Cellular immunity driving HIV-1 evolution

Navis, M.

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Chapter 13

Discussion: Cytotoxic T lymphocyte responses in HIV-1-infected long-term nonprogressors: lessons for vaccine design

Marjon Navis¹, Frank Miedema² and Hanneke Schuitemaker⁴

¹Dept Experimental Immunology, Sanquin Research, Landsteiner Laboratory, and Center for Infectious Diseases and Immunity Amsterdam (CINIMA) at the Academic Medical Center of the University of Amsterdam, Amsterdam, the Netherlands and
²Dept Immunology, University Medical Center Utrecht

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Summary

Cytotoxic T lymphocytes (CTLs) are considered to play an important role in the containment of HIV-1 infection. Their efficacy is, however, limited as they also continuously select for HIV-1 variants with escape mutations in CTL epitopes. Moreover, it remains to be established whether the preservation of high frequencies of HIV-1-specific CTLs in long-term nonprogressive HIV-1 infection are cause or consequence of controlled HIV infection. On the positive side, some escape mutations seem to come at a fitness cost to the virus, which may imply that some CTLs, by selecting HIV-1 variants with reduced replication competence, still contribute to a reduced viral load. The implications of current knowledge on HIV-specific cellular immunity for vaccine development will be discussed.

The clinical course of HIV-1 infection

Humans display a large variability in their susceptibility to HIV-1 infection and disease progression after infection. In the absence of antiviral therapy, AIDS develops typically within 5-7 years after infection, although very rapid disease progression in less than 2 years or virtually no disease progression for more than 25 years are observed as well (Figure 1). Individuals with a long-term nonprogressive HIV infection (long-term nonprogressors, LTNPs), defined by us as an asymptomatic HIV-1-positive follow-up of at least 9 years with stable CD4 counts above 400 cells in the ninth year of follow-up, comprise approximately 5% of the total HIV-1-infected population. These individuals have maintained HIV RNA levels below 50 copies/ml for at least 1 year in the absence of antiretroviral therapy and constitute less than 1% of the HIV-1 infected population.

Several factors have been identified that influence the rate of HIV-1 disease progression. Individuals infected with attenuated viruses, for instance HIV-1 variants with a deletion in the viral nef gene, showed prolonged asymptomatic survival, whereas a high viral load set point, which may relate to the replication potential of the virus, is highly predictive for accelerated disease progression.

Host factors have also been implicated in influencing the clinical course of infection. For example, heterozygosity for a 32-base pair deletion in the CCR5 gene which encodes one of the coreceptors for HIV-1 has been associated with delayed disease progression. Obviously, a role for HIV-1-specific immune responses in the control of viremia and disease course has been envisaged as well. Although neutralizing antibodies are important...
in protection from infection, their role in delaying or even preventing disease progression seems limited. By contrast, coincident with the decline in viremia after acute infection, there is an increase in HIV-specific CD8+ T cells that are able to directly kill HIV-infected cells. This observation, plus the consistent association between certain human leukocyte antigen (HLA) class I molecules and virus control, have contributed to the widely held assumption that effective HIV-specific CD8+ T-cell immunity is a dominant factor driving the containment of HIV, although the exact mechanism by which control is exerted is largely unknown.

Cytotoxic T lymphocytes & the clinical course of infection

Vigorous HIV-1-specific cytotoxic T lymphocyte (CTLs) activity in LTNPs has suggested a causal relationship between cellular immunity and control of HIV-1 infection. This was further emphasized by the temporal relationship between the development of virus-specific CTL responses and a decline in viremia during acute infection. Although there is no clear association between the frequency of HIV-specific CD8+ T cells (as defined by IFN-γ production) and control of viremia, with regard to the function of these cells, LTNPs and elite controllers differ compared with progressors and non-controllers, including the ability of HIV-specific T cells to proliferate, to produce the cytolytic protein perforin, and to produce multiple cytokines (IFN-γ, MIP-1β, TNF-α, IL-2, and/or CD107a) in response to HIV antigens. Moreover, the antiviral cytolytic potential of freshly isolated CD8+ T cells against autologous CD4+ T cells was higher for LTNPs and elite controllers than for progressors and non-controllers. Finally, CD8+ T cells from LTNPs are more frequently targeted against Gag, while CD8+ T cells in progressors more frequently target Env and the accessory/ regulatory proteins. Collectively, these data strongly suggest that potent CD8+ T-cell responses directed at HIV are causally related to the complete or near complete control of HIV in at least some HIV controllers. It should be emphasized, however, that almost all of these studies are by necessity correlative in nature, making it difficult to rule out the possibility that the preservation of potent HIV-specific responses are a consequence rather than a cause of HIV control.

To overcome this problem, several studies have been performed in the simian immunodeficiency virus (SIV)-infected macaque model, which allows a more careful definition of the immunologic mechanisms for virus control in vivo. As in humans, a small subset of macaques is able to spontaneously control pathogenic SIV infection. Antibody-mediated depletion of CD8+ T cells in these animals led to a rapid rise in SIV load. Additionally, in animals with detectable viral load who therefore seemed to lack natural control of viremia, depletion CD8+ T cells was associated with a rise in viral load. These observations seem to argue that control of viremia is at least partially mediated via CD8+ T cells. However, CD8+ depletion in rhesus macaques is associated with marked changes in the dynamics and, potentially, function of nondepleted subsets, including CD4+ T cells. Obviously, these changes might also effect viral dynamics (Picker L. Pers. Comm.)

Although the re-emergence of effective CD8+ T cells was associated with a decrease in viral load in all studies, it cannot be excluded that other CD8+ cells such as natural killer (NK) cells, were depleted as well, and that the control of viremia is not or only partially associated with CD8+ CTL function. Re-emergence of effective CD8+ T cells was associated with a decrease in viral load, suggesting a re-establishment of virus control. Although these data are strongly supportive for a role of HIV-specific CTLs in the control
of viremia, several observations in longitudinal studies still argue that CTLs do not always fulfill this protective role. Indeed, the earliest studies in which assays were used that detect memory CTL precursors, showed that both rapid progressors and LTNPs had high CTL precursor frequencies early in infection. However, while these CTL precursor frequencies were preserved over time in LTNPs, in progressors they were lost during subsequent follow-up\(^{25,47}\).

In line with these data is the outcome of a recently performed prospective cohort study in 96 participants from the Amsterdam Cohort Studies who seroconverted for HIV-1 antibodies during follow-up. They could not demonstrate a correlation between T-cell immunity and viral load set point early after infection and, more importantly, abundant T-cell immunity evidenced by IFN-γ and IL-2 production in response to HIV-1 peptides early in asymptomatic infection did not prevent or delay progression to AIDS (Schellens I. et al. Submitted 2008). Although progressors and LTNPs had indistinguishable CTL responses early in infection, progressors seem to lose their HIV-specific T-cell immunity more rapidly during the course of infection. The observation that loss of immunity must thus be considered a consequence rather than a cause of disease progression is supported by observation in HIV-infected individuals during strategic treatment interruption (STI). In the face of increasing viral load during STI, an expansion of IFN-γ-positive T cells was observed that apparently could not control viral replication. Thus, an increase in viral load drives the expansion of HIV-specific T cells, as opposed to HIV-specific T cells contributing to the control of viral load\(^{48}\). These observations indicate that viral load during chronic infection might not be, or might only partially be, controlled by T-cell immunity, and, moreover, that antigen levels seem to determine T cell function and phenotype, and not the other way around\(^{49,50}\). Increased expression of inhibitory receptors programmed cell death-1 (PD-1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) on HIV-specific T cells from patients with high viral load is in agreement with this\(^{51-53}\).

**Viral escape from CTLs**

The aforementioned may argue against a pivotal role for CTLs in the control of HIV infection. The fact that HIV-1 variants with mutations in CTL epitopes are continuously selected, however, provides strong evidence that CTLs do have an effect on the virus. Indeed, owing to an error-prone reverse transcriptase enzyme that lacks proofreading activity, at least one point mutation per genome per replication cycle occurs, which with approximately \(10^{10}\) new virions being produced each day means that in theory every possible mutation at each site in the genome could be generated every day, including mutations in CTL epitopes. As the mutant is “invisible” for a specific CTL population, this virus will have a relative advantage compared the wild-type virus.

The first clear examples of HIV-1 escape from CTLs stem from two papers in which the occurrence of CTL escape mutations during the acute phase of infection was described\(^{54,55}\). However, escape mutations were also shown to occur later in infection, even after long-term effective immune control for more than a decade\(^{56}\). After the appearance of HIV-1 variants with escape mutations in CTL epitopes, rapid progression to AIDS was seen. Subsequent studies in SIV macaque models have shown that escape mutations occur frequently in both acute as well as during the chronic phase of infection\(^{57-60}\). Multiple mechanisms of escape from CTLs have described. If mutations occur at the so-called anchor residue positions of the epitope, binding of the peptide to the MHC class I
molecule is no longer possible, resulting in the complete loss of epitope presentation on the surface of the infected cell.\textsuperscript{54,56,61,62} Furthermore, mutations flanking CTL epitopes can affect antigen processing\textsuperscript{63}. Mutations in the epitope, even some at anchor residue positions, do not impair peptide/MHC class I binding. In such cases the epitope is still presented on the cell surface in association with MHC class I, but recognition by the T-cell receptor and subsequent activation of CTL effector functions can be profoundly affected\textsuperscript{64,65}.

In the case of escape mutations at anchor residue positions that result in loss of epitope presentation a \textit{de novo} CTL response will not be generated. However, mutations in the part of the epitope that is recognized by the CTLs, that do not affect peptide presentation will not interfere with the generation of \textit{de novo} CTL responses against the escape variant.

Allen et al. analyzed HIV-1 CTL responses and autologous viral sequences in an HIV-1-infected individual for 6 years after acute infection and found that \textit{de novo} CTL responses restricted by the same HLA class I allele could be generated against HIV-1 CTL escape variants harboring sequence variations within residues that determine T-cell antigen receptor binding\textsuperscript{66}. The ability to generate \textit{de novo} responses against escape variants of CTL epitopes has also been demonstrated in a cross-sectional study in a cohort expressing HLA A11. The majority of these subjects had CTL responses against the escape variant, while the wild-type consensus sequence was significantly less frequently recognized\textsuperscript{66}.

\textbf{CTL escape & viral fitness}

As mentioned previously, the emergence of CTL escape variants of HIV-1 can be followed by a fast increase in viral load and rapid progression to AIDS\textsuperscript{54-56}. However, some CTL escape variants do not have an impact on the clinical course of infection. The most plausible explanation for this observation is that some CTL escape mutations come at a fitness cost to the virus. Depending on the severity of the fitness cost associated with CTL escape mutations, the host may benefit from a reduced viral load, despite loss of immune control. Indeed, by selecting for SIV or HIV-1 escape variants with impaired fitness, CTLs indirectly contribute to host control of viral burden. The fitness cost associated with CTL escape mutations may be reflected in the reversion of these mutations upon transmission of SIV or HIV-1 to MHC class I-mismatched recipients (Figure 2)\textsuperscript{67-72}.

Leslie et al. were the first to conclude that reversions may be driven by a gain of fitness during HIV-1 infection, implying that at least some CTL escape mutations come at a substantial fitness cost\textsuperscript{68}. They monitored the T242N mutation in the HLA B57-restricted TW10 epitope during mother-to-child transmission. The N242T reversion was observed when the virus was transmitted from an HLA B57 positive mother to an HLA B57 negative child while the 242N residue was conserved when the virus was transmitted to an HLA B57 matched child. In agreement with the hypothesis that reversion of mutations is driven by gain of fitness, Li et al. observed that reverting mutations preferentially arose within highly conserved residues, and suggested that the severity of fitness loss associated with CTL escape mutations, so the strength of back selection, determines the kinetics by which escape mutations and reversions occur\textsuperscript{73}. In a recent study on HIV-1 evolution upon transmission between HLA disparate partners, we observed that most CTL escape mutations that had occurred in the donor reverted in the recipient\textsuperscript{74}. Therefore, while HIV-1 may demonstrate a propensity to evade host CTL responses through the development of escape mutations, many immune pressure-driven mutations may exact a significant cost on viral fitness,
explaining rapid reversion upon transmission to a subsequent host. Considering the ease at which HIV-1 may escape from CTL control, it is tempting to speculate that not the cytolytic function of CTLs but rather their selection of less fit HIV-1 escape variants is the most important contribution of CTLs to reducing viral burden.

**Figure 2** Selection pressure in relation to fitness cost. (a) Targeting of WT by CTLs may lead to positive selection of viruses with escape MT in these epitopes that are no longer presented to or recognized by CTL. Each selected escape MT may come, however, at a potential replicative fitness cost (†: mutations that are incompatible with viral replication; light grey: intermediate fitness cost; dark grey: high fitness cost; white: no fitness cost). (b) Transmission of selected mutants to a host that shares HLA alleles with the donor. In theory, mutations may revert during the early period in the new host because of the absence of CTLs. When new CTLs arise there can be a positive selection again for the same mutant viruses. (c) When the selected mutants are transmitted to a nonselecting environment, that is, to a host that does not share HLA alleles with the donor, reversion of mutations to the consensus sequence will be driven by the gain of fitness associated with the consensus sequence.

CTL: Cytotoxic T lymphocyte; HLA: Human leukocyte antigen; MT: Mutation; t: Time point; WT: Wild-type

**Association between HLAs & the clinical course of HIV-1 infection**

HLA molecules present peptides to CTLs and provide the mechanism by which the immune system generates a specific response to a pathogen. The diversity of HIV-specific immune responses plays a crucial role in containment of the virus and it is HLA molecules that control that diversity. Thus, HLA polymorphisms should affect disease progression. Investigation of the effect of specific alleles has revealed that heterozygosity of any MHC class I HLA alleles appears to delay progression, while rapid progression has been associated with some alleles in particular, for example, HLA B35 and Cw4. The HLA B57 allele, present in 11% of the Caucasian population and around 9% of HIV-positive individuals, has been linked to long-term nonprogression, a lower viral load set
point and a symptom-free acute HIV infection \cite{75,77}. Similarly, the HLA B*5703 allele, which is the prevalent B57 subtype in Africans, is highly enriched among African populations who are able to maintain low viral loads \cite{78,79}. The exact mechanism by which HLA B57, and to a lesser extent HLA B27, protect from rapid disease progression is still unknown. HLA B57 may target more conserved regions in HIV-1, and escape mutations in these regions may consequently have a higher impact on viral replication fitness than escape mutations in more variable regions \cite{80}. The dominant epitope that is targeted during acute infection in HLA B57 individuals is the TW10 epitope in Gag p24. In the majority of HLA B57-positive individuals, HIV-1 escape occurs early in infection via a threonine to asparagine substitution at position three of the epitope (T242N). As described before, this mutation reverts upon HIV-1 transmission from an HLA B57-positive individual to an HLA B57-negative individual, indicative of the fitness loss associated with it. This was further supported by a study that showed that in direct competition, a wild-type HIV-1 NL4-3 outgrew an HIV-1 NL4-3 in which the T242N mutation was introduced via site-directed mutagenesis. However, replication of wild-type and T242N mutant virus was not significantly different in a single cycle replication assay, suggesting that the absolute fitness loss associated with the T242N mutation may be limited but sufficient to be outcompeted by wild-type virus and sufficient to give rise to reduced viral burden \cite{81}. Interestingly, in a study in HLA B57 elite controllers, the T242N mutation in the TW10 epitope was absent in the majority of individuals \cite{33}. This suggests that absolute suppression of viral replication prevents selection for escape variants. In this model, suboptimal suppression may select for escape variants, provided that the fitness cost associated with the escape mutation outweighs the antiviral effect of the selecting CTL (Figure 3).

Gao et al. demonstrated that HLA B57 and HLA B27 may exert their protective effect on disease course in different phases of the infection \cite{82}. While HLA B57-mediated protection seems to occur early in infection, as shown by the rapid appearance of viral escape variants with the T242N mutation in the TW10 epitope, HLA B27 was not associated with significant protection from progression to a CD4 of less than 200, but rather with delayed progression to an AIDS-defining illness and death primarily after CD4 counts had dropped \cite{82}. HLA B27-infected individuals mount an immunodominant CTL response against the KK10 epitope in p24 Gag. However, the relatively late emergence of HIV-1 variants with CTL escape mutations in this epitope may imply that the selection pressure exerted by HLA
B27-restricted CTLs on the virus is not as great as that exerted by HLA B57-restricted CTLs. Alternatively, escape mutations in the immunodominant HLA B27-restricted KK10 epitope may come at a much higher fitness cost than mutations in HLA B57-restricted epitopes. If this is the case, escape mutations in the KK10 epitopes may arise late, even when selection pressure of HLA B27 restricted CTLs is much stronger than that of HLA-B57 restricted CTLs due to the stronger back selection towards the wild-type KK10 epitope sequence. Although this alternative explanation may explain why KK10 mutant viruses appear late in the course of infection, it does not explain the late protective effect associated with HLA B27. However, the observation that the predominant CTL escape mutation R264K in the HLA B27-restricted KK10 epitope indeed dramatically compromised in vitro viral replication capacity is in line with this hypothesis. Interestingly, replication fitness of the R264K escape variant was restored to wild-type levels by a rare upstream compensatory mutation S173A. These data support the idea that in some individuals, the loss in viral fitness introduced by escape mutations can be partially overcome by the introduction of compensatory mutations that restore viral fitness. This was further supported by several studies involving HIV-1 variants from HLA B57 typed individuals. Indeed, an accumulation of specific, potentially compensatory, amino acid substitutions in the Gag capsid in HIV-1 T242N escape variants of HLA B57 individuals coincided with a progressive disease course and was associated with higher viral loads in recipient of these virus variants. We found supporting evidence for a role for compensatory mutations in restoring viral replication fitness in HIV-1 variants that have escaped HLA B57-restricted via the T242N mutation in Gag. In a longitudinal analysis on the dynamics of CTL escape mutations in HLA B57/5801-restricted epitopes in Gag we compared HLA B57/5801 LTNPs and progressors. No differences in the prevalence of the T242N escape mutation in the TW10 epitope and other CTL escape mutations in HLA B57/5801 restricted epitopes in Gag were observed between HIV-1 variants isolated from LTNPs and progressors, and early HIV-1 variants from both patient groups has similarly slow replication kinetics. However, while viral replication rates of early and late virus variants from LTNPs were similar, a significant increase in replication rate was observed for late viruses isolated from progressors. In agreement, late HIV-1 variants from HLA B57 progressors tended to have more potential compensatory mutations than late virus variants from LTNPs. Interestingly, any combination of two of these potential compensatory mutations was associated with disease progression in HLA B57/5801-positive individuals, indeed confirming a role for compensatory mutations in the course of HIV-1 disease progression.

**Immune activation & disease progression**

As outlined previously, most individuals elicit an HIV-specific CTL response that may contribute to the control of viral load early in infection. However, it is not only the emergence of CTL escape mutations can abrogate the effect of CTLs, it also seems that lack of preservation of CTL function underlies progressive HIV-1 infection. Indeed, CTL function seems to be much better preserved in LTNPs than in progressors. The early loss of HIV-1-specific cellular immunity in progressors is most likely due to exhaustion driven by HIV-associated systemic immune activation, which appeared to be independent from viral load. Because of this it seems that the time to exhaustion of cellular immune responses and loss of CD4+ T-cell numbers is determined by the strength of the systemic immune activation associated with HIV infection. Indeed, after the viral set point is
established, the ‘set point’ of immune activation, reflected by expression of Ki67 and CD38 on CD4+ and CD8+ T lymphocytes, is the best and independent predictor for progression, over-riding viral load and early CD4+ T-cell counts as prognostic parameters. In line, the natural hosts for SIV, the African green monkeys and sooty mangabeys, do not develop any immunodeficiency after infection and exhibit minimal T-cell activation, despite high viral load. The hyperimmune activation in humans, which is separate from the HIV-induced activation of the adaptive immune system, has been shown to be induced by microbial products, including lipopolysaccharides, which enter the bloodstream as a consequence of permeability of the gastro-intestinal (GI) tract that is secondary to the massive and irreversible loss of memory CCR5+ CD4+ T cells in the GI tract during acute infection. However, the observation that expression of activation markers on immune cells is immediately downmodulated upon initiation of effective antiretroviral therapy strongly argues for a direct contribution of HIV-1 itself in the hyperimmune activation, as observed in HIV-1-infected individuals. It remains to be established at what stage in infection LTNPs and progressors differentiate in their clinical course of infection. Indeed, LTNPs and progressors may already differ in the severity of memory CD4+ T-cell depletion in the GI tract and subsequent microbial translocation to the peripheral blood compartment. Alternatively, polymorphisms in genes involved in innate immune pathways may determine the level of immune activation in response to microbial products and subsequent HIV disease progression. Indeed, epidemiological studies on polymorphisms in the NK immunoglobulin-like receptor (KIR) family and their ligands have revealed an important role for NK cell responses in the control of viral load and progression to disease. The inhibitory receptor KIR3DL1 in combination with its ligand Bw4-80I, has been associated with control of plasma viral load and delayed progression to AIDS. The Bw4 motif is contained in HLA B molecules, including the protective HLA B57 and -B27 alleles that are overrepresented in LTNPs. In addition, the activating KIR3DS1 receptor in the presence of Bw4-80I is also associated with lower viral load and slow progression to disease. Although functional studies are needed to support the hypotheses, the protective effect on HIV disease course might indeed relate to NK cell activation, due to either the engagement of the activating KIR3DS1 or to the loss of the signal mediated by the highly inhibitory KIR3DL1 alleles when in contact with HIV-1-infected cells with nef-mediated downregulated expression of the Bw4-80I HLA B molecules.

Conclusions & future perspective
A vaccine-eliciting HIV-specific T-cell immunity may contribute to a reduction of the viral load set point, and thereby not only delay disease progression but also reduce the risk of transmission to a new individual. However, for vaccine-elicited HIV-specific T-cell immunity, conditions need to be such that T-cell immunity is preserved. The recent STEP trial, which aimed for a reduction of the viral load set point by eliciting potent HIV-specific immunity prior to infection has demonstrated that even a head start of cellular immunity is no guarantee for preservation of immune responses or a lower viral load set point in HIV infection. Indeed, although vaccination with a combination of 3 recombinant Ad5 vectors (Ad5-gag, Ad5-pol, and Ad5-Nef) elicited HIV-specific CD8+ T lymphocytes with several effector-cell characteristics, it did not reduce viral load set point in those individuals who became infected during follow-up. The fact that the CD8+ T-cell responses to HIV antigens

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were not very broad may, at least in part, explain the lack of viremic control in vaccinated individuals. The observation that not the cytolytic activity of CTL, but rather their selection of HIV-1 variants with impaired replication fitness contributes to a lower viral set point, should be explored in more depth. Indeed, although it may be a logistical challenge, one could aim for HLA specific immunogens, eliciting CTLs that target the most conserved epitopes presented by the HLA B alleles of that individual, assuring that CTL escape mutations will coincide with a severe loss in viral fitness and a reduction in viral load set point. The presence of such CTLs at the time of infection may prevent the severe depletion of CD4+ cells during acute infection, and thereby the subsequent cascade of events leading to immune activation and deterioration of the immune system. However, to achieve protection from HIV-1 infection, a vaccine should elicit a broad and potently neutralizing antibody response, probably in parallel to efficient CTL responses. The fact that almost 25 years of research has not delivered a vaccine that may protect against infection or disease progression may seem to imply that more sophisticated approaches are warranted to achieve this goal.

Executive summary

The clinical course of HIV-1 infection
- AIDS develops typically within 5-7 years after infection, although very rapid disease progression in less than 2 years or virtually no disease progression for more than 25 years are observed as well.
- Individuals with a long-term nonprogressive HIV infection comprise approximately 5% of the total HIV-1-infected population.

Cytotoxic T lymphocytes & the clinical course of infection
- Vigorous HIV-1-specific cytotoxic T lymphocytes (CTL) activity in long-term nonprogressors (LTNPs) has suggested a causal relationship between cellular immunity and control of HIV-1 infection.
- The functions of HIV-specific CD8+ T cells are better preserved in LTNPs and elite controllers as compared to noncontrollers.
- Targeting of the HIV-1 Gag protein and the breadth of Gag-specific responses are associated with slow progression.

Viral escape from CTLs
- HIV-1 variants with mutations in CTL epitopes are continuously selected, thereby providing evidence of CTL effect on the virus.
- *De novo* CTL responses restricted by the same human leukocyte antigen (HLA) class I allele could be generated against HIV-1 CTL escape variants harboring sequence variations within residues that determine T-cell antigen receptor binding.

CTL escape & viral fitness
- Fitness cost associated with escape mutations may reduce viral load and may therefore be beneficial to the host despite loss of immune control.
- The fitness cost associated with CTL escape mutations may be reflected in reversion of these mutations upon transmission to an HLA-disparate partner.
- The selection for less fit HIV-1 escape variants might be the most important contribution of CTLs to reducing the viral burden, even more so then the functionality of the CTL.
**Association between HLA & the clinical course of HIV-1 infection**

- HLA molecules present peptides to CTLs and provide the mechanism by which the immune system generates a specific response to a pathogen.
- The HLA B57 and B27 alleles have been associated with long-term nonprogression.

**Immune activation**

- The loss of HIV-specific cellular immunity is most likely due to exhaustion driven by HIV-associated systemic immune activation.
- This hyper immune activation, which is separate to HIV-induced activation of the adaptive immune system, has been shown to be induced by microbial products, including lipopolysaccharides, resulting from permeability of the gastrointestinal (GI) tract, secondary to the massive and irreversible loss of memory CCR5+ CD4+ T cells during acute infection.
- LTNPs and progressors may already differ in the severity of memory CD4+ T cell depletion in the GI tract and subsequent microbial translocation to the peripheral blood compartment.
- Polymorphisms in genes involved in innate immune pathways may determine the level of immune activation in response to microbial products and subsequent HIV disease progression.

**Conclusions & future perspective**

- A vaccine-eliciting HIV specific T-cell immunity may contribute to a reduction of the viral load set point and thereby delay disease progression.
- Not only the induction of HIV-specific T-cell immunity but rather the preservation of these responses should be the target for vaccine development.
- The observation that not the cytolytic activity of CTLs, but rather their selection of HIV-1 variants with impaired replication fitness contributes to a lower viral set point, should be explored in more depth.

**Reference list**

Papers of special note have been highlighted as either of interest (*) or of considerable interest (***) to readers

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20. Keet IP, et al.: Consistent associations of HLA class I and II and transporter gene products with progression of human immunodeficiency virus type 1 infection in homosexual men. *Demonstrated that the principal focus of HIV-specific activity is at the HLA-B locus. Furthermore, it was shown that the functional profile of HIV-specific CD8+ T cells in progressors was limited compared with that of nonprogressors, who consistently maintained highly functional CD8+ T cells. The limited functionality was independent of HLA type and T-cell memory phenotype, was HIV-specific rather than generalized and was not effectively restored by therapeutic intervention.

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31. Zimmerli SC, et al.: HIV-1-specific IFN-gamma/IL-2-secreting CD8 T cells support CD4-independent proliferation of HIV-infected CD4+ T cells. *Demonstrated that the principal focus of HIV-specific activity is at the HLA-B locus. Furthermore, it was shown that the functional profile of HIV-specific CD8+ T cells in progressors was limited compared with that of nonprogressors, who consistently maintained highly functional CD8+ T cells. The limited functionality was independent of HLA type and T-cell memory phenotype, was HIV-specific rather than generalized and was not effectively restored by therapeutic intervention.


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** Described that the cytotoxic T lymphocyte response dominating acute infection in HLA-B57:5801-positive subjects drove positive selection of an escape mutation that reverted to wild-type after transmission to HLA-B57:5801-negative individuals. A second escape mutation within the epitope, by contrast, was maintained after transmission.


Discussion


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