Human Leucocytes Antigens Alleles and the Evolution of the Infection with the Human Immunodeficiency Virus Type 1

Alele ale complexului major de histocompatibilitate uman şi evoluția infecției cu virusul imunodeficienței umane tip 1

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Abstract

Differences in host susceptibility to infectious diseases are well documented. While the mechanisms underlying these differences are far from elucidated, recent progress in the genomics of pathogen-host interactions has increased our understanding of the phenomenon.

An increasing number of studies demonstrate that the major histocompatibility complex molecules modulate the overall susceptibility to HIV infection, the risk of vertical transmission from mother to child, the risk of horizontal transmission in HIV discordant couples, the rate of progression to an AIDS-defining illness, and the risk of severe reactions to antiretroviral treatment. These data can influence new diagnostic, therapeutic and prophylactic strategies.

Keywords: *HIV, elite supressors, AIDS progression*

Rezumat

Deşi mecanismele care determină diferențele în receptivitatea la boli infectioase nu sunt inca deplin elucidate, progresele recente în genomica interacțiunii patogen – gazdă au ameliorat intelegerea acestui fenomen.

Un număr crescut de studii demonstrează că antigenele de histocompatibilitate modulează receptivitatea la infecția HIV, riscul transmiterii verticale de la mamă la făt, riscul transmiterii orizontale în cadrul cuplurilor discordante, rata progresiei spre SIDA, precum şi riscul unor reacții adverse severe la antiretrovirale. Aceste date pot influența noi strategii diagnostice, terapeutice şi profilactice.

Cuvinte cheie: *virusul imunodeficientei umane, progresia SIDA, elite supresoare*

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Clinical observations that indicate a role of the host genetics in HIV infection

Several clinical observations suggest that the host's genetic factors may have an effect on the evolution of the HIV infection. First, the existence of highly exposed persistent seronegative individuals, subjects who remain seronegatives, despite being at high risk for HIV transmission (1). Second, the AIDS-free survival without treatment is approximately 10 years for most of the patients, but can be less than 5 years in rapid progressors or more than 15 years in long-term non progressors (LTNP). A standard definition for LTNP status is a subject with documented infection for ten years or more, stable CD4-positive T cell counts above 500 cells/ml, and plasma viral load below 10,000 RNA copies/ml in the absence of antiretroviral therapy. Depending on the definition of "non-progression" used, this population has been estimated to represent 2–4% of all infected patients (1). HIV-1 elite suppressors (ES), also termed elite controllers (EC), are individuals who control HIV RNA levels to levels below the limit of detection of current assays (50 copies /ml) for at least 1 year in the absence of antiretroviral therapy. HIV-1 ES are estimated to occur at a frequency of approximately 1 in 300 infected persons (2).

The mechanisms involved in HIV control have not been fully elucidated. Several studies showed that some ES are infected with defective viruses. More recent studies demonstrated that other ES are infected with non defective (2), replication-competent HIV-1 (3), and that ongoing viral replication and escape from HIV-specific cytotoxic T lymphocytes are present even in these patients (4). These data suggest that the spontaneous control of HIV replication is not attributable to viral genetic defects or viral polymorphisms and that host factors may be playing a key role in the control of viral replication in ES.

Control of HIV by CD8 T cells

The temporal association between the first appearance of HIV-1-specific CD8+ T cells in the peripheral blood and the initial decline of HIV viremia during primary infection suggests a decisive role of these early virus-specific T cells in the control of viral replication (5).

Despite this immune-mediated decline in acute viremia, HIV-1-specific CD8+ T cell responses in primary infection are of lower magnitude and more narrowly directed against a limited number of epitopes than are HIV-1-specific CD8+T cell responses detected in chronic infection. This indicates that the quality and specificity, rather than the quantity of virus-specific CD8+ T cell responses may be associated with the initial control of viral replication. Only a subset of known CD8+ T cell epitopes is frequently and consistently targeted in the initial stages of HIV-1 infection (5).

Three additional lines of evidence support the central role of CD8+ T cells in the control of the HIV infection. First, certain HLA alleles, like B57 and B27, are over-represented among EC (observed in 44 and 15% of EC, respectively) (6) as compared with individuals with progressive infection (7). Second, more rapid disease progression is observed in individuals with HLA class I homozygosity (8). Third, the selection of particular viral mutants that escape CD8+ T-cell recognition is temporally associated with loss of immune control of the infection. Set against these findings are the observations that high-frequency HIV-specific CD8+ T-cell responses are usually detectable in HIV-infected individuals who have developed AIDS, that the majority of HLA class I alleles seem to have little impact on the disease outcome of the HIV infection (9) and that most selected viral escape mutants do not significantly affect viremia (10).

The activity of the cytotoxic CD8+ T lymphocytes (CTLs) and the frequency of particular HLA class I molecules in elite control-

lers caused speculation that controllers might exhibit increased magnitude or breadth of CTL response to HIV. However, several studies found that the magnitude of the HIV-specific CTL response is actually lower in elite controllers than in chronically infected progressors (11). Breadth of response (number of peptides to which there was response) is also statistically smaller in elite controllers (12).

The HLA Region

The major histocompatibility complex (MHC) genomic region is one of the most gene-dense and best-defined regions within the human genome (13). While their role in the presentation of antigens to T cells initially sets the HLA molecules firmly as initiating (effectors) and maintaining (memory) acquired T-cell immunity, it became apparent that class I molecules could also be recognized by killer cell immunoglobulin-like receptor (KIR) molecules on the surface of natural killer (NK) cells (14). This created an additional role for classical HLA molecules in driving the innate immune response.

The MHC is recognized as the most variable region in the human genome, with the nucleotide diversity being up to two orders of magnitude higher than the genomic average (15). The significance of HLA polymorphism is that the differences among the various HLA molecules and the peptides they present are of sufficient functional importance to be subject to natural selection. Though seemingly insignificant, single amino-acid differences between closely related HLA alleles may have crucial consequences in terms of outcome of particular infections (16).

Control of HIV by Gag specific T-cell responses

Recent studies suggest that the control of HIV-1 is associated with the specificity of the CD8+ T-cell response, or the targeting of specific regions of the virus, since the development of CTL escape mutations in these regions may significantly impair viral replication (17). Growing numbers of studies suggest that CTL targeting Gag, particularly the p24 capsid protein, play an important role in controlling viremia (10, 18-20). Preferential targeting of Gag has been associated with lower viral loads (10, 17, 20, 21), in contrast to Nef or Env-specific responses, which are associated with higher viremia (10). Many of the protective MHC class I alleles, such as HLA-B27, HLA-B57, preferentially restrict CD8+ T-cell responses targeting the Gag protein (20, 22).

There are several reasons why Gag might be critical for raising a protective immune response. First, the Gag protein, in particular the p24 subunit, is a key structural component of the virus and is thus highly conserved. The HIV proteins p24 Gag (capsid) and Pol are the most conserved, Nef is relatively variable and Env (gp120) is the most variable protein. Second, Gag is the most immunogenic of the HIV proteins, followed by Pol and Nef. A potential explanation for the difference in importance between Gag and Pol in natural infection is the large amount of Gag within mature virus particles (1,000–1,500 capsid molecules in each mature virion) and the consequent immunodominance of Gag-specific responses in most subjects who show effective control of HIV replication (7, 23, 24). Gag's dominance as a target of the cellular immune response may be due to its preferential processing and presentation by infected cells (5, 25). Third, Gag-derived epitopes can be presented very early after infection because a majority of the capsid molecules derived from the Gag p24 subunit of the infecting virion can be rapidly degraded and presented on the surface of an infected cell prior to de novo protein synthesis of Nef and other viral proteins (23) and to the Nef –mediated downregulation of MHC class I molecules.

Fourth, CTL escape mutations in HIV-1 Gag, in particular p24, are associated with sig-

nificant fitness costs, whereas most escape mutations in the Env gene are fitness neutral (17, 22, 26, 27, 28). This is important because one of the major factors limiting the effectiveness of CD8+ T-cell responses is the ability of HIV-1 to evade these responses through sequence evolution (17).

Recent studies demonstrate that many CTL escape mutations will revert upon transmission of HIV-1 to a new host (17, 29). The rate of reversion for a transmitted mutation is an in vivo measure of its associated fitness cost. The more rapidly reverting mutations have been observed to preferentially occur at conserved residues, indicating that structurally conserved regions of the virus may be particularly refractory to sequence changes (29). In support of these data, many CTL escape mutations have now been observed to directly impair viral replication (22, 30, 31), in particular those known to either revert or require the presence of secondary compensatory mutations (22, 30, 32-34). In both the *gag* and *pol* genes, reversions occur early— generally within the first year of infection— but with a ten-fold faster rate of escape in the *gag* gene (35). Taken together, these data suggest that, whereas CTL escape mutations provide a benefit to the virus to enable the evasion of host immune pressures, some of these mutations may come at a substantial cost to viral replication. Therefore, despite the inevitable evolution of viral escape, viremia can be controlled through the selection of mutations that are detrimental to viral fitness. Recent data suggest that for some viral variants a dual mechanism is responsible for the control of HIV replication: viral fitness loss resulting from CTL escape mutations and strong CD8 T-cell immune responses to the arising variant epitopes (18, 36). These data may imply that the association between Gag-specific responses and the control of HIV-1 may be due to the targeting of highly conserved regions of the virus that are difficult to evade through sequence evolution (7, 17, 19, 37).

A crucial observation of recent studies associating Gag-specific CD8+ T cell responses with control of HIV-1 viremia was that the breadth of the Gag-specific responses appears to be important for this control (10, 23, 38). CD8 + T cell responses against two or more epitopes in Gag are associated with markedly lower viral set points, whereas CD8 + T cell responses against one or no epitope in Gag are not associated with viral control. The most protective HLA class I allele, B57, restricts four immunodominant CTL epitopes in the p24 capsid protein (18). The number of Gag-specific amino-acid polymorphisms strongly correlates with the median viral load, but this correlation is driven purely by Gag mutations that are likely to revert to the wild-type sequence post-transmission, i.e., those that inflict a fitness cost to the virus. Therefore, it is not just the number of Gag epitopes presented by each allele that is important, but also the ability of the Gag-specific CD8+ T-cell response to drive the selection of escape mutations that have an impact on viral replication (19, 39). It is noteworthy that this relationship applies predominantly to HLA-B alleles and Gag-specific responses. These data strongly suggest that the accumulation of either multiple Gag-specific CD8 + T cell responses or the resulting mutations within Gag is critical for viral containment.

Control of HIV by HLA-B-restricted T-cell responses

Investigations of the role of HLA antigens have concentrated on three areas: zygosity of HLA loci, sharing of alleles, and specific HLA allelic/ haplotypic association with the outcome of the disease. It has been shown that homozygosity at the class I loci is associated with relatively rapid progression to disease compared with heterozygotes. This effect appears to be additive: homozygosity at two or three loci had stronger effects than homozygosity at a single locus (8, 16, 40).

This heterozygote advantage probably stems from the ability of such individuals to

present a wider array of virus-derived epitopes to a more diverse CTL repertoire. This heterozygous repertoire will not only enable recognition and destruction of a greater range of infectious agents but will also require many more escape mutations for effective avoidance of the CTL response. Hence, heterozygosity may be associated with delayed progression to AIDS (40). However, it is also conceivable that the virus may become adapted and resistant to highly frequent alleles more easily in that population, and so a rare allele may have selective advantage in HIV disease progression (41). The rare allele selective advantage may work in conjunction with heterozygote advantage, as the protective rare alleles are more likely to be present as heterozygotes.

Another genetic component that predisposes to the progression of AIDS is HLA sharing. Where the MHC class I is common to the donor and recipient, it would lead to increased susceptibility to viral infection. Significant increase in susceptibility to HIV has been shown to be associated with concordance at the HLA-B locus but not at HLA-A or HLA-C.

HLA-B has a dominant influence in HIV-specific immune response: a significantly greater number of CD8 T-cell responses are HLA-B- restricted, compared to HLA-A. Variation in viral set-point, in absolute CD4 count and, by inference, in rate of disease progression, is strongly associated with particular HLA-B but not with HLA-A allele expression. Moreover, substantially greater selection pressure is imposed on HIV-1 by HLA-B alleles than by HLA-A (9). It is clear that a greater diversity of peptides can be presented by HLA-B compared with HLA-A alleles, and the alleles presenting the most Gag epitopes are likely to be HLA-B alleles.

The role of other HLA class I in HIV infection: HLA-C, HLA-E and HLA-G

In a genome-wide association study of major genetic determinants of host control of HIV-1, the two strongest determinants were a polymorphism in complete linkage disequilibrium with HLA-B*5701 and a polymorphism in the region of the HLA-C locus (42). The HLA-C polymorphism is strongly associated with differences in expression of HLA-C alleles, higher expression being associated with lower viral setpoint.

Although HLA-C-restricted CD8+ T-cell responses represent a relatively small minority — approximately 12% — of the total number of HIV-specific CD8+ T-cell responses (10), there is evidence that some HLA-C alleles are associated with lower levels of viremia independent of linkage disequilibrium with HLA-B alleles.

As a classical MHC class I gene, HLA-C has the potential to restrict HIV-1 by presenting epitopes to cytotoxic T cells, resulting in the destruction of infected cells. However, HLA-C has the least diversity of the three classical MHC class I loci. Also, the potential ability of HLA-C to present epitopes to CTLs is severely limited by its poor expression at the cell surface (10-fold lower than either HLA-A or -B). Interestingly, HLA-C is also a potent inhibitor of NK cells. HIV has evolved a strategy to selectively down-regulate HLA-A and -B but not HLA-C, via the regulatory protein Nef, that confers to the virus the capacity to escape NK cell attack (43). The resistance of HLA-C to the Nef-induced downregulation confers to the virus not only the capacity to escape NK cells control but also a higher replicative capacity suggesting that high HLA-C expression is advantageous to the virus and not the host.

In addition, HLA-C molecules incorporated within the HIV-1 envelope have been shown to bind to the envelope glycoprotein gp120 and enhance viral infectivity (43). HLA-C positive cells co-expressing HIV-1 gp120/gp41 fused more rapidly and produced larger syncytia than HLA-C negative cells.

HLA-G is a non-classic major histocompatibility class I molecule, which is characterized by limited polymorphism and restricted tissue distribution. Although capable of acting as a peptide-presenting molecule, its strong immune in-

hibitory properties identify HLA-G as a mediator of immune tolerance at immune-privileged sites such as cytotrophoblast or thymus (44). HLA-G interacts with the NK cells receptors KIR2DL4 (45) and helps in downregulation of NK cells at fetomaternal interface. The expression of HLA-G could be enhanced in the natural course of HIV infection due to the increased interleukin-10 and to the inability of viral Nef to downregulate HLA-G (40). HLA-G polymorphism influences the heterosexual (46) or the mother to child in-utero HIV-1 transmission (47).

HLA-E has a wide tissue distribution including T cells, B cells, activated T lymphocytes and various other cells such as placenta cells and trophoblasts (40). HLA-E is less polymorphic, having only three alleles identified so far: HLA-ER (0101) and HLA-EG (01031 and 01032). HLA-E has NK-inhibitor properties, due to the interaction with KIR of NK cells. HLA-EG is has better immunoregulating properties than HLA-ER and is associated with protection against HIV infection (46).

Killer cell immunoglobulin-like receptors and HLA

Specific killer cell immunoglobulin-like receptors (KIRs) on the surface of NK cells interact with specific HLA class I ligands, and if the KIR contains an activating allotype, this results in increased NK cell effector function (14). Engagement of KIRs by class I molecules provides positive or negative signals to natural killer cells. Although HLA and KIRs are located on different chromosomes and are therefore inherited independently, both are highly polymorphic, and through gene-gene interaction (or epistasis) there is great potential for certain combinations of class I and KIR alleles to result in beneficial or deleterious interactions (48, 49).

Several studies suggest that certain combinations of HLA-B alleles and KIR allotypes (the activating receptor KIR3DS1 or high expression of the inhibitory receptor KIR3DL1) are associated with slower progression to HIV disease or resistance to HIV infection (49, 50). However, it is also evident that the association of HLA class I alleles, such as HLA-B*57 and HLA-B*27, with control of viremia is independent of KIRs, although interactions of these and other HLA-B alleles have important additional consequences for viral setpoint (51, 52). Overall it seems most plausible that HLA exerts both independent and epistatic effects (with KIRs) on HIV infection.

HLA polymorphism and HIV transmission

Specific classical (mainly HLA-B) and non-classical HLA class I alleles (HLA-E and HLA-G) influence the heterosexual transmission of HIV (46, 53). Sharing of HLA-B alleles is independently associated with accelerated intracouple transmission, after adjustment for other genetic and non-genetic risk factors for heterosexual transmission of HIV-1 (54). Several maternal HLA class I (mainly HLA-B) alleles, maternal HLA homozygosity, as well as the degree of allele sharing between mothers and infants seem to reduce or increase mother to child transmission (47, 53, 55).

As in adult infection, the protective HLA class I alleles that drive the selection of Gag escape mutations are beneficial not only to the infected mother but also to the infected child not expressing the same alleles. If the mother possesses protective HLA alleles not shared by the HIV-infected children, transmission of low-fitness viruses carrying CD8+ T-cell escape mutations could be beneficial for the child (56, 57). Infected children have the potential to generate Gag-specific CD8+ T-cell responses (10, 19) and to delay disease progression if they possess protective HLA-B alleles to which the transmitted maternal virus is not preadapted (56).

If restricted replication of HIV associated with HLA-B57 depends upon CD8 T-cell recognition of B57-restricted epitopes, mother-to-child transmission of escape mutations within these epitopes could nullify its protective effect.

However, if the B57 advantage is largely mediated by selection for fitness attenuating viral mutations within B57-restricted epitopes, then the transmission of such mutations could facilitate viral control in the haploidentical infant. Several data suggest that HLA-B57 confers its advantage primarily by driving and maintaining a fitness-attenuating mutation in p24-Gag (58).

Increased susceptibility to vertical HIV-1 transmission due to mother-child HLA concordance has several possible biological mechanisms. Infants whose HLA is the same as their mothers may be less able to recognize HIV-1 that has evolved to evade maternal immune responses via HLA-mediated selection. Concordance might also decrease the likelihood of infant alloimmune responses against maternally derived lymphocytes. Among mother-infant pairs with more concordance, HLA molecules on the surface of HIV-1–infected or -uninfected maternal cells will be recognized as "self" by cytotoxic T lymphocytes or NK cells and will be less likely to be destroyed. Infant alloimmune responses may also target maternal HLA molecules incorporated into the HIV-1 envelope when virus buds from host cells. Thus, increased concordance could restrict T cell destruction of cell-free HIV-1, in addition to reducing destruction of HIV-1–infected maternal cells (55).

Maternal homozygosity is associated with an increased risk of HIV-1 transmission overall and via breast-feeding. One mechanism through which maternal homozygosity might increase the risk of vertical transmission is the accelerated HIV-1 progression and the higher viral loads in homozygous mothers. However, even after adjusting for maternal HIV-1 load, maternal HLA homozygosity is strongly associated with HIV-1 transmission overall and through breast-feeding. These data suggest that the effect of maternal HLA homozygosity on transmission risk is not due only to its effect on maternal disease progression. It is possible that HIV-1–infected cells of homozygous mothers elicit a weaker alloimmune response in their infants, which in turn may lead to increased survival of maternal HIV-1–infected cells and increased risk of transmission. HLA concordance and maternal homozygosity might have stronger associations with increased risks of in utero and postpartum transmission to the extent that alloimmune responses act primarily on cell-associated virus.

HLA and antiretroviral therapy

The accumulating knowledge of human genomic variation provides opportunities for decreasing the number of adverse drug reactions and increasing the efficacy of drug treatment (59).

A number of the patients receiving abacavir, a nucleoside reverse transcriptase inhibitor, develop a hypersensitivity reaction, which is more severe and may be life threatening if abacavir therapy is restarted. Detailed analysis of the MHC in the abacavir hypersensitivity reaction revealed a highly significant association with the HLA-B*5701 allele. The strength of the association is such that screening for this allele prior to commencing abacavir therapy is cost-effective, and is applicable across different ethnic groups (60-62). Similar but less dramatic associations with adverse reactions to other antiretrovirals have also been described (63).

HIV-specific CTL responses mediated by HLA recognition and antiretroviral drugs exert selection pressure on HIV-1 *in vivo*. These two evolutionary forces share common target residues in HIV-1 Pol (64), at which their selection effects could be synergistic or antagonistic, such that the propensity to develop drug resistance may be influenced by the HLA type (65), and common drug resistance mutations may sustain or even enhance the antigenicity and immunogenicity of HIV-1 Pol CTL epitopes (66). These interactions may explain *in vivo/in vitro* discordance of drug resistance, host-specific susceptibility to drug resistance, and should encourage the individualization of the therapy (67). Also it seems reasonable to develop HIV-1 vac-

cines that can target drug-resistant HIV-1 strains, in order to reduce the transmission or emergence of antiretroviral drug-resistant HIV strains and to enhance the immune response against HIV (68).

HLA and vaccine design

Despite substantial advances in antiretroviral therapies, development of an effective HIV-1 vaccine remains a critical goal (69, 70). Variation in the immunologically dominant epitopes of HIV is one of the major barriers to the development of an HIV vaccine, especially vaccines that rely on protective CTL responses. A majority of these vaccine approaches have focused on inducing T-cell responses, utilizing several regions of the virus in an attempt to induce a broad array of immune responses (14). It is well established that CD8+ T-cell responses play a critical role in the containment of HIV-1, supported in part by the strong association of particular HLA class I alleles with control of HIV (8, 9, 17), and that some HIV-1 – specific immune responses are superior to others in mediating protective immunity. Several studies have demonstrated a protective effect of broadly Gag-specific CD8 + T cell responses and a cumulative effect of immune-driven mutations in Gag on viral replication capacity (23, 39). Vaccines targeting the more variable regions of the virus, such as Nef and Env, have been associated with no protection or with even higher viremia, probably because these responses suppressed the protective Gag-specific responses (39). Thus, it seems reasonable to assume that driving the immune response toward broad Gag-specific responses may be a better strategy in terms of achieving long-term control (11, 23, 37).

Conflicts of interest: none declared.

Abbreviations list

CTL - cytotoxic T lymphocytes
EC - elite controller
ES - elite suppressor
HLA – human leucocyte antigen
KIR - killer cell immunoglobulin-like receptor
LTNP - long-term non progressor
MHC - major histocompatibility complex
NK - natural killer cell

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