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Review Article

The influence of HLA/HIV genetics on the occurrence of elite controllers and a need for therapeutics geotargeting view

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ABSTRACT

The interaction of HIV-1, human leukocyte antigen (HLA), and elite controllers (EC) compose a still intricate triad. Elite controllers maintain a very low viral load and a normal CD4 count, even without antiretrovirals. There is a lot of diversity in HIV subtypes and HLA alleles. The most common subtype in each country varies depending on its localization and epidemiological history. As we know EC appears to maintain an effective CD8 response against HIV. In this phenomenon, some alleles of HLAs are associated with a slow progression of HIV infection, others with a rapid progression. This relationship also depends on the virus subtype. Epitopes of Gag protein-restricted by HLA-B*57 generated a considerable immune response in EC. However, some mutations allow HIV to escape the CD8 response, while others do not. HLA protective alleles, like HLA-B*27, HLA-B*57 and HLA-B*58:01, that are common in Caucasians infected with HIV-1 Clade B, do not show the same protection in sub-Saharan Africans infected by HIV-1 Clade C. Endogenous pathway of antigen processing and presentation is used to present intracellular synthesized cellular peptides as well as viral protein fragments via the MHC class I molecule to the cytotoxic T-lymphocytes (CTLs). Some epitopes are immunodominant, which means that they drive the immune reaction to some virus. Mutation on an anchor residue of epitope necessary for binding on MHC class I is used by HIV to escape the immune system. Mutations inside or flanking an epitope may lead to T cell lack of recognition and CTL escape. Studying how immunodominance at epitopes drives the EC in a geographically dependent way with genetics and immunological elements orchestrating it may help future research on vaccines or immunotherapy for HIV.

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Introduction

HIV has led to a pandemic with significant mortality and morbidity. Its detection in the 1980s changed the world. Understanding the virus and its relationship to the immune system is fundamental for preventive or therapeutic vaccines. HIV is highly mutable. This study will investigate HIV type 1 (HIV-1) and the patients who control the virus without antiretrovirals; “elite controllers” (EC)¹ who maintain very low viral loads and normal CD4 counts, besides the interaction of HIV with human leukocyte antigens (HLA) of these patients. HIV-2 was discovered later, occurring mainly in West Africa² and accounting for a much lower percentage of infections worldwide.³

EC are very rare, approximately 1 in 300 HIV patients or less than 0.5%.⁴ This study will focus on immunological aspects presented by this type of patient, but it will not explain all the occurrences.⁵

The geographical distribution of HIV-1 subtypes has been studied based on data collected between 1990 and 2015.⁶ While subtype B predominates in North America and Western Europe, most infections in sub-Saharan Africa and India involve subtype C. Subtype A is also common in Africa.

In Brazil, there are several subtypes of HIV-1 and their distribution varies. According to Riedel et al.,⁷ B is the most common subtype in Brazil, followed by C, F, and CRF31_BC recombinants, especially in southern Brazil.

Even inside Brazil, there is diversity in HIV subtypes. Subtype B is the most prevalent in the Southeast and Northeast/Midwest regions (90% and 85%, respectively).⁷ In the South Region there is a larger prevalence of subtype C when compared to subtype B: Santa Catarina state 48% and 23%, Rio Grande do Sul state 29% and 23%, and Parana state 36% and 38%, respectively.

A study on sequencing and HLA typing in HIV-infected patients who are undergoing antiretroviral treatment in southern Brazil found a more heterogeneous scenario, where the most frequent subtypes of HIV-1 were B (46%) and C (31%), in addition to single BC recombinants (14%), single BF recombinants (7%) and single BCF recombinants (2%).⁸

A recent review⁹ studied 2447 HIV-1 genotypes collected between 2008 and 2017 from Brazilians who had never used antiretrovirals. The nationwide prevalence of subtype B was 64.19% and 18.37% of subtype C.

HIV penetrates cells through an interaction between glycoprotein gp120 and cell surface receptor CD4, along with co-receptors CCR5 or CXCR4.¹⁰

Despite the importance of CD4+ cells in the viral invasion, the first cells of the immune system to have contact with HIV are usually dendritic cells, found in many human tissues, such as the mucosa of genital and anal areas. Once HIV infection becomes established, cytotoxic response and neutralizing antibodies appear, but generally at insufficient levels to eliminate the virus.¹⁰

A study on the production of cytokines in a cohort of HIV-infected patients found an association between EC and the genetic variant -208A TNF- α (7 of 8 patients).¹⁰ The relationship between TNF- α and natural HIV control requires further studies.

The CCR5 Δ 32 mutation is also correlated with resistance to HIV infection. The deletion generates a truncated protein that

is not carried to the cell surface. Individuals homozygous for this deletion are resistant to infection by HIV-1 with CCR5 tropism, since the mutation prevents the entry of the virus.¹¹

After HIV infection, the RNA is undetectable for a few days (the eclipse stage), and then a peak in viremia occurs, with extensive destruction of CD4+ cells, although EC achieve spontaneous control of the virus.¹¹

HLA and HIV control

CD8+ T lymphocytes recognize and destroy cells that express non-self peptides in MHC molecules on the surface of nucleated cells. These MHC molecules are also called HLA. In this context, EC also appear to maintain an effective CD8 response against HIV.¹¹

HLAs are related to the degree of immune control of HIV, especially among EC. The cellular immune response is linked to the individual's immunogenetic profile, including HLA class I expression.⁸

Some alleles of HLAs are associated with slow progression of HIV infection, such as HLA-B*57, HLA-B*58:01, HLA B*57:03, and HLA-B*27, while others are linked to rapid progression, such as HLA-B*35 and HLA-B*58:02.^{10,12}

An international consortium studied several HIV EC, finding that alleles such as HLA-B*27:05, and HLA-B*14, were also associated with elite control, while supertypes HLA-B*07 and HLA-B*35 were associated with an increased risk of disease progression.¹³ Here is important to highlight that both studies linking HLA-B*35 with rapid progression did not consider its subdivision in Px (B*3502, B*3503, B*3504, and B*5301, e.g.) and Py (HLA-B*3501 and B*3508, e.g.) alleles. Peptides presented by these MHC molecules differ in their F-pocket anchor residue (position 9), where Py alleles bind tyrosine residues, and Px alleles have a more promiscuous pattern in this position. Some studies associate Px alleles with fast progression, while Py seems not to influence disease progression. It denotes the importance of high-resolution HLA sequencing.^{14–16}

Nevertheless, some subjects with Py HLA-B*3501 allele more effectively controlled C-clade-infected African cohorts through NY10₂₅₃₋₂₆₂ Gag-specific epitope, which was not observed in B-clade-infected individuals. It was probably caused by Gag-D260E polymorphism present in ~90% of B-clade sequences, affecting T cell recognition.¹⁷

HLA-B*35:05, structurally related to Py alleles, also presented a protective effect (the strongest among the analyzed alleles) in HIV-1 CRF01_AE-infected Thai patients, regarding viral load.¹⁸ These studies demonstrate the need to consider both genetics of both host and parasite for each considered population.

In another study, among patients on HIV treatment, the HLA-B*14:02:01 allele was related to CD4 counts below 350 cells/mm³, indicating an association with a worst clinical outcome.⁸ The HLA-B*51:01:01 allele and the HLA-B*07-supertype, associated with an HIV viral load below 100,000 copies/ μ l of whole blood before treatment, are considered as potential protective alleles, especially in patients infected with HIV Clade C, while the HLA-B*44 supertype is considered a potential allele for faster disease progression.⁸ Although the HLA-B*07 supertype was considered related to a faster disease

progression in another study,¹³ it is important to remember that, in the first study, patients from Brazil were infected mostly with HIV Clade C,⁸ while in the second there were patients from different countries and mainly with HIV subtype B. Some conflicting results indicate a need for a deeper investigation of HLA, recognized cytotoxic epitopes and patients onset relations.

Another important point refers to the pathogen's genetic features. The HLA-B*57:01 and HLA-B*27:05 alleles, for example, show an association with better control of HIV through cellular immune response depending on HIV subtype.⁸ The HLA type and virus interaction are major determinants of durable immunological control.¹⁹ The interaction between HLA and HIV subtypes is a crucial element discussed in this article.

The population of Brazil is ethnically diverse, including the descendants of indigenous peoples, Europeans, and Africans. Thus, it is expected a highly diverse frequency composition of HLA alleles. We will discuss HLA diversity in Brazil related to HIV.

In a study of allele frequencies in Brazilian bone marrow donors, the most frequent allele groups were A*01, A*02, B*35, B*44, C*07, DQB1*03, DQB1*06, and DRB1*01.²⁰ HLA-B*35 frequency in Brazil is 11.8%,²¹ which is an important issue that could favor rapid progression of HIV in Brazilian patients. A more recent study updated this information, segregating Px and Py B*35 frequencies. In this study, HLA-B*35:01 and -B*35:08 allele frequencies (Py alleles) summed up to 7%. Px alleles (HLA-B*35:02, -B*35:03 and -B*35:04) accounted for 4.2%.²² While we already discussed differential disease progression rates for Px and Py alleles, studies from Mexico and Peru did not find differences in this variable among infected individuals. So, once again, the importance of the considered population remains, positioning a country like Brazil, with a high frequency of HLA-B*35 alleles, as an eligible place for a detailed HIV geotargeting investigation.^{23,24}

On the other hand, the frequency of protective alleles as HLA-B*57:03 in Brazil is low, with about 0,6% among Rio de Janeiro Caucasians. A study in blood marrow donors in Brazil found an HLA-B*57 national frequency of 2.8%, where the South region presented a similar frequency of 2.8%, compared to 2.4% in the North region.²¹

HLA-B*27 frequency in Brazil was 2.23%, with differences between the South and Southeast regions: 2.66% and 2.16%, respectively.²¹ HLA-B*58 frequency in this country was 2.65%, while the frequency in the Southeast region was 2.73 and 1.87% in the South region.

A similar recent study²² in blood marrow donors from Brazil, using high resolution typing data, updated this information for six ethnic groups by classifying them according to self-reported race group. The frequency of HLA-B*57:03 protective allele ranged from 0.3 to 1.5% in *Amarela* (Asian) and *Preta* (Sub-Saharan African Descent), respectively. In relation to B*27, *Preta* presented 1.25% and *Branca* (European) the higher frequency (2.1%). The frequencies of B*58 subtypes among the analyzed groups ranged from 0.4 to 2.7%, with *Branca* showing the lowest value for B*58:02 and *Preta* presenting the highest frequency of B*58:01. These contrasting values point out that in admixed populations, a personalized approach is even more crucial.

HIV epitopes, HLA, and elite controllers

Some HIV viruses undergo epitope mutations that allow them to escape the CD8 cellular immune response. The CD8+ immune response selectively pressures these mutations, and when they reach essential and more conserved regions of the viral genome, the mutations can result in loss of viral "fitness", resulting in their disappearance from a patient's viral population.¹¹

Different HLAs have been associated with relative protection against disease progression and even virus control by the immune system. Goulder et al.²⁵ studied the relationship between the HIV epitopes and HLA and found that it was generally related to changes in the HIV Gag protein, in which some HLA class I alleles are related to a better prognosis and others to greater susceptibility. It seems to be related to HIV subtype analyzed and population affected.

Mixed populations bring a big challenge. A study in Mesoamerican patients found some HLA alleles to be protective against HIV Clade B, including canonical ones like HLA-B*27:05 and HLA-B*57:01, but also new alleles like HLA-B*39:02, with a Canadian population as control.²⁶

The immune response to HIV that leads to control without the use of antiretrovirals seems to be linked to CD8+ lymphocytes. HLA-B*57 is often present in elite controllers. Epitopes of Gag protein restricted to this HLA, such as IW9 (Gag 147–155), KF11 (Gag 162–172), and TW10 (Gag 240–249) generated a considerable immune response measured by interferon and perforin levels in lymphocytes from elite controllers, even with peptide mutations.²⁷

As mentioned earlier, human HLA-B*27, HLA-B*57:01, HLA-B*57:03, and HLA-B*58:01 alleles have shown greater correlation with HIV control. Patients with HIV and HLA-B*27 can mount a CD8+ immune response against the KK10 (KRWILGLNK) epitope of the Gag protein capable of controlling viremia.

According to Ladell et al., the KK10 epitope in the Gag protein appears to be immunodominant in the CD8+ response.²⁸ Other authors have found HLA-B*14:02 to be protector when interacting with HIV-1 subtype B. In the presence of this HLA and this type of virus, an alternative Env epitope (ERYLKDQQL) becomes immunodominant, highlighting the importance of the interaction between the infectious agent and host genetics.²⁹ Whether Gag mutations frequently cause loss of viral replicative capacity, Env protein mutations typically are tolerated by the virus without loss of replicative capacity.

In African American patients with HIV subtype B, certain HLAs were related to better viral control, especially HLA-B*14, HLA-B*57:01, and HLA-B*57:03, while other HLAs were related to worse outcomes (HLA-B*15:10, HLA-B*35:01 and HLA-B*53). HLA-B*81 was shown to be protective in Africans with HIV-1 subtype C virus, but HLA-B*13 did not have the same effect in this population.³⁰

The geographic ethnic component can influence the response to the virus, explained by genetic diversity of the occurring viruses and the local human population. The relationship of HLAs that confers HIV-1 protection/susceptibility is coordinated by some common alleles around the world,

while specific alleles appear depending on the region and the subtype of the virus investigated.

In two African elite controllers infected with HIV-1 virus subtype C, the following protective HLA alleles were found in patient 1 HLA-B*44:03, HLA-B*81:01, and HLA-DRB1*13, while patient 2 expressed HLA-A*74:01, HLA-B*57:03, and HLA-DRB1*13. For one patient, the HLA-B*81:01 Gag response was immunodominant and likely contributed to viral control. p21, the intrinsic cellular inhibitor of HIV reverse transcription, was also more expressed in these patients than in seronegative donors. The response to HIV seems to be more related to cellular immunity than the presence of neutralizing antibodies.³¹ This work emphasizes the importance of a closer look towards the particularities of HIV infection depending on the virus subtype and the population investigated.

Other uncommon alleles were described as protective. A study was conducted on two HIV-infected patients, one characterized as an EC and the other as a progressor. The CD4+ lymphocytes of both were susceptible to HIV with CCR5/CXCR4 tropism, in addition to being heterozygous for the CCR5Δ32 deletion.¹ The HIV subtype of the EC was CRF02_AG, and the subject's partner had the same virus with 100% homology. The EC's HLA was HLA-A*03-A*31, with homozygosity in the HLA-B*07 alleles and HLA-C*07. The elite controller's partner was HLA-B*07-B*52, HLA-C*07 heterozygous and HLA-C*12 heterozygous.¹ The HLA-B*07 is consistently linked to accelerated disease progression in B-clade, but not in C-clade infection.³² Different expressions of the same virus in two patients show the importance of the interaction between the genetics of the host, the source, and the viral strain in the development of an EC, in addition to being a model for future control of HIV infection.¹

HLA, mutations, and loss of immunogenicity of epitopes

According to Buggert et al.,³³ some mutations allow HIV to escape the CD8 response while others do not. A study conducted on patients with HLA-B*57:01 who were infected with HIV-1 subtype B and found that some epitopes were related to better cellular response. In this study, KF11 (KAFSPEVIPMF) epitope, a fragment of the HIV-1 Gag protein, is highly conserved in HIV-1 subtype B and maintains its immunogenicity even with mutations. On the other hand, HQ10 and ISW9 epitopes showed a panel of mutations that caused loss of immunogenicity in patients with HLA-B*57:01 infected with HIV-1 subtype B.

Caucasians have a 16% frequency of HLA-B*27:05 and/or HLA-B*57:05, and the KK10 Gag epitope seems closely related to HLA-B*27:05 protection.³⁴ The reason why not everyone with these HLAs become EC is still under study. The T242N mutation, within the HLA-B*57:01 restricted TW10 (TSTLQEQIGW) epitope, was related to loss of HIV control. Klopper et al.³⁵ found a relationship between protective HLA-selected epitopes, like HLA-B*27 and KK10, and viral fitness. Some mutations cause impaired viral replication capacity and are transmitted with benefit to the host. The dominant observed escape mutation in KK10 epitope, R264K, arises at the anchor position-2 (P2) in the epitope that is believed to require

Arginine for adequate binding to HLA-B*27.³⁵ The mutation L268X (where X represents Met or Ile at P6 in the KK10 epitope) occurs prior to R264K, and this is associated with reduced immune control.

Mutations on HLA-B*57 Gag IW9 and TW10 were associated with faster disease progression. This study found that these HLAs selected epitopes in which many mutations occur have an impaired viral replication capacity, demanding compensatory mutations to maintain their virus fitness.

There are differences in HLA protective alleles, like HLA-B*27, HLA-B*57, and HLA-B*58:01, that are common in Caucasians infected with HIV-1 Clade B but cannot show the same protection in sub-Saharan Africans infected by HIV-1 Clade C and presenting a different genetic HLA composition. The KK10 escape mutation R264K in C clade in individuals HLA-B*27-positive is selected when prior escape at L268 is not present. In this situation, the compensatory mutation is typically S165N.³⁵

Mutations selected in KK10 epitope include R to K in position 2 in HIV Clade B in 5% of patients.³⁶ This is a very conserved region in Gag protein. Other African HLAs, like HLA-B*81:01, are also linked to protection to AIDS progression and select the TL9 Gap epitope in the sub-Saharan population.³⁵

The HLA-B*57:01 allele selects some protective HIV Gag epitopes, like TW10, IW9, QW9, and KF11, by CD8+ T cells response.³⁷ One common escape mutation in TW10 epitope is T3N (TSTLQEQIGW) that changes the conformation of the exposed epitope to abolish immune recognition. This mutation enables HIV-1 immune escape in people with HLA-B*57:01.³⁷

HIV-1 can increase cellular endocytosis of HLA molecules via nef, limit HLA transcription and peptide processing via tat, and suppress TAP-mediated peptide transport into the endoplasmic reticulum.³⁷

Epitope processing and TCR recognition

The endogenous pathway of antigen processing and presentation is used to present intracellular synthesized cellular peptides as well as viral protein fragments via the MHC class I molecule to the cytotoxic-T-lymphocytes (CTLs). In this pathway, the proteins that are destined for the presentation are marked by ubiquitination and subjected to proteolytic cleavage by the immunoproteasome. These fragments of peptides are transported to the lumen of ER by a transporter associated with antigen processing protein (TAP). The TAP proteins also help the loading of the short peptides with appropriate length (nearly nine amino acids) into the cleft of MHC class I molecules. Although proteasome is the main actor in generating the bulk of the CTL epitopes, cytosolic endopeptidases may also be involved in the production of certain CTL epitopes.³⁸

The HLA-I (the human MHC-I class of proteins) will present endogenous peptides. Some HLA-I alleles are linked with protection against infectious diseases, like HIV and hepatitis C virus with HLA-B*27. The antigen processing pathway is also important for study of immunological reactions to viruses.³⁹

Some epitopes are immunodominant, which means that they drive the immune reaction to some virus. These types of

epitopes share some characteristics, especially structural ones, when complexed to the HLA cleft. Discovering common viral immunodominance can help develop viral vaccines.⁴⁰

CD8+T cells exert immune selective pressure on HCV.⁴¹ In HIV it is observed a preferential expansion of CD8+T “escape specific” cells triggered toward altered epitopes selected during the HIV infection course, especially through HLA-B*27 and HLA-B*57 alleles. These alleles are connected to slower disease progression.⁴¹

Mutation on an anchor residue of epitope necessary for binding on MHC class I is one way that HIV uses to escape the immune system.⁴¹

ER aminopeptidase I (ERAPI) is an endoplasmic reticulum resident aminopeptidase involved in antigen presentation.⁴² It was studied in a murine model. One study found that CD8+T cells could not recognize HIV-infected cells containing proline at Gag residue 146.⁴² Failure of ERAPI to process the mutant peptide resulted in an inability of the optimal epitope to be generated and impaired the immune response.

The Ubiquitin-Proteasome System (UPS) interacts with HIV-1 aiding with degradation and removal of viral proteins.⁴³ This virus changes UPS to escape from the human immune system.

Eccleston et al.⁴⁴ simulated the HIV-1 clade C peptide presentation on TCL surface with bioinformatics tools, which predicts the peptidome of an amino acid sequence, the probability of proteasomal cleavage, TAP affinity, and the affinity (IC50) between the peptide and chosen MHC-I. These pieces of information were combined in a score. Four alleles associated with better control of HIV: HLA-B*58:01, HLA-B*57:01, HLA-B*27:05, and HLA-B*44:03, and four alleles associated with fast progression of the disease: HLA-B*18:01, HLA-B*35:03, HLA-B*07:02, and HLA-B*55:01 were studied. In the first group, the average Gag Total Score was one of the lowest for the controlling alleles, with the highest average scores coming from other proteins: Pol, Env, Nef and Vif. The authors also constructed a combined model of HIV intracellular kinetics and MHC class I peptide presentation. Among nine HIV-1 proteins, Gag peptides predominate at the cell surface, with a Gag:Pol ratio of 18:1, a Gag:Vpr ratio of 23:1, and a Gag:Env ratio of 64:1, and the Env protein was the third most abundant in the cytoplasm, but its epitope is just the sixth most abundant on the cell surface.⁴⁴

Immunodominant epitopes tend to accumulate escape mutations faster than subdominant epitopes. HIV-1 proteins are cleaved by the proteasome, and the fragments are transported to the endoplasmic reticulum by TAP. Virus proteins are processed by endopeptidases into epitopes that go to the cell surface for antigen presentation to TCL. Mutations that affect peptide processing stop the best epitopes formation and impair the availability of these epitopes to loading to MHC-1 molecules in the ER.⁴⁵ The Gag epitope ISW9 mutation consists in a change of alanine for proline at position 146 (A146P), blocking recognition of the IW9 epitope by the aminopeptidase I in the ER, which prevents the formation of epitope/MHC-I complex.^{42,45}

The preferential processing of immunodominant epitopes can be explained by the presence of specific N-terminal motifs in the precursor protein of the epitope because when these motifs are integrated near to a subdominant epitope it causes a higher production of the epitope.⁴⁵

The reasons that make an epitope immunodominant may include its production efficiency, including kinetics and quantity of peptide produced. Immune escape may happen through mutations within or outside HIV epitopes, which may impair the complete processing of epitopes or induce degradation by intracellular peptidases.⁴⁶

Mutations flanking an epitope may lead to T cell lack of recognition. A mutation of alanine into proline located in front of dominant HLA-B*57 restricted epitopes can be frequently detected in HIV infected persons who are HLA-B*57 positive. Although this mutation occurs outside the epitope, it prevents the recognition of infected cells by epitope-specific CTLs. This mutation blocked the complete processing of the N-extended peptide into the epitope, thus generating a peptide that does not connect efficiently to MHC-I and leads to CTL escape.⁴⁶

Conclusions

We investigated the relationships among HIV EC and the MHC-I system, discussing the viral genetics and geographic elements that could influence cellular responses. The virus characteristics, especially HIV clades, can drive this interaction. Genetic characteristics can contribute or inhibit cellular virus entrance. Human genetic diversity, considering the HLA-I system, has also a direct impact on virus and immune system interaction. Some HLAs are related to a slower disease progression to AIDS, and EC. These relations can be different depending on HIV-1 clades and HLAs most prevalent in a specific geographic region. HIV and HLA can select different epitopes as immunodominant interactions in a population/individual manner. Mutations on HIV-1 epitopes can cause immune escape from CTLs and loss of EC. Other mutations in the flanking regions of the epitope that may affect other stages of antigen processing, such as cleavage by the proteasome and translocation by TAP, can also impact these aspects.

In summary, there are some gaps that should be filled before we understand the complexity of elite controlling and HIV resistance per se. It seems that cellular response, with all cells and molecules involved, is a pivotal player in this process. The HLA presenting protein rules the targets that will be presented to CTLs. But the HLA pool for each population is highly diverse, making the ligandome region-specific. Besides, the circulating HIV viral strains are divergent as well, in a location-dependent way. As we discussed, in this sense, not only mutations inside the epitope regions will interfere in the individual ability to present and generate a response against a specific target, but the flanking amino acid substitutions have also the potential to abolish a cytotoxic event. Only the understanding of the coordinated interplay of these factors will allow the development of more rational HIV immunotherapeutics.

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Conflicts of interest

None.

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