KIR3DS1. The specific combination of both activating and inhibitory KIR3DS1/KIR3DL1 and HLA-Bw4 alleles has been associated with delayed progression to AIDS.[9–11]

Morvan *et al.*[12] observed that whereas KIR3DL1$^+$ NK cell proliferation and cytotoxicity were inhibited in Bw4$^+$ but not Bw4$^-$ setting, KIR3DS1$^+$ NK cell functions were not influenced by the presence of Bw4 on the target cell. This result could suggest that KIR3DS1 does not recognize HLA-Bw4 molecules in a physiological setting. The authors emphasize the induced expression of KIR3DS1 observed on stimulated NK cells and the higher frequency of KIR3DS1$^+$ NK cells in Bw4 individuals.

The aim of this study was to investigate the presence of KIR3DS1 and KIR3DL1 receptors and the combination with their ligands HLA-Bw4 (loci A and B alleles) by way of establishing whether they can contribute to protection against HIV infection in highly exposed and persistently seronegative (HESN) partners of individuals infected with HIV-1.

Materials and methods

Twenty-three HIV-1 serodiscordant heterosexual couples (23 HIV-1$^-$ individuals and their 23 HIV-1$^+$ partners), 100 HIV-1$^+$ patients and 200 healthy individual organ donors were included in this retrospective case–control study. Of the 23 HIV-1$^-$ people (mean age 36·6 ± 6·9 years), 14 were women and nine were men. Inclusion criteria were: HIV-1$^-$ people who had multiple unprotected sex episodes with their HIV-1$^+$ partners, and were HESN to HIV-1 infection for more than 5 years. Nine couples had between one and three children during that period. The HIV$^+$ couples (mean age of 34·9 ± 7·18 years), had been seroconverted for more than 5 years and they had high viral load at sometime in the 5 years of contact with their partners. They were not included in the group of HIV-1$^+$ patients. A group of one hundred HIV-1$^+$ patients (mean age 32·4 ± 5·8 years) had been seroconverted for more than 8 years, with a history of CD4 counts < 400/ml and high viral load; most received antiretroviral therapy.

The individuals included in this study signed the informed consent according to the Helsinki Declaration of 1975. DNA samples were extracted from mononuclear cells of peripheral blood by using the salting-out or the commercial method (QIAamp DNA Mini kit Qiagen, Valencia, CA) as well. HLA typing was performed in the laboratory before ablation. The control group belongs to the same ethnic background as patients.

HLA typing

HLA-A* and HLA-B* typing was performed by means of PCR followed by sequence-specific oligonucleotide probe reverse hybridization (medium-resolution sequence-specific oligonucleotide). The results of the analyses were interpreted using the DYNAL strip software following the hybridization patterns updated twice a year by the manufacturer, according to the WHO Nomenclature Committee and the IMGT / HLA Database. The latest hit table can be found at www.tissue-typing.com.

KIR genotyping

The inhibitory KIR3DL1 and the activating KIR3DS1 were studied by PCR sequence-specific primers (PCR-SSP) as described by Uhrberg *et al.*,[13] PCR products were electrophoresed on 2% agarose gel to determine the presence of the amplified products (KIR3DS1, 249 bp and KIR3DL1 277 bp). The results of PCR-SSP were previously validated using a commercial Kit [KIR Genotyping SSP KIT; Invitrogen Company (Carlsbad, CA)].

CCR5 genotyping

The presence of mutant CCR5 receptor was investigated by PCR-SSP, according to Huang Y *et al.*[14]

Statistical analysis

The HLA-A and HLA-B alleles and KIR frequencies were expressed in percentages. The degree of association between each group was expressed as the odds ratio (OR), which was calculated according to Woolf's formula. Significance of the observed association was determined using the Chi-square test and corrected by Yates or Fisher's exact test, two-tailed with 95% confidence intervals (95% CI). $P < 0{\cdot}05$ was considered significant.

Deviation from Hardy–Weinberg equilibrium was tested using a chi-squared test goodness-of-fit test for each locus.

Results

We genotyped KIR3DS1/3DL1 and HLA-A and B alleles in 23 HIV discordant couples, 100 HIV-1^+ patients and 200 healthy controls. The results of the HESN participants were compared with each group (Table 1).

We found a significant increase of receptor KIR3DS1 (3DS1/3DL1) (homozygous and heterozygous forms) in HESN participants versus HIV-1^+ partners (OR = 24, $P = 0{\cdot}00003$), versus HIV-1^+ group (OR = 8·15, $P = 0{\cdot}00066$) and versus control group (OR = 4·26, $P = 0{\cdot}0026$).

On the other hand, the KIR3DL1/KIR3DL1 homozygosity was significantly decreased in the HESN participants with respect to discordant partners (OR = 0·04, $P = 0{\cdot}00003$), to the HIV-1^+ group (OR = 0·12, $P = 0{\cdot}00048$) and to the control group (OR = 0·23, $P = 0{\cdot}026$).

When the HLA-Bw4 alleles (loci A and B) were examined, no differences were found between the groups. If we differentiate between Bw4-80I and Bw4-80T, a higher frequency of Bw4-80T was observed in the HESN participants versus discordant partners (OR = 5·13, $P = 0{\cdot}049$). A significant increase of the KIR3DS1(3DS1/3DL1)/Bw4 combination was found in the HESN group compared with their HIV-1^+ partners (OR = 15·24, $P = 0{\cdot}0003$), with the HIV-1^+ patients (OR = 6·86, $P = 0{\cdot}0001$) and with the controls (OR = 2·74, $P = 0{\cdot}049$).

Bw4 alleles present in HESN participants were: A*23, A*24, A*25, A*32, B*27, B*38, B* 44, B*51, B*52, B*57. We found a significant increase of HLA-A*32 in HESN participants versus HIV-1^+ partners (OR = undefined, $P = 0{\cdot}009$), versus HIV-1^+ group (OR = 43·3, $P = 0{\cdot}00002$) and versus control group (OR = 7·52, $P = 0{\cdot}0007$). Besides an increase of HLA-B*44 in HESN participants compared with HIV-1^+ partners (OR = 5·13, $P = 0{\cdot}049$), versus the HIV-1^+ group (OR = 8·85, $P = 0{\cdot}0001$) and versus the control group (OR = 3·76, $P = 0{\cdot}005$; Table 2). Similar results were obtained when we analysed those alleles in combination with KIR3DS1(3DS1/3DL1).

For HLA-B*44, the medium resolution method used in this study allowed us to observe that nine of the ten alleles found in the HESN group were 4403/07/13 and only one was 4469. In the discordant HIV-1^+ group of the three HLA-B*44 alleles, two were 4402/11/19 and one was 4405. The KIR3DS1 receptor was not present in the three HIV-1^+ individuals carrying these alleles. The haplotype HLA-A*32-B*44 was present in five (21·7%) HESN individuals, absent in HIV-1^+ partners and the HIV-1^+ group, and present in only three (1·5%) members of the control group.

To rule out whether protection against HIV infection in HESN participants could be the result of CCR5 receptor mutation, we compared heterozygous (CCR5/ccr5) and homozygous (ccr5 /ccr5) mutation in HESN participants with HIV-1^+ partners and the HIV-1^+ group. The heterozygous mutation was present in seven HESN participants (30%) in one (4%) of the HIV-1^+ partners and in four of the HIV-1^+ group (4%). Homozygous mutation associated with protection against infection was not found in any of the three groups.

Discussion

We found a significant increase in KIR3DS1 receptor (homozygous or heterozygous for this allele) in the HESN group compared with HIV-1^+ partners (OR = 24, $P = 0{\cdot}000003$) and HIV-1^+ group (OR = 8·15, $P = 0{\cdot}00066$). These results suggest that the sole presence of KIR3DS1 could have a protective role in HIV-1 infection in HESN individuals. Similar results were observed when we analysed the combination of KIR3DS1 with HLA-Bw4 alleles in HESN individuals versus their HIV-1^+ partners (OR = 15·24, $P = 0{\cdot}0003$) and the HIV-1^+ group (OR = 6·86; $P = 0{\cdot}0001$; Table 1).

Ravet *et al.*[15] reported in some exposed uninfected (EUs) the concomitant expression of lowered inhibitory KIR3DL1 transcript levels and high activating KIR3DS1 levels resulted a KIR3DS1/KIR3DL1 radio that may confer an enhanced activating NK cell repertoire profile to these EUs.

The specific combination of both activating and inhibitory KIR3DS1/KIR3DL1 and HLA-Bw4 alleles has been associated with delayed progression to AIDS based on epidemiological studies.[9–11] Carrington *et al.*[16] indicate that it is also possible that the various KIR3DL1/KIR3DS1 molecules might differ in their binding affinity for their HLA ligand, which may in turn influence AIDS progression.

HLA ligand binding for KIR3DS1 is still controversial. Carr *et al.*[7] found that the soluble KIR3DS1-Ig fusion proteins did not bind to Epstein–Barr virus-transformed B lymphoid cell lines transfected with HLA-Bw4-80I or 80T allotypes, suggesting that KIR3DS1 does not recognize HLA-Bw4 ligand. This may be peptide-dependent. Conversely, Guerini *et al.*[17] only observed this significant increase in HESN individuals who were homozygous KIR3DS1 in combination with Bw4 with respect to HIV-1^+ individuals. Homozygosity for KIR3DS1 was present at low percentages in all populations analysed in our study. However, the frequency of heterozygosity for KIR3DS1 is found in high levels in the normal population, indicating an important Amerindian influence in northern Argentina, as pointed out by some authors.[3,18]

When we analysed just the Bw4 alleles (homozygous or heterozygous) we found no differences between the studied groups, although Melo da Silva *et al.*[19] reported a significant association between HLA-Bw4 and low levels of viraemia in HIV-infected Brazilian patients. On the other hand, Welzel *et al.*[20] found that the presence of HLA-Bw4 in HIV-1-infected men was associated with a decreased risk of male-to-female HIV-1 transmission, which suggests that these alleles reduce infectivity for HIV-1.

Table 1. Gene frequencies of KIR and HLA-Bw4 /Bw6, KIR-HLA receptor–ligand pairs in highly exposed and persistently seronegative (HESN), HIV$^+$ couples, HIV$^+$ patients and control

					Statistical finding		
HLA-A/B Bw4 and KIR3DL1/3DS1	(1) HESN n = 23 n (%)	(2) Couples n = 23 n (%)	(3) HIV$^+$ n = 100 n (%)	(4) Controls n = 200 n (%)	1 versus 2 Pc	1 versus 3 Pc	1 versus 4 Pc
3DS1/3DS1	3 (13)	0	3 (3)	22 (11)	ns	ns	ns
3DS1/3DL1)	17 (74)	5 (22)	42 (42)	100 (50)	0·0011	0·011	0·05
3DS1 (3DS1/3DL1)	20 (87)	5 (22)	45 (45)	122 (61)	0·00003	0·00066	0·02
3DL1/3DL1[2]	3 (13)	18 (78)	55 (55)	78 (40)	0·00003	0·00066	0·02
HLA-A* Bw4	13 (56)	6 (26)	34 (34)	77 (39)	ns	ns	ns
HLA-B*Bw4/Bw4	5 (22)	5 (22)	13 (13)	23 (12)	ns	ns	ns
HLA-B*Bw4(Bw4/Bw6)	17 (74)	11 (48)	46 (46)	101 (51)	ns	ns	ns
HLA-B*Bw6/Bw6	6 (26)	12 (52)	54 (54)	99 (49)	ns	ns	ns
3DS1/3DL1-B*Bw4-Bw4	3 (13)	0	3 (3)	13 (7)	ns	ns	ns
3DS1/3DL1-B*Bw4/Bw6[3]	10 (43)	1 (4)	14 (14)	42 (21)	0·005	0·0022	0·03
3DS1/3DL1-B*Bw6/Bw6	4 (17)	4 (17)	25 (25)	45 (22)	ns	ns	ns
3DS1(3DS1/3DL1) -Bw4[4]	16 (70)	3 (13)	25 (25)	117 (59)	0·0003	0·0001	0·049
3DL1/3DL1-Bw4 (A/B)	2 (8)	10 (43)	40 (40)	49 (24)	0·018	0·009	ns

Yates corrected and * two-tailed Fisher exact test were used for *P*-values.
Exact confidence limits

		KIR3DS1 (3DS1/3DL1) homozygous and heterozygous form for KIR3DS1	
3DS1 (3DS1/3DL1)	HESN versus HIV-1$^+$ couples: OR (95% CI) = 24 (4·20 < OR < 163·20)	3DS1/3DL1-B*Bw4/Bw6	HESN versus HIV-1$^+$ couples: OR(95% CI) = 16·92 (1·90 < OR < 766·82)
	HESN versus patients HIV-1$^+$: OR (95% CI) = 8·15 (2·18 < OR < 44·84)		HESN versus HIV-1$^+$ patients: OR (95% CI) = 4·73 (1·52 < OR < 14·25)
	HESN versus Controls: OR (95% CI) = 4·26 (1·15 < OR < 18·68)		HESN versus Controls: OR(95% CI) = 21·44 (4·91 < OR < 99·79)
3DL1/3DL1	HESN versus HIV1$^+$ couples: OR (95% CI) = 0·04 (0·01 < OR < 0·24)	3DS1(3DS1/3DL1-B*w4	HESN versus HIV-1$^+$ couples: OR (95% CI) = 15·24 (2·88 < OR < 99·11)
	HESN versus patients HIV-1$^+$: OR (95% CI) = 0·12 (0·03 < OR < 0·48)		HESN versus HIV-1$^+$ patients: OR (95% CI) = 6·86 (2·31 < OR < 21·7
	HESN versus controls: OR (95% CI) = 0·23 (0·05 < OR < 0·87)	3DL1/3DL1[5]	HESN versus HIV1$^+$ couples: OR (95% CI) = 0·12 (0·01 < OR < 0·75) HESN versus patients HIV-1$^+$: OR (95% CI) = 0·14 (0·02 < OR < 0·65)

Table 2. Gene frequencies of HLA-A* and B* alleles and KIR-HLA receptor–ligand pairs in highly exposed and persistently seronegative (HESN), HIV-1^+ couples, HIV-1^+ patients and controls

HLA alleles and KIR combination	(1) HESN n = 23 n (%)	(2) Couples + *n* = 23 n (%)	(3) HIV$^+$ *n* = 100 n (%)	(4) Controls n = 200 n (%)	Statistical finding		
					1 versus 2 Pc	1 versus 3 Pc	1 versus 4 Pc
A*23	2 (9)	2 (9)	4 (4)	15 (7)	ns	ns	ns
A*24	2 (9)	5 (22)	24 (24)	40 (20)	ns	ns	ns
A*25	2 (9)	0	5 (5)	11 (5·5)	ns	ns	ns
A*32	7 (30)	0	1 (1)	11 (5·5)	0·009	0·00002*	0·0007
B*27	0	1 (4·3)	6 (6)	10 (6)	ns	ns	ns
B*38	1 (4·3)	3 (13)	4 (4)	3 (1·5)	ns	ns	ns
B*44	10 (43)	3 (13)	8 (8)	34 (17)	0·049	0·0001*	0·005*
B*51	3 (13)	3 (13)	10 (10)	26 (13)	ns	ns	ns
B*52	3 (13)	0	3 (3)	9 (4·5)	9 (4·5)	9 (4·5)	9 (4·5)
B*57	1.(4·3)	0	6 (6)	6 (3)	ns	ns	ns
A-Bw4-80I	13 (56)	6 (26)	34 (34)	70 (35)	ns	ns	ns
B-Bw4-80I	7 (30)	8 (35)	38 (38)	77 (38)	ns	ns	ns
Bw4$^+$- 80T	10 (43)	3 (13)	24 (24)	68 34)	0·049	ns	ns
3DS1/3DL1-A*32	7 (30)	0	0	4 (2)	0·009*	0·00003*	0·00001*
3DS1/3DL1-B*44	8 (35)	0	1 (1)	20 (10)	0·003*	0·000003*	0·003*
3DL1/3DL1-B*44	2 (9)	3 (13)	7 (7)	8 (4)	ns	ns	ns

Yates corrected and * two-tailed Fisher exact test were used for *P*-values.
Exact confidence limit

A*32	HESN versus HIV-1^+ couples: OR (95 % CI) = Undefined, Relative Risk = 2·44 (1·67 < RR < 3·55) HESN versus patients HIV-1^+: OR (95% CI) = 43·31 (4·75 < OR < 1001·95)	3DS1/3DL1-A*32	HESN versus HIV-1^+ couples: OR (95% CI) = Undefined, RR 2·44 (1·67 < RR < 3·55) HESN versus HIV-1^+ patients: OR (95% CI) = Undefined, RR = 7·25 (4·60 < RR < 11·43
B*44	HESN versus Controls: OR (95% CI) = 43·31 (4·81 < OR < 1970,28) HESN versus HIV1$^+$ couples: OR (95% CI) = 5·13 (1·02 < OR < 33·30) HESN versus patients HIV-1^+: OR (95% CI) = 8·85 (2·56 < OR < 30·49) HESN versus controls : OR (95% CI) = 3·76 (1·34 < OR < 10·09)	3DS1/3DL1-B*44	HESN versus Controls : OR(95% CI) = 21·44 (4·91 < OR < 99·79 HESN versus HIV-1^+ couples: OR (95% CI) = Undefined, RR = 2·53 (1·71 < RR < 11·43) HESN versus HIV-1^+ patients: OR (95% CI) = 52·80 (6·04 < OR < 2364·63) HESN versus Controls: OR (95% CI) = 4·80 (1·62 < OR < 14·3)

Our study showed a significant decrease of KIR3DL1/3DL1 in HESN individuals versus HIV-1^+ couples (OR = 0·04, $P = 0·00003$) and versus HIV-1^+ patients (OR = 0·12, $P = 0·00066$), which could indicate that homozygosity for KIR3DL1 is a factor of susceptibility to HIV-1 infection. We found less significance when this allele was analysed together with Bw4 (Table 1). This agrees with the results of Guerini *et al.*[17] who found that the frequency of the inhibitory KIR3DL1 allele and of the KIR3DL1$^+$/Bw4$^+$ inhibitory complex was reduced in HESN individuals. Ravel *et al.*[15] found that KIR3DL1/Bw4 complex was less frequent in HESN than in HIV-infected individuals. Nevertheless, Jennes *et al.*[21] found that KIR3DL1 homozygosity in the absence of HLA-Bw4 can influence resistance to HIV transmission in HIV-exposed but seronegative female sex workers in Abidjan. Martin *et al.*[22] found, in 1500 HIV-1^+ individuals, that distinct allelic combinations of KIR3DL1 and HLA-B locus significantly and strongly influence both AIDS progression and plasma HIV-RNA abundance in a consistent manner. On the other hand it is interesting to consider the studies of Sanjanwala *et al.*[23] which found that polymorphism at sites throughout the HLA class I can influence the interaction of the Bw4 epitope with KIR3DL1. This influence is probably mediated by changes in the peptide bonds, which alter the conformation of the Bw4 epitope.

We found that HLA-Bw4 alleles present in HIV-1^- partners were: A*23, A*24, A*25, A*32, B*27, B*38, B*44, B*51, B*52, B*57. The most frequent within the HLA-A locus was the A*32 allele among HESN individuals versus HIV-1^+ partners ($P = 0·009$), versus the HIV-1^+ group ($P = 0·00002$) and versus control group ($P = 0·005$). Within locus B, the HLA-B*44 was the most frequent among the HESN versus HIV-1^+ couples ($P = 0·049$), ver-

sus HIV-1$^+$ group ($P = 0{\cdot}0001$) and the control group ($P = 0{\cdot}005$). Strong significance was observed when we analysed the combination with KIR3DS1/3DL1 for both alleles (Table 2). This appeared to show that A*32 and B*44 alone or together with KIR3DS1/3DL1 have an important effect in protecting against HIV infection in HESN individuals. This study shows that KIR3DS1$^+$ has a major role in the protection against HIV-1 infection in HESN individuals when linked to specific HLA alleles, in this case HLA-A*32 and HLA-B*44, both Bw4-alleles. Flores-Villanueva *et al.*[24] found significant association between HLA-B*44 and viraemia control.

It is useful to note that in the HESN group, only two of them who had the HLA-A*32 B*44 haplotype, also had the heterozygous mutation for the CCR5 receptor. It should be noted that protection from HIV infection has been demonstrated in a homozygous mutation of CCR5 receptor.

The Bw4 motifs present at residues 77–83 are SLRIALR in HLA-A*32 and NLRTALR in HLA-B*44. Both differ at position 80, isoleucine in A*32 and threonine in B*44. This difference should be more exhaustively studied, with the aim of establishing the reason why alleles with different epitopes have similar effects.

In our study the HLA-B*4403/07/13 was present only in the HIV-seronegative couples, while 4402/11/19 and 4405 was the most frequent among HIV-1$^+$ couples. It is important to emphasize that the three B*44 alleles found in discordant HIV$^+$ partner pairs were homozygotic for KIR3DL1. The combination of KIR3DS1/KIR3DL1 with the HLA-B*4403/07/13-Bw4 ligand was not present in HIV-1$^+$ partners. These results would support those of Macdonald *et al.*,[25] who comment that cytotoxic T lymphocytes discriminate between HLA-B*4402 and B*4403. Polymorphism between HLA-B*4402 and B*4403 modifies both the peptide repertoire and T-cell recognition.

Alter *et al.*[11] performed *in vitro* tests to examine the functional ability of NK cells to differentially control HIV-1 replication *in vitro* based on their KIR-HLA types. Functional testing should be performed with specific HIV-1 peptides to establish the true participation of the alleles B*4403 and A*32 .

Herman *et al.*[26] conclude that the B44 specificity of T cells results mostly from distinct conformations adopted by the same peptides in the two B44 molecules. They found several peptides, different from the three mentioned above, that contain the canonical HLA-B44 binding motif and bind to B*4403 but not to B*4402 molecules. This was consistent with the stronger T-cell alloreactivity toward B*4403 in comparison with B*4402.

Numerous observations suggest that CD8$^+$ T cells play an important role in constraining infection. We can add that there might be selective expression of activating and inhibitory KIR depending on the HLA alleles in each individual. If KIR gene evolution were pathogen-driven, some diversity would be expected to correlate with resistance or sensibility to certain infectious diseases.

Conclusion

This study observes that KIR3DS1(3DS1/3DL1) could have a greater effect on protection against HIV-1 infection in HESN individuals when linked to a specific HLA allele, in this case HLA-A*32 and HLA-B44, both Bw4. Besides KIR3DL1/KIR3DL1 homozygosity could be considered as a risk factor in the susceptibility to HIV infection.

These results could add epidemiological data to the understanding of complex KIR-HLA interactions that trigger different responses to the disease, depending upon genetic characteristics of studied population.

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Disclosures

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