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Impact of Human Leukocyte Antigen Polymorphisms in Human Immunodeficiency Virus Progression in a Paediatric Cohort Infected with a Mono-phyletic Human Immunodeficiency Virus-1 Strain

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Abstract

Objective: HLA polymorphisms within the peptide binding pocket have been associated with rapid and slow-progression to AIDS, suggesting that the capability to present efficiently HIV-1 epitopes is crucial for the infection control. To minimize the effects of genetic background due to population coming from different geographic area and viral strain variability in the cohort, an analysis of all the polymorphisms associated with the HLA-A, -B and -DR alleles has been performed in a cohort of children with a monophyletic HIV-1 infection (CRF02_AG) during an outbreak in Libya.

Methods: High-resolution HLA-typing has been performed in 58 children infected with a monophyletic strain of HIV-1: 26 Long-Term Non-Progressors (LTNP), 9 Slow-Progressors (SP) and 23 Fast-Progressors (FP). HLA amino acid polymorphism frequency has been compared in the in FP respect to LTNP.

Results: HLA-B resulted the most interesting locus of the study; 10 positions located in B- and F-pocket for peptide-binding have been found significant after Bonferroni's correction: 11S (LTNP=7.69% FP=34.78% OR=0.156 P<0.05), 74D (LTNP=15.38%, FP=52.17%, OR=0.167; p<0.015) and 94T (LTNP=15.38%, FP=52.17%, OR=0.045; p<0.001), resulted associated with AIDS progression; 66N (LTNP=42.31% FP=8.7% OR=7.7; p<0.02), 80I (LTNP=80.77%, FP=34.78%, OR=7.86; p<0.036), 81A (LTNP=84.61%, FP=47.83%, OR=6; p<0.015), 82L (LTNP=88.46%, FP=47.83%, OR=7.86; p<0.006) and 83R (LTNP=88.46%, FP=47.83%, OR=7.86; p<0.006), has been associated with non-progression. Further, carrying Bw4-epitope resulted associated with LTNP (phenotype-frequency: LTNP=88.46%, FP=47.83%, OR=8.36; p<0.006), with homozygosis for Bw4 (LTNP=30.8%, FP=8.7%, p<0.05) associated with delayed progression and homozygosis for Bw6 (LTNP=11.5%, FP=52.1%, p<0.05) associated with fast progression to AIDS.

Conclusion: The progression to AIDS might be in part determined by the binding capability of B-pocket and F-pocket of HLA-B and in part by the interaction of NK's inhibitory receptor with HLA-B Bw4-epitope which regulate innate immune response and might have important implications for a better disease control.

Keywords: Children; Epitope; HIV-1; HLA; Peptide binding motif; Susceptibility

Introduction

Susceptibility to HIV-1 infection, disease progression and clinical outcome are strongly influenced by differences observed in viral strains and host genetic factors [1].

Between a variety of genetic factors, certain specific alleles of human leukocyte antigen (HLA), both class I and II, have shown an effect on the outcome of HIV-1 infection, with many alleles found positively or negatively associated with disease progression to AIDS [1-3]. These findings are consistent with the role of HLA, particularly of class I molecules, in shaping the cell-mediated arm of anti-HIV immune response and in determining plasma viral load [4,5].

However, the HLA association studies with HIV disease progression and outcome have been limiting by multiple issues such as: the involvement of multiple HLA loci, the linkage disequilibrium, the diploid genome, the cohort effects, the different measures of outcome and the viral strain variability within the study subjects [1,2].

Recently, the study of variation among the entire HLA molecules showed that the major genetic control of HIV progression is due to polymorphisms within the HLA binding groove [6,7].

In fact, apparently dissimilar HLA alleles may have similar antigen binding grooves, and thereby overlap in their capacity to present antigens [8]. The analysis of the single amino acid polymorphisms

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might provide more relevant information on severity and diseases progression than the simply HLA allelic association.

The structure function studies indicate that the selection of antigenic peptides by the HLA receptors is dictated by the chemical-physical interaction between the amino acid side chains, lining receptor-like pockets on the floor of the HLA antigen binding groove, and the amino acid side chains of the antigenic peptide.

Therefore, in each subject the polymorphisms in HLA molecules could influence the capability to bind HIV-1 epitopes i.e. the phenotype of HIV-1 recognition, could be at the basis of the susceptibility to a more rapid progression to AIDS more than the carrying of a susceptible allele *per se*.

To test this hypothesis and to minimize the effects of (i) genetic background due to population coming from different or large geographic area and (ii) viral strain variability in the cohort, an analysis of all the polymorphisms associated with the HLA-A, -B and -DR alleles has been performed in a cohort of children infected with a monophyletic strain of HIV-1 (CRF02_AG) during an outbreak in the Benghazi Children Hospital in Libya [9].

Materials and Methods

Study population

The cohort involved in the outbreak of HIV infection at the "El-Fath Children's Hospital" of Benghazi, includes 418 children, 18 mothers and 2 nurses. All the children resulted infected after attending the outpatients' service of the hospital or during hospitalization for at least once. The HIV infection and outbreak viral characterization has been confirmed as previously described [9], indicating in the cohort the presence of a defined cluster of HIV-1 clade A/G virus (CRF02_AG).

All the samples have been collected with the consent of children parents' and/or guardians. HLA-typing has been performed upon residual blood sample availability, after informed consent, from a subgroup of 114 children. They were 60 males and 54 females, all from the Libya Cyrenaica. This study population is representing a defined ethnic group geographical related with other populations from North Africa and Mediterranean areas as recently reported [10]. HCV co-infection was identified in 46 out of 114 children of the study population [9,11].

The cohort subgroup evaluated in this study does not differ in its overall from the entire cohort for the mean value of CD4 cell counts, viral load, and frequency of subject in the different groups of classification for progression to AIDS. Thus, as far as the infection is concerned, the patients can be considered a homogeneous pool of subjects.

According to different definitions from the literature [12], these children have been divided in four groups. (1) Long Term Non Progressors (LTNP) includes patients with 6 or more years of infection, never on antiretroviral therapy (ARV), without any critical events; (2) Slow Progressors (SP), patients with 6 or more years of infection with moderate clinical manifestation (CDC class A or B) or moderate immunosuppression (CDC class 2) without ARV; (3) Fast Progressors (FP), patients with severe clinical manifestation or immunosuppression before 6 years from infection, regardless the beginning of ARV and (4) Uncertain (U), subjects on treatment for which therapy do not allowed an univocal classification. In order to clearly evaluate the association with HIV progression uncertain subjects have been excluded by this study.

HLA typing and polymorphism assignment

High Resolution HLA-A, -B and –DRB1 typing was performed through the ABI Prism 310 Genetic Analizer (Applied Biosystem, Foster City, CA, USA). Briefly, genomic DNA was obtained for each study subject by the salting-out method (Nuclear Laser Medicine, Italy) in according to protocol. Allele SEQR HLA-A and -B and allele SEQR HLA-DRB1 PCR/Sequencing kits (Abbott, Wiesbaden, Germany) have been used for HLA-A and -B or HLA–DRB1 typing respectively.

Supertype assignment of each HLA allele, i.e. based upon sharing the peptide binding motif, was performed accordingly the classification of HLA alleles in supertypes [13,14].

Polymorphism assignment has been performed translating every HLA alleles found in the cohort in the corresponding amino acid sequence considering only the polymorphic amino acid position obtained by protein sequence alignment in the IMGT/HLA database (http://www.ebi.ac.uk/imgt/hla/) as previously described [15]. Therefore, the phenotypic frequency of each polymorphic amino acid position has been evaluated between study groups.

Statistical analysis: All the data are expressed as frequency percentage. Comparison between frequencies is made by Chi-square, with Yates and Bonferroni's correction when appropriate. As previously reported [15]: (i) for HLA alleles' comparison, Bonferroni's correction has been performed using the total numbers of HLA alleles found in the study; (ii) for HLA supertype's comparison, Bonferroni's correction has been performed considering the total number of HLA supertypes found in the study; and (iii) for HLA amino acid polymorphisms Bonferroni's correction has been performed considering, within each position, the number of polymorphic amino acid residues found.

When in the comparisons the number of observations was below 5 a Chi-square per trend has been used. The Odds Ratio has been calculated as the ratio of the HLA polymorphisms frequency on FP respect to LTNP. GraphPad Prism version 5.0 has been used for all statistical analyses and graphs.

Results

Study groups characteristics are summarised in Table 1.

In the study population have been identified 30 alleles in HLA-A locus, 37 alleles in HLA-B locus and 31 alleles in HLA-DR locus (see

	Patients	Sex (% male)	Median age at the first observation (IQR[a])	Median Nadir %CD4+ (IQR[a])	HIV viral load Median (range)	% ARV[b]
Long Term Non-Progressor	26 (22.8%)	23.1%	5.42 (1.50-10.29)	28.5% (25.0-32.0)	400 (50-2500)	0.0
Slow Progressor	9 (7.9%)	88.9%	5.51 (4.51-7.20)	23.0% (19-25)	2300 (50-30000)	0.0
Fast Progressor	23 (20.2%)	60.9%	3.97 (2.10-6.68)	13% (9-17)	73000 (5280-500000)	68.2
Uncertain	56 (49.1%)	57.1%	1.79 (1.32-28.88)	21.5% (17-34)	14500 (400-270000)	100.0

[a]IQR Inter-quartile range.
[b]% of patients which started antiretroviral therapy.

Table 1: Demographic, immunological and therapeutic characteristics of the study groups classified according clinical progression.

Supplementary information S1 and S2). In its overall, the population resulted in Hardy-Weinberg equilibrium for all the HLA loci evaluated.

None of the HLA alleles and supertypes resulted associated after Bonferroni's correction with being LTNP or FP (see Supplementary information S1 and S2).

To assess the role of single amino acid positions in HIV progression, HLA alleles have been translated into the different amino acid position polymorphisms (Figure 1).

In HLA-A locus, 65 amino acid polymorphic positions have been evaluated. Figure 1A shows all the amino acid positions evaluated in our study and the location of the amino acid significant positions 76 (P=0.032) , 77(P=0.023) and 89 (P=0.028) within the HLA-A peptide binding pocket.

However, none of the 144 HLA-A polymorphisms evaluated showed a significant association with being LTNP or FP after Bonferroni's correction (Table 2 and S3).

In HLA-B locus, among the 49 amino acid polymorphic positions studied, 10 positions located in B and F peptide binding pocket have been found significant after Bonferroni's correction (Figure 1B).

Specifically, B-pocket related amino acid positions 24 (P=0.016), 45 (P=0.018), 62(P=0.012), 65(P=0.006), 66(P=0.006), and F-pocket related amino acid positions 11(P=0.016), 74(P=0.006), 77(P=0.013),

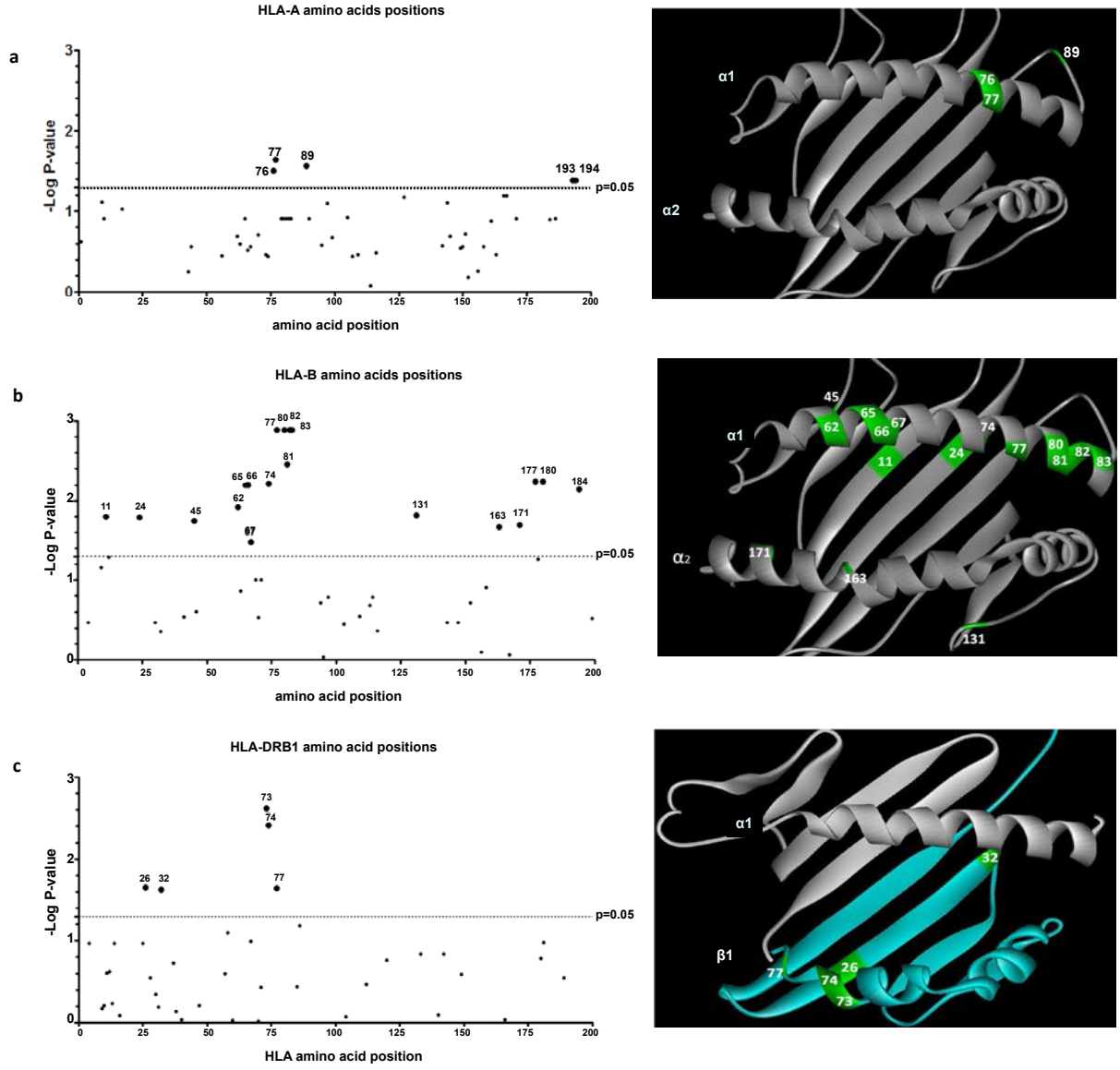

Figure 1: Analysis of all polymorphic binding pocket amino acid positions in the study population. On the left panels, are shown the -Log P values of all the amino acid positions of peptide binding pocket, all the significant positions are shown in the graph. On the right panels, are shown the significant amino acid positions within the peptide's binding pocket. (A) Analysis of polymorphic HLA-A amino acid positions. (B) Analysis of polymorphic HLA-B amino acid positions. (C) Analysis of polymorphic HLA-DRB1 amino acid positions. All statistical analysis has been performed using Chi-square test with Bonferroni correction considering the number of polymorphisms founded in the population for each HLA amino acid position evaluated. When in the comparisons the number of observations was below 5 a Chi-square per trend has been used.

	Binding pocket#	LTNP	Fast progressor	Odds Ratio (OR)	LTNP vs. Fast progressor	LTNP vs. Fast progressor
HLA-A		**N**	**N**		**Uncorrected p value**	**Bonferroni's corrected p value**
62Q	B	18 (69.23%)	8 (34.78%)	4.2187	**0.0336**	0.2881
HLA-B						
11S	F*	2 (7.69%)	8 (34.78%)	0.1562	**0.0463**	**0.0463**
24A	B	21 (80.77%)	11 (47.83%)	4.5818	**0.0343**	0.1344
24S	B	4 (15.38%)	13 (56.52%)	0.1398	**0.0066**	0.0546
45E	B	4 (15.38%)	13 (56.52%)	0.1398	**0.0066**	0.1165
45T	B	20 (76.92%)	8 (34.78%)	6.25	**0.0072**	0.2921
62G	A and B	10 (38.46%)	2 (8.7%)	6.5625	**0.0370**	0.351
65R	A and B	11 (42.31%)	2 (8.7%)	7.7	**0.0195**	0.6277
66N	B	11 (42.31%)	2 (8.7%)	7.7	**0.0195**	**0.0195**
67M	B	11 (42.31%)	2 (8.7%)	7.7	**0.0195**	0.2429
70S	B	11 (42.31%)	2 (8.7%)	7.7	**0.0195**	0.1775
74D	F	4 (15.38%)	12 (52.17%)	0.1667	**0.0149**	**0.0149**
77N	F	22 (84.61%)	11 (47.83%)	6	**0.0149**	0.085
80I	F	21 (80.77%)	8 (34.78%)	7.875	**0.0029**	**0.0353**
81A	F	22 (84.61%)	11 (47.83%)	6	**0.0149**	**0.0149**
82L	External§	23 (88.46%)	11 (47.83%)	8.3636	**0.0056**	**0.0056**
83R	External§	23 (88.46%)	11 (47.83%)	8.3636	**0.0056**	**0.0056**
94T	F	13 (50%)	22 (91.3%)	0.0454	**0.0013**	**0.0013**
95L	F	6 (23.08%)	13 (56.52%)	0.2307	**0.0354**	0.2244
97S	F	5 (19.23%)	14 (60.87%)	0.153	**0.0071**	0.1783
HLA-DR						
26Y	4	2 (7.69%)	8 (34.78%)	2.380952381	**0.0463**	0.912684596
73A	4	26 (100%)	18 (78.26%)	N.A.	**0.0417**	**0.0417**
73G	4	9 (34.62%)	16 (69.56%)	0.231617647	**0.0311**	**0.0311**
74R	4	2 (7.69%)	8 (34.78%)	0.15625	**0.0463**	0.372758417
77N	4	2 (7.69%)	8 (34.78%)	0.15625	**0.0463**	0.158747122
77T	4	26 (100%)	18 (78.26%)	N.A.	**0.0417**	0.149950893

Table 2: HLA phenotypic analysis of binding pocket amino acid polymorphism significantly associated with the study groups.

80(P=0.013), 81(P=0.003) resulted associated either with LTNP or FP (Figure 1B).

Further it has been evaluated the 114 amino acid polymorphisms in the HLA-B locus (see S3).

Considering B-pocket, amino acid polymorphism 66N resulted significantly associated with LTNP after Bonferroni's correction (LTNP=42.31% FP=8.7% OR=7.7; p<0.02, Table 2).

In the context of F-pocket, amino acid polymorphisms 11S (LTNP=7.69% FP=34.78% OR=0.156 P<0.05), 74D (LTNP=15.38%, FP=52.17%, OR=0.167; p<0.015) and 94T (LTNP=15.38%, FP=52.17%, OR=0.045; p<0.001) have been found associated with FP after Bonferroni's correction (Table 2).

Further, the analysis has been focused to another pattern of amino acid positions (80, 81, 82 and 83) located in or in the proximity of the F-pocket and belonging to α_1 (Figure 1B, right panel).

In particular, 80I (LTNP=80.77%, FP=34.78%, OR=7.86; p<0.036), 81A (LTNP=84.61%, FP=47.83%, OR=6; p<0.015), 82L (LTNP=88.46%, FP=47.83%, OR=7.86; p<0.006) and 83R (LTNP=88.46%, FP=47.83%, OR=7.86; p<0.006) have been found significantly associated with LTNP after Bonferroni's correction (Figure 1B and Table 2).

Considering that these four amino acid polymorphisms belong to epitope Bw4, previously found associated with HIV delayed disease progression [16-18], all the HLA-B alleles have been classified accordingly to carry Bw4 (77N, 80I/T, 81A, 82L, 83R) or its counterpart Bw6 (77S, 80N, 81L, 82R, 83G) epitope to performe a genotypic analysis.

As for the analysis of the polymorphisms, the phenotype frequency of Bw4 epitope resulted associated with LTNP (LTNP=88.46%, FP=47.83%, OR=8.36; p<0.006). To further deep the analysis, genomic distribution of Bw4 and Bw6 epitopes in the study groups has been evaluated (Figure 2). An overall significantly different distribution of the homozygous and heterozygous for Bw4 and Bw6 in the study groups has been found (p<0.002), with Bw4 and Bw6 homozygosis resulted significantly increased in LTNP and FP, respectively (Figure 2). No differences in the heterozygous Bw4/Bw6 frequency in LTNP vs FP have been observed (Figure 2).

Finally, the study of the 44 amino acid polymorphic positions in HLA-DR locus showed amino acid positions 26 (P=0.022), 32 (P=0.024), 73 (P=0.002), 74 (P=0.004) and 77 (P=0.023) significant after Bonferroni's correction (Figure 1C).

The analysis of the 114 amino acid polymorphisms in HLA-DR showed only for amino acid position A73 a significant association with LTNP (LTNP=100%, FP=78.26%, OR=N.A.; p<0.042) and for G73 with FP (LTNP=34.62%, FP=69.56%, OR=0.23; p<0.032) after Bonferroni's correction (Table 2 and S3).

Discussion

HIV-specific T-cell response, and in particular CTL, plays a key role

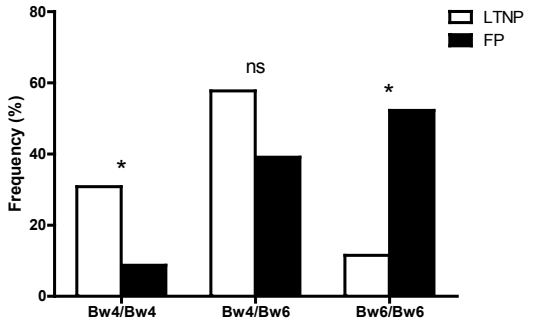

Figure 2: Genotype frequencies of HLA-B Bw4 and Bw6 epitopes in the study groups. Frequency of Bw4/Bw4 homozygous, Bw4/Bw6 heterozygous and Bw6/Bw6 homozygous is reported as percentage for LTNP (black bars) and FP (open bars). Statistical analysis between groups has been performed with chi-square and chi-square per trend test as appropriate. *p<0.05; ns=not significant.

in controlling HIV infection [1,19]. As the T-cell response is dictated by HLA molecules, the individual's variation in the HLA class I and II alleles has a profound effect on the outcome of infection and disease progression to AIDS [2,19].

In this study, in a defined cohort of children infected during an hospital outbreak with a monophyletic strain of HIV-1 [9], the role of amino acid polymorphisms determining specific characteristics of the HLA peptide binding pocket have been defined. In agreement with previous observations, but with the limitation of the small study population studied, the data indicate that the ability of certain HLA peptide binding pockets to present a specific set of epitopes against which the subject can mount an immune response, might represent the basis of the susceptibility to AIDS progression, at least for the HLA-B locus [1,2,6,19].

Only limited studies have been focused on the HLA class I and II amino acid polymorphisms that might play a role in the disease progression to AIDS. In a recent large multinational study focused on the model of HIV controllers [6], one polymorphic position of HLA-A (position 77) and three polymorphic positions of HLA-B (67, 70 and 97) have been found to play a major role in controlling HIV infection. With limit of the small study population and the different study design, but the strong advantage of the minimal HIV strain variability and other genetic background, this study is in agreement with these observations (see also Figure 1B).

Specifically, 67M and 70S resulted associated with HIV controllers and 97S associated with progressors in Pereyra et al. 2010. In this study the same associations are observed even if the significant P value is loss after Bonferroni's correction, due to the small number of patient analyzed in this study (see Supplementary information S3).

As expected from previous immunogenetic studies, the large number of residues found associated with LTNP or progression to AIDS, have been located in the HLA-B locus [2,6,20], particularly in the primary anchor binding B-pocket and F-pocket of HLA-B (see also Table 2).

This study shows a strong contribution of the F-pocket of HLA-B in HIV disease progression and non progression. Specifically, two patterns of polymorphism have been identified. A first pattern includes polymorphic variants 80I, 81A, 82L, 83R associated with LTNP, while a second pattern includes 74D and 94T polymorphic variants associated with progression to AIDS.

The polymorphic variants 74D and 94T are involved in positions located in F-pocket playing a minor role in peptide binding [21]. However, when these residues are present, they are associated with the binding of hydrophobic amino acid variants [14,22].

On the opposite, residues 80, 81, 82 and 83 are playing a primary key role in the interaction with the peptide in F-pocket of HLA-B [21]. The LTNP associated pattern 80I, 81A, 82R, 83L is typical of HLA-B alleles falling in supertypes such as B58 (grouping most of the HLA-B*57 and HLA-B*58 alleles) and B27, already found associated with slow progression to AIDS [2].

The same amino acid positions are involved in the epitope Bw4 and Bw6. When HLA-B alleles are classified according with carrying Bw4/Bw6 epitope, a strong contribution of Bw4 in delaying HIV progression has been observed. These results are in agreement with previous association of Bw4 homozygous and the control of HIV viremia [18].

The importance of epitope Bw4 is not only in its direct interaction with the bound peptide which therefore modify the CD8+T cell recognition. In fact, it is also a ligand for KIR3DL1, an NK's inhibitory receptor [23,24], suggesting a strong contribution of the innate immune response in controlling HIV progression and confirming the key role played by HLA-B molecules [16].

Other amino acid polymorphic positions of HLA class I molecule, might play an additional role in HIV progression upon interacting with NK receptors. Among them, amino acid position 194 located in HLA-Bα_3 domain might contribute to HIV progression (see also Figure 1). This polymorphic position not only influence the KIR3DL1 interaction [25], but represents also the binding site for LILRB1, another NK's receptor [26]. In this context, we have recently reported an immunoinformatic approach assessing the contribution of the different amino acid polymorphisms at position 194 of HLA-B in the interaction with LILRB1 and their role in HIV progression [27].

HLA-DR polymorphisms presented a lower impact in HIV progression, as already underlined in previous studies [6,28]. Only polymorphic residues in pocket 4, determining the peptide bound allele specificity and repertoire of antigenic peptides presented by HLA-DR molecules [13,29], seems to play a role in HIV progression. However, the specific contribution of Ala/Gly 73 polymorphisms to peptide binding capability is difficult to assess.

Altogether, these observations suggest that the progression to AIDS might be in part determined by the binding capability of B-pocket and F-pocket of HLA-B and in part by the interaction between HLA-B molecules and NK's inhibithory receptor which therefore regulate also the innate immune response.

In conclusion, with the limit of the small study population but the strong advantage of the homogeneous ethnic background and monophyletic HIV-1 strain infection in the evaluated cohort, the observations here reported might have important implications for a better control of the disease. The extension of this study by using immunoinformatic tools for the prediction of T-cells epitopes to the entire HIV-1 genome products, might shed new light on the mechanisms behind the association of genetic susceptibility to HLA in HIV-1 and represent a powerful tool for a more effective strategy in vaccine and diagnostics design ensuring wider coverage of the populations, including genetically susceptible subjects.

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