Association of KIR3DS1+HLA-B Bw4^{Ile80} Combination with Susceptibility to Tuberculosis in Lur Population of Iran

Farhad Shahsavar[1], Tahereh Mousavi[2,3*], Alireza Azargoon[4], Kobra Entezami[2]

[1]Department of Immunology, Lorestan University of Medical Sciences, Khorramabad, [2]Department of Immunology, Tehran University of Medical Sciences, [3]Antimicrobial Research Center, Tehran University of Medical Sciences, Tehran, [4]Department of Internal Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran

ABSTRACT

Background: Natural killer (NK) cells are the effector cells of innate immunity that respond to infection and tumor. Interactions between killer cell immunoglobulin like receptors (KIR) and human leukocyte antigen (HLA) class I molecules regulate NK cells responses to eliminate infected and transformed cells. **Objective:** To investigate the impact of KIR genes, HLA ligand genes, and KIR-HLA combinations on susceptibility to tuberculosis (TB) in Lur population of Iran. **Methods:** The genomic DNA of 50 patients with TB from Lorestan province of Iran was genotyped for sixteen KIR genes and their five major HLA class I ligands were determined by a polymerase chain reaction-sequence-specific primers (PCR-SSP) assay. The results were compared with those of 200 healthy unrelated Iranian individuals. **Results:** In Lur population of Iran, a significant decrease in frequency of KIR3DS1 was found in TB patients compared to control group (24% vs. 44.5%, OR=0.394, CI=0.194-0.798, p=0.013). Also, among the three activating genes that may use HLA class I molecules as their ligands, a significant decrease was shown in frequency of KIR3DS1 with HLA-B Bw4^{Ile80} ligand in TB patients compared to control group (4% vs. 23%, OR=0.14, CI=0.033-0.596, p=0.004). **Conclusion:** These findings imply a genetic imbalance between activating and inhibitory KIR genes and KIR-HLA combinations in Lur TB patients. Low level of activating KIR3DS1 and its combination with HLA-B Bw4^{Ile80} ligand might have an influence on the susceptibility to TB in Lur population of Iran.

Keywords: HLA, KIR, NK Cells, Tuberculosis

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*Corresponding author: Dr. Tahereh Mousavi, Department of Immunology, Tehran University of Medical Sciences, Tehran, Iran, Tel: (+) 98 021 88622652, Fax: (+) 98 021 88622652, e-mail: tshabestari@sina.tums.ac.ir

INTRODUCTION

Tuberculosis (TB), caused by Mycobacterium Tuberculosis (Mtb), with more than nine million new cases and almost two million we showed in a year is an important public health problem in the world. Generally, human immune responses prevent Mtb spread and the infection remains in a latent state (1). Both, innate and adaptive immune responses are involved against TB. However, the role of the innate immunity is still not well clear (2). Through mechanisms such as cytotoxicity and cytokine production, NK cells are among the first line of defence against mycobacterial infection (3). The ability of NK cytotoxicity is related to Killer cell immunoglobulin-like receptors (KIRs) found on the cell surface (4).

The KIR gene cluster on chromosome 19q13.4 within the leukocyte receptor complex (LRC) consists of a centromeric and telomeric region (5,6). To date, 14 KIR genes and 2 psuedogenes have been described. Haplotypes A and B are the two basic haplotypes that have been defined on the basis of gene content. Haplotype A is uniform in terms of gene content and is composed of KIR2DL1, 2DL3, 2DL4, 3DL1, 3DL2, 3DL3, 2DS4, 2DP1 and 3DP1 genes. The B haplotypes contain variable numbers of inhibitory and activating receptors and are the primary contributors to the extraordinary differences in gene profiles observed in distinct ethnic populations across the world (7-9). Segregation of different A and B haplotypes generates diversity in the type and number of KIR genotypes (10).

KIRs and their ligands, such as Human Leukocyte Antigen (HLA) class I molecules, play a critical role in activity regulation of NK cells (11). The KIR2DL1 binds HLA-C2 group. KIR2DL2/3 recognize HLA-C1 group (12,13). KIR3DL1 is known to bind HLA-Bw4 allotypes that present on 40% of the HLA-B allotypes (14,15) and certain HLA-A molecules (16,17). KIR2DS1 has been shown to bind weakly to HLA-C2 allotypes and KIR2DS2 may bind weakly to HLA-C1. KIR3DS1 is thought to interact with HLA-Bw4 allotypes (18).

KIR at chromosome 19q13.4 and HLA at chromosome 6p21.3 are polymorphic. The independent segregation of these gene loci produce diversity in the KIR-HLA combinations inherited in individuals. As a result of various combinations in individual genomes that could lead to either triggering or blocking NK cell activity, innate immune response to infections may vary among individuals (19). Thus, failure in the control of infection in individuals may be the result of genetically determined KIR and HLA ligands gene content. This may lead to a dominance of inhibition over activation in NK cells.

Our preliminary observations on KIR/HLA genes in Lur population of Iran showed the possible involvement of these genes in susceptibility to tuberculosis (data are not shown). Thus, to clarify this preliminary finding, the present study was designed to investigate the impact of KIR genes, HLA ligand genes, and KIR-HLA combinations on susceptibility to TB in Lur population of Iran.

MATERIALS AND METHODS

The patient group consisted of 50 unrelated individuals with TB from Lorestan province of Iran (30 males, ranging in age from 17-75 years and 20 females, ranging in age from 15-66 years). Ethnic information was obtained on the place of birth of the patients and

the place of birth of their parents and grandparents. The patients were diagnosed at Khorramabad city health center (Khorramabad, Lorestan Province, Iran) according to their sputum smear and culture. Blood samples were collected with the written consent of the patients or of their legal guardians. Local Ethics Committees' approval was also obtained.

For control group, because of some limitations, we compared the results obtained from Lur TB patients with the results previously reported by Ashouri et al. on healthy Lur population (20). Moreover, due to the close consistency between previous published results by Ashouri et al. (20) and Tajik et al. (21,22) which were obtained from a larger sample size of 200 individuals from different Iranian ethnic groups, we also considered the data reported by Tajik et al. for the analysis of our results.

Table 1. The Comparison of frequencies for KIR genes in previous studies (References 20-22).

KIR genes	Iranian (n=200)* %F	Lur (n=96)** %F
Inhibitory		
2DL1	96.5	94.8
2DL2	56.5	54.1
2DL3	86.5	89.6
2DL4	100	100
2DL5	61.5	54.1
3DL1	91.5	95.8
3DL2	100	100
3DL3	100	100
Activating		
2DS1	45.5	42.7
2DS2	57.5	49.0
2DS3	38.0	27.1
2DS4	91.5	97.9
2DS5	40.0	39.6
3DS1	44.5	45.8
pseudogenes		
2DP1	96.5	96.9
3DP1	100	100

F: Frequency
*Tajik et al. 2009, 2010
** Ashouri et al 2009

Genomic DNA was extracted from peripheral blood leukocytes using the EXTRA GENE I kit (BAG, Lich, Germany). DNA samples were genotyped for the presence or absence of sixteen KIR genes by KIR TYPE kit (BAG, Lich, Germany) and their five major HLA class I ligands (HLA-C1, C2, B $Bw4^{Ile80}$, B $Bw4^{Thr80}$ and A Bw4) by EPITOP TYPE kit (BAG, Lich, Germany), based on polymerase chain reaction-sequence-specific primers (PCR-SSP) assay. Samples with detection of at least 1 of the KIR B loci (KIR2DL2, 2DL5, 2DS1, 2DS2, 2DS3, 2DS5, or 3DS1) were assigned the geno-

type Bx. Samples lacking all KIR B loci were assigned as the AA genotype (23). HLA-A, HLA-B and HLA-C alleles were also grouped according to their specificity for the major inhibitory and activating KIR-HLA combinations.

The frequencies for KIR and HLA ligands genes were calculated by direct counting. In addition, the frequencies for KIR genotypes, HLA ligand genotypes and inhibitory and activating KIR-HLA combinations were defined. The significance of associations was determined using the $\chi 2$ test with Yate's correction or Fisher's exact test. The labeling with $^{((a))}$ indicates significant difference after correction (p after correction <0.05). The odds ratio (OR) was calculated by the cross-product ratio and exact confidence intervals (CI) of 95% were obtained.

Genotype group	KIR genotype #	KIR Gene																			Controls% (n=200)	TB Patients % (n=50)
		Inhibitory KIR								Activating KIR						Pseudogene		No. of genes				
		KIR 2DL1	KIR 2DL2	KIR 2DL3	KIR 2DL4	KIR 2DL5	KIR 3DL1	KIR 3DL2	KIR 3DL3	KIR 2DS1	KIR 2DS2	KIR 2DS3	KIR 2DS4	KIR 2DS5	KIR 3DS1	KIR 2DP1	KIR 3DP1	Inhibitory	Activating	Pseudogene	Total		
AA	1	■		■	■		■	■	■				■			■	■	6	1	2	9	27.5	34
Bx	2	■		■	■	■	■	■	■	■			■	■	■	■	■	7	4	2	13	10	8
	3	■	■	■	■		■	■	■		■		■			■	■	7	2	2	11	10	14
	4	■	■	■	■	■	■	■	■		■	■	■			■	■	8	3	2	13	10	12
	5	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	8	6	2	16	7.5	6
	6	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	8	5	2	15	5.5	4
	7	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	8	5	2	15	4	4
	8	■	■		■	■	■	■	■		■	■	■			■	■	7	3	2	12	3.5	8
	9	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	7	6	2	15	3	2
	10	■	■	■	■	■		■	■	■	■	■		■	■	■	■	7	5	2	14	2	-
	11	■	■		■	■		■	■	■	■	■		■	■	■	■	6	5	2	11	2	-
	12	■	■	■	■	■	■	■	■	■	■		■	■		■	■	8	4	2	14	1.5	2
	13	■		■	■	■		■	■	■				■	■	■	■	6	3	2	11	1.5	-
	14		■		■	■	■	■	■	■	■		■	■			■	6	4	1	11	1.5	2
	15	■	■	■	■	■		■	■	■	■			■	■	■	■	7	4	2	13	1.5	-
	16	■	■	■	■	■	■	■	■		■	■	■		■	■	■	8	4	2	14	1	-
	17		■		■		■	■	■		■		■				■	5	2	1	8	1	2
	18	■		■	■	■	■	■	■	■		■	■		■	■	■	7	4	2	13	1	-
	19	■		■	■	■	■	■	■	■	■		■	■	■	■	■	7	5	2	14	1	-
	20	■		■	■	■	■	■	■	■		■	■	■	■	■	■	7	5	2	14	1	-
	21	■		■	■	■	■	■	■			■	■		■	■	■	7	3	2	12	1	-
	22	■	■		■	■	■	■	■	■	■	■	■		■	■	■	7	5	2	14	1	-
	23	■	■		■	■	■	■	■	■	■		■	■		■	■	7	4	2	13	0.5	2
	24		■		■	■		■	■		■	■		■	■		■	5	4	1	10	0.5	-
	25	■		■	■	■		■	■	■		■		■	■	■	■	6	4	2	12	0.5	-
	26		■		■	■		■	■	■	■			■	■		■	5	4	1	10	0.5	-

Figure 1. The frequencies of KIR genotypes in the controls and TB patients.

RESULTS

First of all, we compared the frequency of KIR genes in Lur healthy population reported by Ashouri et al. (20) with those obtained from a mixture of Iranian populations (21,22). As represented in Table 1, we found no significant differences between the two studies. The distribution of frequencies for KIR and HLA ligand genes in the controls and TB patients of Lur population of Iran is presented in Table 2.

Table 2. The Comparison of frequencies for KIR genes, HLA ligand genes, and KIR genotypes in the controls and TB patients.

Genes and genotype	Controls (n=200) %F	TB patients (n=50) %F
KIR genes		
Inhibitory		
2DL1	96.5	96.0
2DL2	56.5	58.0
2DL3	86.5	84.0
2DL4	100	100
2DL5	61.5	50.0
3DL1	91.5	100
3DL2	100	100
3DL3	100	100
Activating		
2DS1	45.5	30.0
2DS2	57.5	58.0
2DS3	38.0	32.0
2DS4	91.5	100
2DS5	40.0	26.0
3DS1	44.5	24.0[a]
Pseudogenes		
2DP1	96.5	96.0
3DP1	100	100
HLA Ligand genes		
C1	76.0	84.0
C2	72.0	60
B Bw4 ^{Ile80}	56.5	46.0
B Bw4 ^{Ile80}	10.0	4.0[a]
A Bw4	36.0	40.0
KIR genotypes		
AA	27.5	34.0
Bx	72.5	66.0

F: Frequency
[a] Corrected significant difference
*Tajik et al. 2009, 2010

Only, the frequency of KIR3DS1 was significantly lower in TB patients compared to control group (24% vs. 44.5%, OR=0.394, CI=0.194-0.798, p after correction =0.013) (Table 2). We identified a total of 13 different KIR genotypes in TB patients vs. 26 genotypes in the control individuals (Figure 1). Also, 6 HLA ligand genotypes were identified in our study groups (Figure 2). There was no significant difference in the frequency of KIR and HLA ligand genotypes among study groups.
Although 89% of the controls and 96% of the TB patients carried three inhibitory KIR genes (2DL1, 2DL2/3 and 3DL1), their ability to trigger inhibitory responses depends on the availability of the cognate HLA class I ligands (24).

HLA ligands genotype #	HLA-C1	HLA-C2	HLA-Bw4	% of controls (n=200)	% of TB patients (n=50)
1	■	■	■	37.5	34
2	■		■	23	28
3		■	■	16	6
4	■	■		10.5	10
5		■		8	10
6	■			5	12

Figure 2. The frequencies of HLA ligand genotypes in the controls and TB patients.

Thus, we established the frequency of inhibitory KIR-HLA combinations (2DL2/3+HLA-C1, 2DL1+HLA-C2, 3DL1+HLA-B Bw4^{Ile80}, 3DL1+HLA-B Bw4^{Thr80} and 3DL1+HLA-A Bw4) and activating KIR-HLA combinations (2DS2+HLA-C1, 2DS1+HLA-C2, 3DS1+HLA-B Bw4^{Ile80}, 3DS1+HLA-B Bw4^{Thr80} and 3DS1+HLA-A Bw4) in the controls and TB patients of Lur population of Iran (Table 3).

Table 3. The frequencies of coinheritance for inhibitory and activating KIR genes and their specific HLA class I ligands in the controls and TB patients.

KIR-HLA combinations	Controls (n=200)* %F	TB patients (n=50) %F
Inhibitory		
2DL2/3+C1	76.0	84.0
2DL1+C2	69.5	56.0
3DL1+B Bw4^{Ile80}	52.5	46.0
3DL1+B Bw4^{Thr80}	8.5	4.0
3DL1+A Bw4	31.0	40.0
Activating		
2DS2+C1	44.0	48.0
2DS1+C2	31.0	24.0
3DS1+B Bw4^{Ile80}	23.0	4.0[a]
3DS1+B Bw4^{Thr80}	6.5	2.0
3DS1+A Bw4	19.5	8.0

F: Frequency
[a] Significant corrected difference
*Tajik et al. 2009, 2010

Only, the frequency of KIR3DS1+HLA-B $Bw4^{Ile80}$ was significantly lower in the TB patients compared to control group (4% vs. 23%, OR=0.14, CI=0.033-0.596, p after correction=0.004) (Table 3).

DISCUSSION

As it was expected from the preliminary study, there was a significant relationship between KIRs and susceptibility to tuberculosis in Lur Iranian population. Indeed, a decreased frequency of an activating KIR gene alone and in combination with its HLA ligand was shown in TB patients of Lur population.

NK cells are one of the most important parts of the innate immune system due to their ability to limit the dissemination of infection in the absence of adaptive immune responses. They are involved in the control of cytokine releases such as tumor necrosis factor, a critical cytokine against the establishment of Mtb infection (25). According to an article reviewed by Abi-Rached and Parham, activating receptors KIR are involved in resistance to infection, reproduction success and susceptibility to autoimmune diseases (26).

On the other hand, there are several reported studies on the TB and NK cell relationships in Iranian populations (27-29). Some of these studies indicate no significant influence of KIR/HLA genes in TB (27), and some imply a role for these molecules in TB (29). In fact, as the minority of individuals infected with Mtb develop clinical TB, it is feasible that different genetic factors such as SLC11A1, NOS2A, TLRs, IFNGR1, and KIRs play a role in the resistance to TB (30-32). Thus, we investigated the associations between susceptibility to TB and KIR genes, HLA ligand genes, and KIR-HLA combinations in Lur population of Iran.

In the present study, In contrast to a previous study reporting a significant increase in KIR2DL1 and KIR2DL3 in patients with TB (32), we showed that the frequencies for these KIR genes are similar in TB patients and control group. In fact, In Lur population of Iran, we found no significant differences in the frequency of inhibitory KIR genes, HLA ligand genes, KIR genotypes, and HLA ligand genotypes between TB patients and healthy controls. Conversely, among activating KIR genes, we showed that the frequency of KIR3DS1 was significantly decreased in TB patients (24% vs. 44.5%, OR=0.394, CI=0.194-0.798, p after correction =0.013) (Table 2). Interestingly, the results of KIR frequencies which were reported by Ashouri et al. (20) in Lur population confirmied our finding regarding to this activating KIR gene (24% vs. 45.8%, p after correction=0.016). We suggest that the reason for such opposing results may be related to genetic diversity in the two populations and remains to be investigated.

As the regulation of response of NK cells depends mainly on KIR-HLA combinations in individual genomes, it is proposed that these combinations may be important in diseases. In this regard, we lay particular emphasis on KIR-HLA combinations to determine their relative contribution to TB susceptibility in Lur population of Iran.

In a study performed by Mendez et al. (32), a significant decrease was reported in frequency of KIR2DS2 in combination with their ligand group (HLA-C1) in TB patients (30.9% vs. 49% in controls). But, this result lost significance after correction. Here, we studied the frequencies of the inhibitory and activating KIR genes that may use HLA class I molecules as their ligands. In Lur population of Iran, we showed only a significantly decreased frequency of KIR3DS1 with HLA-B $Bw4^{Ile80}$ ligand in the TB patients

compared with the controls (Table 3). It may be concluded that lower frequency of KIR3DS1+HLA-B Bw4^{Ile80} combination may shift the NK cell responses from activating to the inhibitory situation which is detrimental in Mtb infection.

Altogether, we indicated that TB patients could possess a lower frequency of KIR3DS1 than the healthy controls. Thus, a genetic imbalance between activating and inhibitory KIR genes might have an influence on the susceptibility to TB in Lur Iranian Population. Moreover, susceptibility to TB could be determined by the overall balance of activating and inhibitory KIR-HLA combinations. Therefore, we conclude that KIR3DS1+HLA-B Bw4^{Ile80} combination may be associated with susceptibility to TB in Lur population of Iran and the absence of KIR3DS1+HLA-B Bw4^{Ile80} may result in genetic predisposition for decreased activity of NK cells. These findings may imply a role for lower activation of NK cells through KIR-HLA combination in TB.

This study almost confirmed our preliminary findings about the possible role of the KIRs and their HLA ligands in Lur TB patients. However, we suppose that further studies using larger sample sizes are needed to confirm the exact role of KIR and HLA gene combinations in different Iranian ethnic groups including Lur populations.

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