Published in final edited form as:

Curr Opin Immunol. 2010 August ; 22(4): 488–496. doi:10.1016/j.coi.2010.06.006.

Immune mechanisms of HIV control

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Summary

HIV-1 can be contained by the immune system, as demonstrated by the existence of rare individuals who spontaneously control HIV-1 replication in the absence of antiretroviral therapy. Emerging evidence points to the importance of a very active cellular immune response in mediating HIV-1 control. The rapid induction of interferon-dependent HIV restriction factors, the presence of protective MHC class I alleles, and the development of a high avidity T-cell response may all cooperate in limiting HIV replication at an early stage. This review will focus on recent advances in understanding the immune mechanisms of HIV control, and on the lessons that may be drawn for the development of candidate HIV vaccines.

Introduction

HIV-1 infection does not always progress to AIDS. A small number of infected individuals spontaneously control HIV-1 replication in the absence of antiretroviral treatment and maintain a healthy status in the long term. Less than 0.2% of HIV-1 sero-positive patients show stringent HIV control, as defined by a viral load <50 copies HIV-1 RNA/ml for over 10 years, but these rare individuals have a remarkably low risk of progression to AIDS [1]. Patients with spontaneous HIV control have been variously called HIV controllers [2], HIV elite controllers [3], long term non progressors [4], or natural virus suppressors [5]. We will use the term “HIV controller” throughout this review. Importantly, the majority of HIV controllers appear infected with replication competent virus [6], indicating that host factors must play a key role in limiting HIV-1 replication and disease progression. We will review recent advances suggesting that both innate and adaptive immune mechanisms cooperate in establishing HIV control very early in the course of infection.

The early type I IFN response induces an array of antiretroviral restriction factors

One of the earliest antiviral defense mechanism is the induction of interferon (IFN) synthesis. “Danger” sensing systems (Toll-like-receptors [TLR], RIG-I-like-receptors)

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converge in activating the synthesis of type I IFN (Figure 1A, [7]). IFNs curb viral replication by a variety of mechanisms, including the shut-down of protein synthesis and the degradation of foreign nucleic acids [7]. Once produced, IFN α/β bind to the IFNAR1 receptor of the same or neighboring cells and initiate a signaling cascade resulting in the induction of hundreds of IFN stimulated genes (ISG) that constitute the “antiviral state” (Figure 1A, [8]).

The group of type I IFN inhibits both the early as well as late steps of the HIV-1 life cycle [9], decreases HIV-1 infection of several cell types, and impairs HIV-1 transmission from dendritic cells (DC) to CD4+ T-cells [10]. Systemic administration of IFN α reduces HIV-1 plasma viremia [11] and improves production of antiviral antibodies [12] but multiple studies also indicate that IFN activity against HIV-1 is transient and/or suboptimal. For instance, HIV cell-to-cell transmission is much less susceptible to IFN inhibition than cell-free viral spread [13]. Plasmacytoid DC (pDC) are the main natural IFN α producers *in vivo* [14], but this DC subpopulation appears depleted in chronic HIV infection [15]. Viable HIV-infected CD4+ T-cells are excellent inducers of pDC [16] but the capacity of pDC to produce IFN α is impaired during acute HIV-1 infection, suggesting that these cells have reached a refractory or exhausted state [17]. This early impairment of IFN responses may contribute significantly to HIV dissemination in progressor patients.

Intrinsic retroviral restriction factors such as TRIM5 α , APOBEC3 and Tetherin are constitutively expressed but are also strongly up-regulated in response to IFN in a cell-type dependent manner (Table 1, Figure 1, [18,19]). Phylogenetic analyses show that these restriction factors have been under strong positive selection throughout primate evolution, indicative of a continuous evolutionary battle between the host and ancient retroviruses or other parasites [18,19]. HIV-1 has developed means to escape most of the human restriction factors: for instance APOBEC3G and Tetherin activities are counteracted the HIV-1 Vif and Vpu proteins, respectively (Figure 1B/C [18,19]). Tetherin and APOBEC3 molecules prevent viral spread (if left unchecked) while TRIM5 α variants with activity against HIV-1 would protect the cell from productive infection (Figure 1B/C/D). HIV restriction factors are highly polymorphic, which may contribute to individual variations in susceptibility to HIV. While single nucleotide polymorphisms in TRIM5 α [20], Vif-interacting protein Cullin 5 [21] and APOBEC3G [18], have been linked to CD4+ T-cell loss and/or rapid disease progression, these genetic associations need to be replicated in large-scale genomic studies comprising individuals of different ancestry.

The clearest implication of a restriction factor in HIV disease progression has emerged from studies of copy number variation in the APOBEC3 locus. A large deletion eliminating the entire coding region of APOBEC3B [22] was found to be associated with an increased risk of HIV-1 acquisition, accelerated progression to AIDS and higher viral setpoints [23]. The homozygous deletion of APOBEC3B occurs commonly in East-Asians, Oceanic and Ameri-Indian populations [22] suggesting that certain populations may be more susceptible to infections with viruses known to be targeted by cytidine deaminases (HIV-1, HBV, HPV, HTLV1). APOBEC3B is expressed constitutively at low level in HIV target cells [24,25], but is, in contrast to APOBEC3G, resistant to Vif-mediated degradation [23]. Higher expression levels of such “HIV resistant” restriction factors, either at baseline or upon IFN induction, could conceivably contribute to HIV control.

HIV particles induce type I IFN responses mainly through the TLR7/8/ pathways [14]. Chronic IFN production may be deleterious for the infected host in the long-term, because it induces death receptors, increases expression of the HIV coreceptor CCR5 [26], and contributes to abnormal immune activation. The activation of the TLR7/IFN pathway by HIV in pDC appears to have a lower threshold in women than in men, which may contribute

to higher immune activation levels and faster disease progression in HIV infected women [27]. It is relevant that the IFN response appears swiftly resolved in HIV controllers but not in progressor patients, as demonstrated by ISG expression patterns in whole-genome transcriptome studies [28]. How HIV controllers achieve optimal IFN responses while limiting IFN-dependent immunopathology remains to be elucidated. It is attractive to speculate that early containment of HIV at mucosal transmission sites by ISGs such as TRIM/APOBEC3/Tetherin creates a window of opportunity for the infected host to mount an efficient adaptive immune response (Figure 3).

Genetic studies suggest that CD8+ T-cells and NK cells are involved in HIV-1 control

HIV control shows a strong genetic association with MHC class I loci on chromosome 6, with alleles HLA B*5701 and B*5703 having the clearest protective effects in Caucasians and Africans, respectively [29]. Whole genome analyses have confirmed the HLA B association and pointed to an independent effect of HLA C, while the HLA-A association remains debated [30]. The HLA class I and CCR5 loci were the only regions to display significant associations with plasma viral load at the genome-wide level, emphasizing the potentially central role of class I restricted CD8 responses in HIV control [30]. The fact that protective HLA class I alleles disproportionately contribute to the initial CD8 response during acute HIV-1 infection further supports a role of CD8+ T-cells in rapidly establishing viral control [31]. The effects of protective MHC class I alleles appear also mediated by their interaction with KIR receptors at the surface of NK cells. The combination of certain HLA class I molecules of the Bw4 serological group with the KIR3DL1 and KIR3DS1 receptors is more protective against HIV disease progression than the class I molecule alone [32]. Importantly, HLA-Bw4 molecules include the B*57 alleles that are markedly overrepresented in HIV controllers.

Remarkable efficiency of effector CD8+ T-cells in HIV Controllers

Initial analyses of CD8 responses in HIV controllers revealed a high degree of heterogeneity in terms of cytokine secretion and differentiation status of HIV specific CD8+ T-cells [3,33]. However, it was noted early on that a hallmark of HIV control was a high proliferative capacity of specific CD8+ T-cells [4]. Consistent with an optimal survival/expansion capacity, HIV-specific CD8+ T-cells were detected at a particularly high frequency in mucosal tissues of HIV controllers [34].

The development of an *in vitro* “viral suppression” assay, based on the inhibition of HIV-1 replication in activated CD4+ T-cells by autologous CD8+ T-cells, has revealed the remarkable potency of HIV-specific CD8+ T-cells from controllers [35]. CD8+ T-cells from controllers inhibited HIV replication without being pre-activated *in vitro*, pointing to the presence of a pool of HIV-specific CD8+ T-cells with immediate or rapidly inducible antiviral effector functions. This efficient viral suppression was contact dependent and mediated predominantly by CD8+ T-cells directed against Gag, rather than Env or Nef proteins, [36,37], a finding in agreement with the good prognostic value of high anti-Gag responses measured *ex vivo* [38]. These studies have spurred the realization that classical ELISPOT assays, which rely on a massive antigenic stimulation by exogenous peptides, may not best reflect *in vivo* CD8+ T-cell efficacy, and that the development of assays based on antigenic presentation at physiologic doses, such as that occurring in a productively infected CD4+ T-cell, may be more informative. Next generation immunomonitoring assays are now being developed for HIV pathogenesis and vaccination studies.

The basis for CD8⁺ T-cell efficacy in HIV controllers is not entirely elucidated, but recent findings point to the importance of lytic granule loading. In particular, effector CD8⁺ T-cells from controllers are distinguished by their capacity to upregulate granzyme B to high levels and to deliver it efficiently to target CD4⁺ T-cells, a property that correlates with a high cytotoxic activity per effector cell [39]. Multiparametric flow cytometry analyses have also shown that CD8⁺ T-cells from HIV controllers are more polyfunctional, i.e. capable of secreting multiple cytokines and chemokines (IFN- γ , TNF- α , IL-2, MIP-1 β) as well as degranulating (CD107a surface expression) upon HIV specific stimulation [34,40]. Polyfunctionality is associated with a higher production of individual cytokines per cells, and hence with a more efficient secretion of effector molecules. While polyfunctionality is a proven correlate of the quality of CD8⁺ T-cell responses, it less clearly distinguishes HIV controllers from progressor patients than viral suppression assays [41]. Hence, it is not yet clear how cytokine/chemokine secretion contribute to viral control. The recent identification of distinct subsets of polyfunctional CD8⁺ T cells, endowed either with IL-2 secretion or with the capacity to upregulate perforin, may help further refine the correlates of control [42].

Importantly, not all HIV controllers show evidence for potent CD8 responses. CD8⁺ T-cells endowed with HIV suppressive capacity and polyfunctionality appear less frequent in HIV controllers devoid of protective HLA class I alleles [36,43]. It is also intriguing that SIV-infected rhesus macaques with a “controller” phenotype lack signs of potent CD8 antiviral responses [44]. These observations point to either a local containment of HIV/SIV by tissue-associated responses, which would not achieve systemic dissemination, or to novel mechanisms of control.

CD4⁺ T-cells: more than just sitting targets

HIV controllers show an intact or slightly decreased CD4⁺ T-cell population which harbors very low levels of HIV proviral DNA, indicative of a limited seeding of the viral reservoir [2]. CD4⁺ T-cells from controllers are endowed with IL-2 secretion capacity and a particularly high proliferative potential upon HIV-specific stimulation [45,46]. This last property has been ascribed to a resistance of the central memory CD4⁺ T-cell population to activation-induced apoptosis, through inactivation of the transcription factor FOXO3a [47]. The pool of HIV-specific CD4⁺ T-cells from controllers do not show signs of immune exhaustion typically seen in progressor patients, such as loss of poly-functionality and increased expression of the negative regulatory molecules CTLA-4 and PD-1 [3,48].

It has been argued that the lack of immune exhaustion is just a reflection of a persistently low antigenemia, and that the properties of HIV controller CD4⁺ T-cells are a consequence rather than a cause of viral control [49]. However, CD4⁺ T-cell responses of controllers remain quantitatively and qualitatively different from those of treated patients with similarly undetectable viral loads. Differences are most marked in the frequencies of IFN- γ producing CD4⁺ T-cells, which are of similar magnitude in HIV controllers and in viremic patients, while they are significantly lower in treated patients and tend to further decrease with treatment duration [46,50]. In contrast, proliferative CD4 responses of patients efficiently treated for over 10 years may indeed recover to levels equivalent to those seen in HIV controllers [50]. Thus, while low antigenemia may account for high proliferative capacity, other characteristics intrinsic to HIV controllers must account for an unusually high effector function.

It is not yet clear whether CD4⁺ T-cell from controllers can directly contribute to HIV control by killing infected cells. The fact that CD4⁺ T-cell clones from controller monkeys do inhibit SIV replication in autologous macrophages suggests that this could be the case

[51]. CD4⁺ T-cells are known to have cytotoxic properties in other chronic viral infections. It is also well established that CD4⁺ T-cell help is required for the persistence of efficient cytotoxic activity mediated by CD8⁺ T-cells in chronic viral infections [52]. Emerging evidence suggests that IL-21 could be a key mediator of help, since this cytokine produced predominantly by CD4⁺ T-cells is a potent inducer of cytotoxic granule loading in CD8⁺ T-cells, and is necessary to viral control in the murine models of chronic infections [52]. Importantly, IL-21 production and IL-21 circulating levels are decreased in progressor patients but not in HIV controllers [53].

High avidity equals quality

Recent evidence suggests that HIV controllers harbor a high avidity memory CD4⁺ T-cell population directed against Gag [54]. The capacity to recognize minimal amounts of the immunodominant Gag 293–312 peptide results from a high avidity TCR/peptide-MHC interaction, as demonstrated by MHC class II tetramer binding. High avidity TCR are known to confer extensive proliferative potential and progressive immunodominance to CD4⁺ T-cells [55], consistent with findings in HIV controllers. The capacity to detect minimal amounts of virus may play a key role in HIV control, by keeping the immune system in constant alert and allowing the induction of rapid recall responses. The presence of a high avidity CD4⁺ T-cell population may also explain why HIV controllers show signs of persisting immune activation, in spite of very low viral loads [46,56]: the pool HIV-specific CD4⁺ T-cells, being easily triggered, could drive this immune activation through repeated reactivation and cytokine secretion.

HIV-specific CD8⁺ T-cell responses may also be of high avidity in HIV controllers, though this remains to be formally demonstrated. It is noteworthy that patients carrying the protective HLA B*27 allele frequently develop high avidity responses against the KK10 epitope, and that this response inversely correlates with viral load [57]. A recent study of HIV-specific CD8⁺ T-cell clones suggests that polyfunctionality and HIV suppressive capacity, which are hallmarks of HIV control, correlate with a high avidity for antigen [58]. A high cytotoxic activity per CD8⁺ T-cell, another correlate of HIV control, has been linked to a high avidity TCR/MHC-peptide interaction in murine models of viral infections [59].

Progressor patients show a loss of high avidity CD8 responses after primary infection, suggesting that high quality CD8⁺ T-cells become rapidly exhausted when viremia persists [60]. This finding is consistent with the higher susceptibility of high avidity T-cells to overstimulation. Further studies are needed to understand how HIV controller avoid excessive clonal turnover and maintain a high avidity response in the long term. An initially higher precursor frequency of high avidity T cells may avoid their exhaustion, through a very rapid containment of viral replication. In this respect, it is intriguing that shared clonotypes, which are frequently associated to a high precursor frequency, are predominant among CD8⁺ T-cells of vaccinated monkeys that resist SIV challenge [61].

Taken together, it is remarkable that the defining features of the antiviral T-cell response in HIV controllers, including high proliferative potential, polyfunctionality, and high cytotoxic capacity, are all known attributes of high avidity T-cells (Figure 2). Importantly, high avidity T-cells have been associated with the control of chronic viral infections in mice, monkeys, and humans [59,62,63]. Improving the avidity of T-cell responses, for instance by adjuvant combinations [64], should thus become a key objective of future HIV vaccination studies.

Conclusions

Retrospective analysis of primary HIV-1 infection cohorts show that the HIV controller status can be established within months of the initial infection event, and that the viral replication peak is reduced, though not absent, in future controllers [65,66]. These findings emphasize the role of very early events in determining the outcome of the competition between HIV-1 replication and the host response. Signs of immunosuppression, such as dysfunctional non-proliferating T-cells, can be detected during primary infection in progressor patients, indicating that the host response has already been undermined at this early stage. In contrast, any parameter that may delay viral replication or accelerate the development of the antiviral response early on may favor the acquisition of a controller status. For instance, a reduced susceptibility of target cells due limited CCR5 expression, a pre-existing antiviral state due to a concomitant infection, a favorable combination of HIV restriction factors, or a high precursor frequency of high avidity T-cells clonotypes may all play a role in containing viral spread and in protecting the CD4+ T cell pool (Figure 3).

In conclusion, studies of HIV controllers have started yielding a wealth of information on the components of an efficient response against HIV. Genetic studies have revealed a role for NK cells in HIV control, and have pointed to the possible involvement of innate restriction factors. Recent evidence for a high antibody-dependent cell-mediated cytotoxic activity in controllers' sera suggests that humoral response parameters should be further explored [67]. Last and importantly, multiple studies have highlighted the key role of cellular immunity, and have helped identify correlates of control that should prove instrumental in evaluating future candidate HIV vaccines.

Acknowledgments

We regret the fact that we were unable to cite many of the relevant original articles because of space limitations. We thank Ana Fernandez Sesma, Florence Buseyne and Asier Saez-Cirion for critical reading of the manuscript.

The authors receive funding from the National Institutes of Health/ National Institute of Allergy and Infectious Diseases (R01AI064001, R01AI089246, VS), the Alexandrine and Alexander L. Sinsheimer Fund (VS), the Clinical and Translational Science Award to Mount Sinai School of Medicine (UL1RR029887, VS), the Agence Nationale de Recherche sur le SIDA et les Hépatites Virales (ANRS EP36, LC), Sidaction (LC), and the Pasteur Institute (LC).

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Figure 1. Innate immune mechanisms that may contribute to HIV control

A: Virus recognition by TLR7/8 and RIG-I activates IRF7 and IRF3 respectively, leading to IFN transcription. IFN is secreted and sets off signaling cascades resulting in up-regulation of >100 interferon stimulated genes (ISG), creating an “antiviral state” (symbolized by grey color). TLR7/8 are located in endosomal compartments of DC while RIG-I is found in the cytoplasm of many cells. TLR7/8 sense predominantly single stranded RNA and cellular mRNA while the substrates for RIG-I are double-stranded RNA or RNA with 5'-triphosphate. HIV virions and HIV infected cells preferentially trigger TLR7/8. Intrinsic restriction factors are intracellular molecules that inhibit HIV. They are constitutively expressed but also inducible by IFN. Their mode of action in the absence of viral counterstrategies is depicted. Grey color symbolizes the antiviral state of the cell.

B: Tetherin reduces virion release by tethering mature virions to the plasma membrane or/and to each other. Viral counterstrategy: HIV-1 accessory protein Vpu.

C: TRIM5α interferes with the uncoating step early in the viral life cycle. The known TRIM5α variants have little activity against HIV-1 but restrict multiple other retroviruses including SIVmac. Viral counterstrategy: TRIM5α-insensitive HIV-1 capsid protein.

D: The APOBEC3 family comprises seven distinct cytidine deaminases, which differ both in their antiviral activity and their susceptibility to HIV-1 Vif-mediated proteosomal degradation. APOBEC3 activity becomes only apparent in the next cycle of infection when, during reverse transcription, virion-encapsidated APOBEC3 lead to proviral mutagenesis. The red color in the core of the mature virions represents incorporated APOBEC3 molecules. Viral counterstrategy: HIV-1 accessory protein Vif induces APOBEC3G/3F degradation.

Figure 2. Consequence of a high avidity CD4+ T-cell response against HIV

The properties associated with a high avidity TCR / peptide-MHC class II interaction include (1) the detection of minimal amounts of HIV particles, which allows a rapid triggering of the antiviral response (2) potent effector functions, including the secretion of cytokines at high levels and the possible acquisition of cytotoxic function after advanced differentiation (3) long term proliferative potential, leading to a preferential amplification of high avidity CD4+ T-cell populations, and (4) a possible contribution to deleterious chronic immune activation, through repeated reactivation by low level viral replication. Thus, high avidity CD4+ T cells provide both long term memory maintenance and immediate effector functions. Whether distinct CD4+ T-cell lineages ensure these two major functions, or whether memory cells rapidly and continuously differentiate into effector cells remains to be determined (dashed arrows).

Proven (blue) and putative (black) factors involved in determining the outcome of the race between HIV replication and the early immune response. Multiple factors may slow the kinetics of HIV replication during the acute infection stage, thus avoiding a massive depletion of CD4⁺ T-cells within mucosal tissues, and preserving CD4⁺ T-cell help needed for the maintenance of an efficient adaptive antiviral response. HIV control can result from direct viral attenuation, though the occurrence of severe attenuation through gene deletion seems a very rare event. Experiments in the SIV model suggest that a low viral inoculum may also lead to viral control. Host factors include those that limit CD4⁺ target cell susceptibility, that accelerate or potentiate the innate response, and that favor the development of the adaptive response. Factors acting at these three levels may synergize in establishing HIV control.

Table 1

List of human restriction factors, their mode of action, the targeted retrovirus as well as the known viral countermeasures.

Family	Restriction factor	Mode of action	Virus target	Viral counter measure
APOBEC3 (A3)	A3B	Deamination of Cytosine in single stranded DNA results in Guanosine to Adenosine mutations in the provirus Additional non-editing mechanisms have been described	HIV-1	Resistant to HIV-1 Vif
	A3A, A3C		(HIV-1)	Sensitive to HIV-1 Vif
	A3F, A3G		HIV-1	Sensitive to HIV-1 Vif
	A3H (HapI, HapII)		(HIV-1)	Partially resistant HIV-1 Vif
TRIM	TRIM5 α	Interference with viral uncoating	HIV-1	HIV-1 Capsid
	TRIM22	Inhibition of viral assembly/release	HIV-1	?
	TRIM28	Repression of transcription	MLV	?
Tetherin	Tetherin	Inhibition of HIV-1 virions detachment from the plasma membrane	HIV-1	HIV-1 Vpu
Other ISGs	ISG-15	Possible inhibition of viral assembly	HIV-1	?
	RNAseL	?	XMRV	?

Abbreviations: A3H (HapI, hapII): APOBEC3H haplotype I and haplotype II differ in expression, antiviral activity and sensitivity to HIV-1 Vif mediated degradation. Limited HIV restriction is denoted by parenthesis (HIV). MLV: Mouse leukemia virus XMRV: Xenotropic murine leukemia virus related (XMRV) virus ISG: Interferon stimulated gene