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MINIREVIEWS

Key role of human leukocyte antigen in modulating human immunodeficiency virus progression: An overview of the possible applications

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Abstract

Host and viral factors deeply influence the human immunodeficiency virus (HIV) disease progression. Among them human leukocyte antigen (HLA) locus plays a key role at different levels. In fact, genes of the HLA locus have shown the peculiar capability to modulate both innate and adaptive immune responses. In particular, HLA class I molecules are recognized by $CD8^+$ T-cells and natural killers (NK) cells towards the interaction with T cell receptor (TCR) and Killer Immunoglobulin Receptor (KIR) 3DL1 respectively. Polymorphisms within the different HLA alleles generate structural changes in HLA class I peptide-binding pockets. Amino acid changes in the peptide-binding pocket lead to the presentation of a different set of peptides to T and NK cells. This review summarizes the role of HLA in HIV progression toward acquired immunodeficiency disease syndrome and its receptors. Recently, many studies have been focused on determining the HLA binding-peptides. The novel use of immune-informatics tools, from the prediction of the HLA-bound peptides to the modification of the HLA-receptor complexes, is considered. A better knowledge of HLA peptide presentation and recognition are allowing new strategies for immune response manipulation to be applied against HIV virus.

Key words: Human immunodeficiency virus progression; Human leukocyte antigen; Epitope; Immunoinformatics; $CD8^+$ T lymphocytes

Core tip: Human immunodeficiency virus (HIV) disease progression depends on several host factors. Among them human leukocyte antigen (HLA) locus has a main role due to the peculiar capability to modulate both innate and adaptive immune response. In this review, the role of HLA molecules and its receptors in HIV progression toward acquired immunodeficiency disease syndrome is summarized. A better knowledge about HLA-peptide presentation and recognition by immune cells will open new applications in HIV vaccine and diagnostics design.

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INTRODUCTION

Different host's genetic factors have been associated both with rapid and slow progression to acquired immunodeficiency disease syndrome (AIDS). This suggests that the efficient control of human immunodeficiency virus (HIV) -1 infection lays on different variants of immune response associated genes. In this context, genetic association studies have been strongly limited by different factors. HIV-1 is a quasi-species virus with large variability among the population even if small geographical areas are examined. In this review, the strong contribution of human leukocyte antigen (HLA) locus in HIV progression is highlighted. The use of immune-informatics is capable to efficiently predict the HLA binding peptides, adding important information in this context. Overall, this might lead to the design of preventive vaccine and immunotherapies capable to improve the HIV immune response.

HIV IMMUNE RESPONSE

HIV immune response depends on both innate and adaptive compartment of the immune system. The primary HIV infection typically occurs in the mucosa. At this level, resident memory $CD4^+$ T cells are infected together with dendritic cells, granulocytes, natural killer (NK) cells and macrophages[1]. Subsequently, infected cells and virus particles bounded by dendritic cells and B lymphocytes reach the lymph nodes. Within the lymph nodes, HIV-1 infects also the effector-memory and the activated $CD4^+$ T cells.

These processes are responsible for the increase of viral spread, viremia and decrease in the number of $CD4^+$ T cells[1]. Early events, which occur directly after HIV infection, determine the course of HIV disease progression. The reduction of viral replication often occurs before the development of the adaptive immune response against HIV, suggesting that the innate immune system has an essential role in controlling the infection[2,3].

Studies on primary HIV infection before the seroconversion show the presence of HIV-specific adaptive immune response exert by $CD8^+$ T lymphocytes (CTL)[4-6]. CTL immune responses play a central role in the control of viral replication as it has been observed in Long Term Non-Progressor (LTNP) patients. Different mechanisms for viral inhibition mediated by CTL immune response have been observed.

HIV infected cells are recognized by the TCR of HIV-specific CTLs when viral peptides are presented at the cell surface in the context of HLA class I molecules. This recognition leads to CTL cytotoxic immune response[7].

Humoral immune response has a secondary role in the control of HIV infection. Although neutralizing antibodies reduce the virus particles and therefore the viral spread. However, serum of the infected patients does not reduce the viral infectivity *in vitro* and the efficacy of gp120 neutralizing antibodies is reduced. This is due to the fact that gp120, HIV glycoprotein responsible for the viral entry, has a high mutation frequency which leads to conformational changes impairing the antibody binding[7].

Due to the lack of capability of the immune response to eradicate HIV, the infection becomes chronic and the virus is integrated in a latent form in the human genome. Despite the return of circulating $CD4^+$T cells to normal levels, massive immune activation and accelerated cell turnover takes place. The ultimate consequence of immune activation is the depletion of $CD4^+$ T cells. In absence of T helper response the immune system is not able to control other infections, therefore opportunistic infections occur and lead to AIDS[1].

In general, HIV protective immune response is associated with recognition and activation of the cytolytic function exerted mostly by NK and $CD8^+$ T cells. Thus, the contribution of HLA molecules and its ligands play a key role in controlling HIV disease progression[8].

HIV PROGRESSION

The progression of HIV infection has different phases. In the primary infection, HIV infects mainly macrophages and dendritic cells by using the co-receptor C-C chemokine receptor 5 (CCR5) together with the CD4 molecule. Virus replication in the lymph nodes leads to the viremic peak characteristic of acute infection[4,5]. The viremia increases the viral spread in the other lymph nodes of the entire organism. The immune system mounts a response to control the viremia, which decreases towards a stationary phase named "set point". In most of the cases, the immune response is not capable to eradicate the infection. Therefore, an equilibrium between host and virus occurs and the viral DNA is integrated in a latent form that could not be detected by the immune system[6].

In the late phase of the infection, the constant viral replication induces a tropism shift. The virus prefers C-X-C chemokine receptor type 4 co-receptor (CXCR4) and infects mainly the $CD4^+$ T-cells. The $CD4^+$ T-cells depletion (< 200 cell/mm^3) and the increase of the viral load lead to an impairment of the entire immune system. Therefore, opportunistic infections occur, leading to AIDS and often to death[7]. Clinical latency period has a large variability in the HIV-infected subjects with different disease progression rates in absence of antiretroviral therapy.

Most of the infected individuals (70%-80%) are defined as slow progressors (SP). SP are characterized by increasing of viral load and $CD4^+$ T-cell count decline towards AIDS within 6-10 years of HIV infection. A smaller percentage of individuals (10%-15%), defined as fast progressors, have a fast CD4 count decline and develop AIDS within few years after infection. The LTNP represent about 5% of the infected cases and do not have significant changes in CD4 count, viral load or clinical symptoms for over 10 years[7-9]. Among them, a subgroup named elite controllers (EC) is characterized by stable $CD4^+$ T-cell count, undetectable viremia and no clinical symptoms overtime[10].

Overall, the strong individual variability to HIV infection highlights the importance of the host factors in delaying HIV progression toward AIDS. Different host factors have been widely associated with HIV progression and can be classically divided into two different groups: one related to a reduction in the viral entry capability and the other one with the interference with the viral replication process.

Reduction of viral entry has been associated with different receptors, co-receptors and ligands. Among them the CCR5Δ32 in combination with higher C-C Chemokine ligand 3-like 1 (CCL3L1) copy number and RANTES or Stromal cell–derived factor 1 chemokine variants have been extensively studied[9,11-14]. Regarding the viral replication processes, a pioneer work of Brass led to the identification of all the possible host endogenous proteins related with HIV infection[15].

Among them Zinc Ribbon Domain-containing 1 (ZNRD1), HLA Complex P5, (HCP5) Apoipoprotein B mRNA editing enzyme catalytic polypeptide-like 3G (APOBEC3G) genes have been extensively studied in association with delayed HIV progression. However, further studies regarding other possible interacting proteins still need to be addressed[16-18].

More recently, a contribution of micro-RNA has been described in HIV context leading towards interesting alternative approaches[19].

In addition, other immune related mechanisms have been associated with HIV control by immune response. This is the case of TNF-α and Ig enhancer HS1, 2 last but not least in showing a role in controlling HIV progression. Although, these factors barely play a role in delaying HIV progression compared with other host factors[20,21].

Beside the constant discovery of novel host variants, multiple issues such as population dependency might increase the difficulty to perform an association with HIV progression. For these reasons, HLA locus remains the unique factor clearly associated with HIV progression among the human population. However, different HLA alleles play a main role in HIV disease progression depending on the population considered.

Moreover, the HLA locus is the only one capable to modulate both innate and adaptive immune responses against viral infections respect to other immune related genes. Therefore, HLA locus might be used not only for diagnostic purpose, but also for drug and vaccine design approaches.

HLA

The *HLA* gene products are highly polymorphic molecules, characterized by co-dominant expression and polygeny. The combination of polygenicity and polymorphism has two important consequences. First, it ensures that each individual will be able to present a broad range of peptides. Second, the population will be consisted of individuals presenting different peptide's repertoires[22].

It is possible to distinguish the HLA molecules in two different classes: HLA class Ⅰ and HLA class Ⅱ[23].

HLA class Ⅰ is expressed on all nucleated cells and are recognized by $CD8^+$ T-cells[23]. The overall structure of HLA class Ⅰ molecule is shown in Figure 1A. The β2-microglobulin is a monomorphic polypeptidic chain and its main role is to keep the tridimensional structure of HLA class Ⅰ molecules. The α-chain is responsible for the peptide binding and interacts with TCR, CD8 and innate immune receptors. The binding of the peptide as well as the TCR interaction are mediated by α1 and α2 domains. Both of them present two main interaction pockets (B and F), which directly interact with the bound peptide (Figure 1B). HLA class Ⅰ molecules bind peptides between 8–12 amino acids long which are derived from proteolysed endogenous protein fragments[23].

HLA class Ⅱ is expressed only on antigen presenting cells and are recognized by $CD4^+$ T-cells[23].

HLA class Ⅱ molecule is composed by two polypeptidic chains (α and β) with a similar structure and belong to Ig superfamily. Both α and β chains participate in the peptide binding (Figure 2A). The two chains are bound in a non-covalent manner and can be further divided in two different domains. The first domain of each chain (α1 and β1) is responsible for the peptide binding and TCR interaction. The second domain of each chain (α2 and β2) has an important role in the HLA class Ⅱ structure and in the interaction with CD4 molecules.

The two HLA molecules have a distinct pattern of expression and cellular interaction. HLA class Ⅰ molecules are expressed by all nucleated cells and recognized by CTL. HLA class Ⅱ molecules are selectively expressed on antigen presenting cells such as macrophages, monocytes, B lymphocytes and dendritic cells. HLA class Ⅱ molecules are recognized by T helper lymphocytes[24]. The main role of HLA molecules is to present the antigen to different immunological receptors. In first approximation, HLA class Ⅰ molecule presents peptides derived from endogenous/cytosolic proteins, while HLA class Ⅱ presents peptides derived from exogenous proteins[25].

In addition, HLA class Ⅰ molecules play an important role in the activation of the innate immune response. In fact, HLA class Ⅰ molecules interact also with innate immune receptor expressed by NK cells[26]. The wide inter- and intra-population diversity in HLA locus

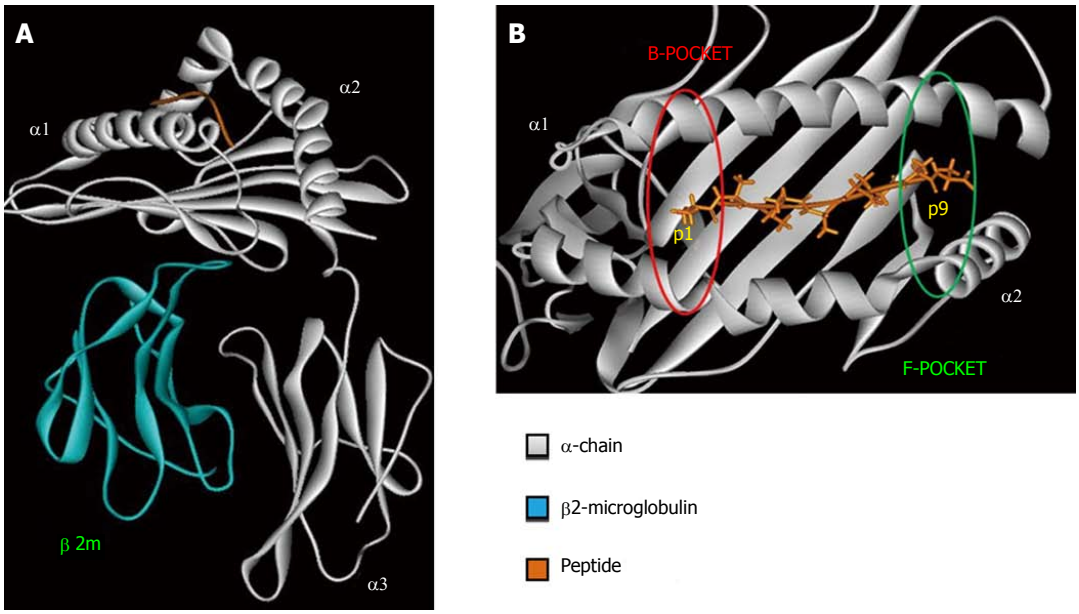

Figure 1 Human leukocyte antigen class I tridimensional structure. Crystal structure of the HLA-B*57:03 (PDB ID: 2YPK); HLA α-chain in gray, β2-microglobulin in blue, the peptide in orange. A: HLA class I overall structure; B: HLA class I peptide binding pocket. In red is shown the HLA pocket B, in green HLA pocket F the most polymorphic regions in HLA peptide binding pocket. The figure has been made using WebLab Viewer Pro 3.7. HLA: Human leukocyte antigen.

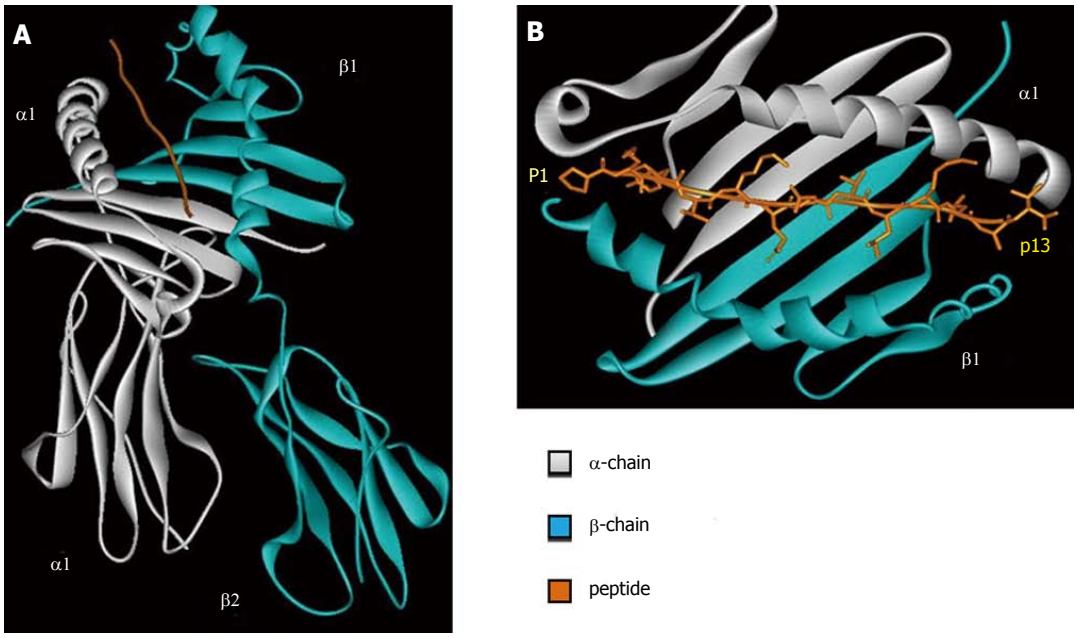

Figure 2 Human leukocyte antigen class II tridimensional structure. Crystal structure of the HLA-DR1 (PDB ID: 1DLH) in gray HLA α-chain, in blue HLA β-chain, in orange the peptide. A: HLA class II overall structure; B HLA class II peptide binding pocket. The figure has been made using WebLab Viewer Pro 3.7. HLA: Human leukocyte antigen.

and the presence of other immune associated genes increases the difficulty to select the genetic variant(s) responsible for the disease susceptibility. However, HLA alleles' association with particular immunological profile has been consistently assessed for different chronic viral infections including HIV.

In this context, heterozygosis for HLA class I molecules has been associated with HIV delayed disease progression and lower mortality in HIV infected patients[27,28]. In addition, various HLA alleles have been associated with an increase or decrease risk of HIV vertical and horizontal transmission and hypersensitivity to anti-HIV therapy[29,30].

HLA IN HIV PROGRESSION

HLA/HIV association studies are useful to evaluate the host-pathogen interaction. HLA is important not only for the adaptive immune response but also for innate immune response. Polymorphisms within the

different HLA class I alleles generate structural changes in peptide-binding pockets. Amino acid changes in the peptide-binding pockets lead to the presentation of a different set of peptides to CTLs[31-33].

The ability of particular HLA alleles to induce a viral selection could predict the HIV viral load. This could provide an "a priori" information about the disease progression[34]. Evaluations of HLA supertypes, group of alleles that share specific peptide-binding preferences, simplify the association studies with different disease progression.

The study of EC sheds light on the contribution of Human Leukocyte Antigen B (HLA-B)*57:01 (Supertype B*58) allele with HIV delayed disease progression. This allele is able to recognize a conserved epitope of HIV Gag protein, leading to a higher $CD4^+$ T-cell count and lower viral load in absence of Highly Active Antiretroviral Therapy therapy (HAART). HLA-B*57:01 is also characterized by the presence of unique valine at position 97 that contributes to the formation of the C-pocket in the peptide-binding cleft[31,33].

When a subject that do not carry HLA-B*57:01 allele is infected with a viral strain derived from a B*58 patient, it resembles the same $CD4^+$ T-cell count and viremia of the B*58 patient. This observation suggests that HLA exerts a strong restriction on the viral replication and the viral mutant selected have a lower fitness[35].

Other studies have associated HLA-B*27 and HLA-B*58 with a low viral load and higher $CD4^+$ T-cell count. In this context, the selectivity exerted by CTL after antigen recognition by HLA class I molecule is responsible for delaying the HIV progression[28,31,33,36-38].

Several HLA-B alleles have been associated with HIV rapid disease progression. Among them HLA-B*35 supertype contributes to a reduction of CTL peptide recognition and therefore leads to a non-efficient viral control[28,37]. Further, supertype B*7 has been associated with high viral load, decrease CTL response and consequently rapid HIV progression towards AIDS[28,31].

Multiple issues such as the viral strain variability within the subjects and the different genetic background of the population have limited the association studies related with HIV progression.

In this context, we performed a study in a defined cohort of children infected during a hospital outbreak with a monophyletic strain of HIV-1[39]. The role of HLA amino acid polymorphisms determining specific characteristics of the HLA peptide-binding pocket has been assessed. In particular, HLA-B peptide binding pockets present a specific set of epitopes against which the subject can mount a HIV-specific immune response. According to previous observations, these findings might represent the basis of the HIV disease progression[40-44].

As expected from previous immunogenetic studies, a large number of residues found in association with LTNP or progression to AIDS have been located in the HLA-B locus[42-46]. Recently, we have further supported this notion with in silico identification of the HIV *gag* protein epitopes. The study has been performed on the same outbreak cohort using HIV-1 viral sequences and HLA alleles. Peptides deriving from the HIV-1 sequences and recognized by the HLA allele combinations of the study subjects have been further analyzed.

Non-progressors recognized a higher number of epitopes compared to progressors in any HLA locus analyzed[47]. This is in agreement with previous observations showing an important contribution of CTL immune response in controlling the HIV disease progression. In a nutshell, HLA class I molecules and the recognition of large set of CTL epitopes are the key factors for delaying HIV progression[48-50].

CTL also determines escape mutants of the virus in different genes of HIV-1 such as Protease, Reverse Transcriptase (RT), Vpr and Nef[38,51]. Different HLA alleles, such as HLA-B*580[52], efficiently cross-recognize HIV-1 $CD8^+$ T-cell epitopes leading to delayed progression[53].

Recently, many studies have been focused on determining the HLA binding-peptides. The approaches are from direct measurement to the development of different Major Histocompatibility Complex (MHC) class I binding prediction systems[54-56]. Different online databases are capable to extract epitopes obtained from experimental and *in silico* studies giving also the opportunity to predict HLA binding epitopes using any target protein sequence[57-60]. The choice of the prediction system is very important and often the combination of more than one prediction system has shown the best performance[56,61-63].

Once obtained the predicted epitope, it is always very useful to perform a comparison with literature data. Thanks to the large *in vitro* characterization of HIV epitopes, it has been determined that most of the *in silico* predicted epitopes are also described within the literature. This supports the efficiency of prediction methods related with the epitope discovery[59,60].

Overall, HIV-specific T-cell response, and in particular CTL, plays a key role in controlling HIV infection[40,41]. T-cell response depends on HLA molecules. Thus, the individual's variations in the HLA class I and II alleles has a profound effect on the outcome of infection and disease progression toward AIDS[40,42].

NOVEL ASPECT IN HLA-HIV INTERACTION

HLA-B polymorphic variants 80I, 81A, 82L, 83R have been associated with LTNP[46]. These positions interact with the peptide in the F-pocket of HLA-B[46,64]. The LTNP associated pattern 80I, 81A, 82R, 83L is typical for HLA-B supertypes B58 and B27 which are already found associated with a slow progression to AIDS[42]. The same amino acid positions are involved in the formation of the structurally related HLA serotyping epitope Bw4 and Bw6. When HLA-B alleles are classified accordingly with carrying Bw4/Bw6 epitope, we have shown a

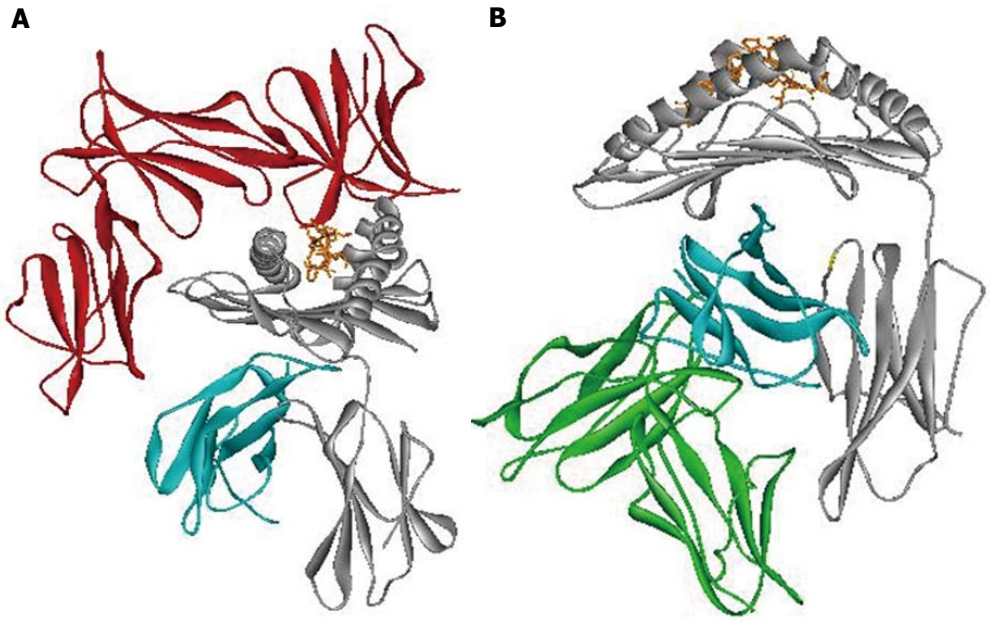

Figure 3 Human leukocyte antigen class I interaction with innate receptor. Crystal structure models of the HLA-B*57:01 interacting respectively with (A): KIR3DL1 receptor (red) (PDB ID: 3HV8); (B): LILRB1 receptor (green). HLA α-chain in gray, β2-microglobulin in blue, the peptide in orange. The figure has been made using WebLab Viewer Pro 3.7. HLA: Human leukocyte antigen.

strong contribution of Bw4 homozygosis in delaying HIV progression[46,65]. These results are in agreement with previous associations between Bw4 homozygosis and the control of HIV viremia[66].

The importance of epitope Bw4 is due to different aspects. First, it has a direct interaction with the HLA bound peptide involved with $CD8^+$ T cell recognition. Second, it is also a ligand for Killer Immunoglobulin Receptor 3DL1 (KIR3DL1), an NK's inhibitory receptor (Figure 3A)[67,68].

This evidence suggests a strong contribution of the innate immune response in controlling HIV progression and confirming the key role played by HLA-B molecules[2]. Recent studies evaluated the different contribution of KIR3DL1/HLA-B allele's interaction in modulating the innate immune system[68-71]. The presence of HLA-B Bw4 epitope leads to a stronger interaction with all the different KIR3DL1 alleles. This is particularly evident within the HLA-B alleles belonging to the same supertype, in agreement with previous data[72-75].

Different studies evaluate the contribution of Leukocyte Immunoglobulin-Like Receptor subfamily B member 1 (LILRB1) interaction with HLA class Ⅰ in the context of several infections (Figure 3B)[76-78]. Among HLA class Ⅰ polymorphisms, we associated the HLA-B alpha 3 domain amino acid position 194 with different HIV progression[46,65]. Amino acid position 194 of HLA-B has been found to take a part in the interaction with LILRB1 receptor (ILT2/LIR1/CD85j) when the Val variant is present[69,78,79]. Moreover, Val 194 was in association with LTNP[46,65]. Change in the strength of interaction between HLA-B alleles carrying Ile 194 and LILRB1 receptor might lead to rapid HIV progression. Previous data suggests that the expression of LILRB1 receptor on the cell surface remains unchanged in subjects with different HIV progression[80]. However, the presence of different amino acids at the polymorphic position 194 of HLA-B might modify the interaction with LILRB1. This might influence the LILRB1 strength of binding, as already reported for the LIR1-HLA-A interaction[77]. These results show the influence of HLA allelic variation and conformation on LILR binding capability. These findings are according to recent studies particular in the HIV context[77,78].

The contribution of the HLA-bound peptide seems to be the key point able to disrupt HLA interaction with the different immune receptors (Figure 4). In the context of HLA-B/KIR3DL1 interaction, the HLA-bound peptide position P8 is the main one that is able to disrupt KIR3DL1 binding. This has been previously observed in KIR3DL1 interaction with HLA-B*27:05 and HLA-B*57:01 alleles due to the conserved amino acid residue Glu282 of KIR3DL1 receptor[68,81-85]. The strong influence of the HLA bound peptide in the modulation of the innate immune response, point out similarity between T-cell and NK cell immune response. Individual selection pressures exerted on HLA class Ⅰ by T-cell and NK-cell might cause a competition between the two different immune responses. Therefore, depending on the HLA class Ⅰ allelic variant and the antigenic peptide loaded on HLA molecule we might observe a beneficial NK or T-cell response with detrimental consequences for the other one[86].

Altogether, the observations suggest that each peptide binding pocket position of the HLA class Ⅰ molecule is capable of modulating innate and adaptive immune

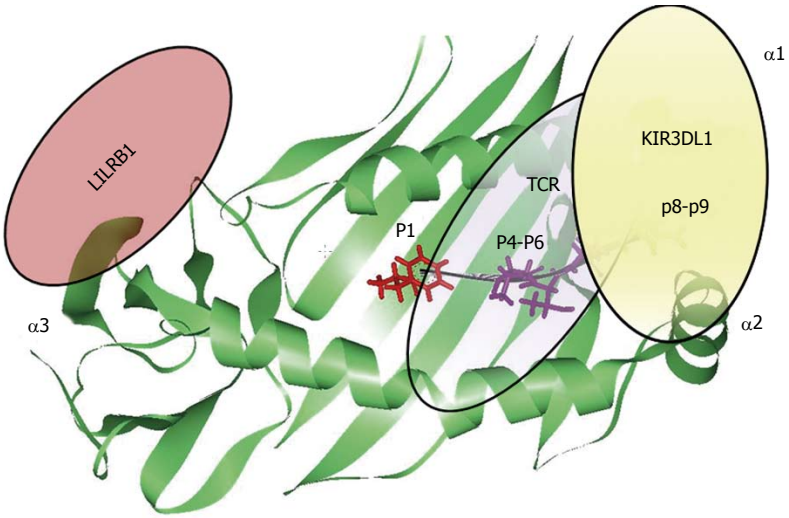

Figure 4 Peptide recognition. Schematic representation of the contribution of each HLA bound peptide position in the modulation of the interaction between HLA-B molecules (green) with TCR (violet) and KIR3DL1 (yellow), respectively. The figure has been made using WebLab Viewer Pro 3.7. HLA: Human leukocyte antigen; TCR: T cell receptor.

receptors leading to different immune responses (Figure 4).

Notably, identification of T-cell epitopes is actually made with the strategy of the reverse vaccinology. This strategy is based on HLA binding specificity and takes in consideration only the interaction with adaptive immune receptor. Future studies should be focused on the prediction of binding epitopes with wider characteristics. Peptides should be capable not only to be recognized by adaptive immune receptor, but also to modulate the innate immune receptor. These peptide characteristics could allow better fitting strategies for vaccination and diagnostics.

CONCLUSION

In conclusion, HLA molecules play a key role in modulating both adaptive and innate immune responses. The protective cytotoxic immune response is modulated by the interactions with TCR as well as other innate receptors[31,33]. The modulation of innate immune responses depends also on the peptide-binding capability of HLA-B and on the interaction between HLA-B and NK's inhibitory receptors such as KIR3DL1 and LILRB1. The observed fine tune regulation might play a key role in the progression of HIV infection. The application of immune-informatics to immunogenic studies might shed new lights on the mechanisms behind the association of HLA genetic susceptibility to viral infections. This represents a powerful tool for novel design of vaccine and diagnostics, ensuring wider population coverage with the inclusion of genetically susceptible subjects.

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