SUPPLEMENT ARTICLE

T Cell Immunity in Acute HIV-1 Infection

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Exceedingly high viral loads and rapid loss of CD4$^+$ T cells in all tissue compartments are a hallmark of acute human immunodeficiency virus type 1 (HIV-1) infection, which is often accompanied by clinical symptoms such as fever, maculopapular rash, and/or lymphadenopathy. The resolution of the clinical symptoms and the subsequent decrease in plasma viremia are associated with the emergence of HIV-1–specific CD4$^+$ and CD8$^+$ T cell responses. The remarkable early inhibition of viremia by CD8$^+$ T cells appears to be precipitated by only a limited number of specific CD8$^+$ T cell responses, and the plasma viremia is reduced to a "set point" level. Over time, the breadth and magnitude of CD8$^+$ T cell responses increase, but without a change in the control of viral replication or further reduction in the viral set point. Moreover, the early viral set point, consequent on the first CD8$^+$ T cell responses, is highly predictive of the later course of disease progression. Thus, HIV-1–specific CD8$^+$ T cell responses in acute HIV-1 infection appear uniquely able to efficiently suppress viral replication, whereas CD8$^+$ T cell responses generated in the chronic phase of infection appear often impaired.

The temporal association between the emergence of human immunodeficiency virus type 1 (HIV-1)–specific CD8$^+$ T cell (cytotoxic T lymphocyte [CTL]) responses and the decrease in viral load in the acute phase of HIV-1 infection has been the first and one of the strongest arguments for CTLs as a major factor in the initial control of viral replication [1–4]. Subsequent studies were able to demonstrate that CD8$^+$ T cells can efficiently inhibit viral replication ex vivo [5], and escape mutations in the CTL-targeted epitopes develop early during infection [6]. In addition, there is a strong association between the rate of disease progression and the different human leukocyte antigen (HLA) class I alleles, underpinning the hypothesis that the interaction between the T cell receptor of the CD8$^+$ T cells and the HLA of the antigen-presenting cell is a key element in the overall control of HIV-1 replication. After the initial peak in viremia, an early viral set point develops, which has been repeatedly associated with later disease outcome [7, 8]. However, the first CD8$^+$ T cell responses are narrowly directed against a limited number of epitopes, and, despite an increase in the breadth and magnitude of the CTL response in the chronic stage of infection, no increased control of viral replication can be observed. This suggests that the first CD8$^+$ T cell responses are unique in their ability to efficiently suppress viral replication, whereas CD8$^+$ T cell responses generated later in infection are progressively impaired. However, it is important to note that so far no study has been able to demonstrate a clear functional correlate of CD8$^+$ T cell–mediated protection in either acute or chronic HIV-1 infection. Thus, it is hypothetically possible that the prominent correlation of CD8$^+$ T cell responses and drop in viral load are driven by other factors, such as loss in activated CD4$^+$ T cell targets or other immune-mediated mechanisms.

FIRST HIV-1–SPECIFIC CD8$^+$ T CELL RESPONSES AND EARLY ESCAPE

During the first weeks of infection, adaptive immunity develops, giving rise to initial HIV-1–specific CD8$^+$

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T cell responses. The early $CD8^+$ T cell response is very narrowly directed against a few epitopes and follows a clear hierarchical immunodominance pattern [9]. In fact, with the knowledge of the HLA class I allele, the early T cell responses can be–to some degree–successfully predicted. This will have important implications for vaccine design (Table 1). Interestingly, individuals able to mount one of the immunodominant responses in acute HIV-1 infection have on average a lower viral set point than those who do not target epitopes in acute HIV-1 infection (Figure 1) [9]. In addition, the preservation of these early responses has been associated with slower disease progression and a preserved $CD4^+$ T cell count [9]. The correlation between first $CD8^+$ T cell responses and early viral set point is even stronger when tested against the autologous virus [10]. In a recent study using peptides based on autologous viral quasispecies, the first $CD8^+$ T cells, despite very rapid virus escape, suppressed HIV-1 as viral load was declining from its peak [10] (Figure 1). The influence of these T cell responses vanished once the virus had escaped from the targeted epitopes. Computational modeling further suggested that a single T cell response was contributing as much as 15%–35% of viral decline with multiple T cell responses [10]. Thus, the generation of immunodominant $CD8^+$ T cell epitope responses in the acute phase of infection appears to have an important impact on the level of the early viral set point and subsequent disease progression.

Some subjects, however, do not develop strong $CD8^+$ T cell responses in acute HIV-1 infection and therefore most likely experience a higher viral set point [9]. This can be partially accounted for by transmitted escape mutations in the CTL-targeted epitopes. Other studies have established that for "protective" $CD8^+$ T cell responses ,such as HLA-B27KK10 or HLAB57-TW10 in p24/Gag, the lack of early responses is due to transmitted mutations within these epitopes. However, transmitted escape mutations do not explain the differences in viral set point for the majority of subjects lacking immunodominant CTL responses in acute HIV-1 infection. Findings of a recent study suggested that this might be due to a gradual adaptation of HIV-1 to host immune pressures occurring at the population level. In a comparison of >2900 viral sequences of different HIV-1 clade B cohorts worldwide, it was noted that HLA allele escape mutations in the HLA-restricted epitopes accumulate at the population level, dependent on the frequency of the respective HLA class I [11]. In line with this observation, it has been suggested that individuals expressing one of the more rare HLA supertypes have a more favorable course of disease [12]. This has now been linked to strong CTL selection pressure on the virus, whereas subjects with a more common HLA allele or HLA class I allele combination do not develop strong responses during primary HIV-1 infection. Thus, the epitopes with the strongest selective pressure are already fixed in the viral sequence at the population level for individuals who have

Table 1. Relationships Between Human Leukocyte Antigen (HLA) Class I Alleles and First T Cell Responses to Infection with Human Immunodeficiency Virus Type 1 (HIV-1).

HLA class I allele	HLA phenotype frequency in North American white population, %	Optimal $CD8^+$ T cell epitopes most likely to be first targeted	HIV-1 protein	Sequence	Recognized in infection, % of subjects expressing the respective HLA allele	
					Acute	Chronic
A*02	50.7	A2-SL9	p17	SLYNTVATL	18	38
B*07	30.2	B7-IL9	gp41	IPRRIRQGL	43	47
A*01	28.7	A1-RY9	gp41	RRGWEVLKY	17	14
B*44	27.1	B44-AW11	p24	AEQASQDVKNW	32	77
B*08	22.5	B8-FL8	Nef	FLKEKGGL	74	75
A*24	21.3	A24-RW8	Nef	RYPLTFGW	50	36
B*35	20.9	B35-VY8	Nef	VPLRPMTY	28	20
A*03	20.6	A3-RK9	p17	RLRPGGKKK	62	56
B*40	14.7	B40-KL9	Nef	KEKGGLEGL	64	43
A*11	14	A11-AK11	p24	ACQGVGGPGHK	46	70
B*15	11.6	B15-GY9	p24	GLNKIVRMY	37	60
B*27	9.2	B27-KK10	p24	KRWIILGLNK	81	43
B*14	8.6	B14-EL9	gp41	ERYLKDQQL	57	50
A*26	8	A26-EL9	p24	EVIPMFSAL	36	83
A*29	7.4	A29-SY10	gp120	SFNCGGEFFY	42	50
A*30	7.4	A30-KYY9	Int	KIQNFRVYY	25	80
B*57	7	B57-TW10	p24	TSTLQEQIGW	74	30

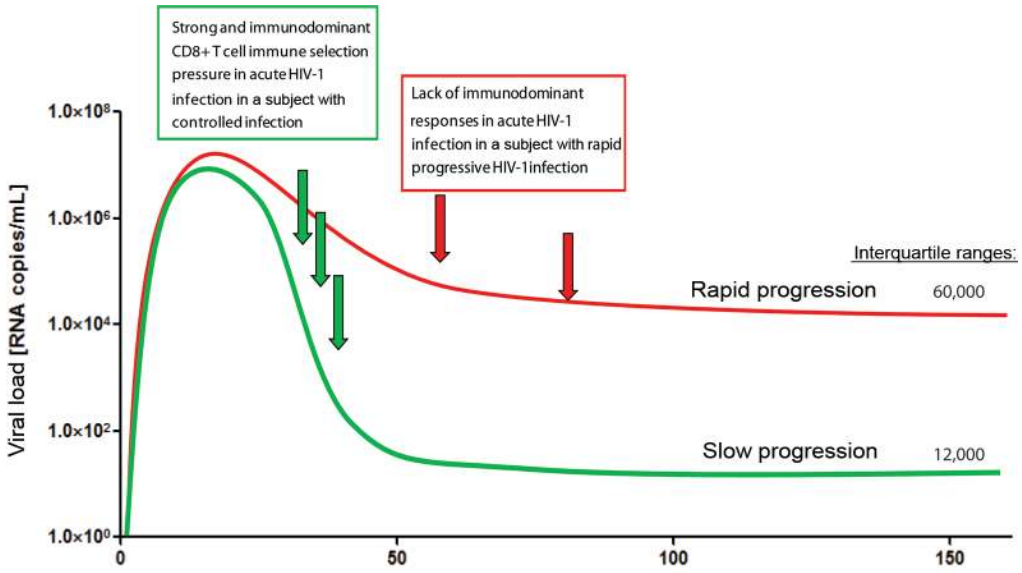

Figure 1. Association between immunodominant CD8+ T cell responses in acute human immunodeficiency virus type 1 (HIV-1) infection and viral set point. Subjects in whom a frequent and immunodominant recognized CD8+ T cell epitope is targeted in acute infection have, on average, a lower early viral set point [7], and subjects in whom such epitopes are not targeted in acute infection have a higher viral set point. This early viral set point is highly predictive of disease outcome.

common HLA alleles, and responses to these epitopes are therefore not observed.

The question remains why early CD8+ T cell responses are so efficient in controlling viral replication, whereas CTL responses generated later in infection appear impaired. Here, several explanations that might equally account for this phenomenon are explored.

CTL RESPONSES AND VIRAL EVOLUTION: A CHASING GAME

Because of ongoing recombination and mutations, HIV-1 permanently escapes recognition by CD8+ T cell responses in the host. The continuous evolution of HIV-1 represents one of the major obstacles for vaccine design and has not only contributed to the already significant viral diversity in a single HIV-1–infected individual but also accounts for the dramatic sequence diversity among circulating viral strains at the population level. However, it has been suggested that the ability of HIV-1 to escape virus-specific immunity is finite and comes at a fitness cost to the virus [13]. This might play a unique role in the acute phase of infection, when the virus has not diversified as much as it has by the chronic phrase of infection. Therefore, early CD8+ T cell responses might have an advantage in forming the diversity of the virus to lower viral fitness [14]. This early impairment of the virus has been suggested to be one of the central mechanisms of effective neutralizing antibody responses, in which the "chase" between antibody response and viral evolution has been successfully overcome. An early viral fitness defect and therefore early suppression of HIV-1 viremia might be critical for the consecutive generation of fully functional CD8+ T cell responses, because important CD4+ T cell helper signals might be preserved. Thus, immediate and early immune selection pressure might be beneficial to arrest the virus at less fit stages.

BENEFITS OF EARLY CD4+ T CELL HELP

In recent years, limited attention has been paid to the impact of HIV-1–specific CD4+ T cell responses to the control of viral replication. This is surprising, because both the clearance of viruses in other viral infections, such as hepatitis C [15–17], Epstein-Barr virus [18, 19], and cytomegalovirus [20–22] infection, and the prognosis in various cancers [23–26] seem to be highly dependent on antigen-specific CD4+ T helper cell responses. Moreover, in HIV-1 infection strong HIV-1–specific CD4+ T cell responses have been associated with better control of viral replication. For example the presence of robust polyfuntional CD4+ T cell responses is an important hallmark that distinguishes nonpathogenic HIV-2 infection from pathogenic HIV-1 infection [27]. Moreover, a vigorous CD4+ T cell response in acute HIV-1 infection has been associated with subsequent control of viral replication [28], and viral escape from CD4+ T cell–targeted epitopes has been observed [29]. However, whether the presence of HIV-1–specific CD4+ T cells is the consequence of low viremia or effectively contributes to viral suppression remains unclear. Interestingly, the immunogenicity data from the Thai RV144 trial suggest that the vaccine

induced both antibody responses and robust CD4+ T cell responses [30]. The rationale underlying the general exclusion of CD4+ T cells from vaccine design strategies originated from other studies showing that HIV-1 preferentially infects HIV-1–specific CD4+ T cells. A vaccine candidate boosting these responses could in theory enhance viral replication. However, although HIV-1 preferentially infects activated HIV-1–specific CD4+ cells, the great majority of HIV-1–specific CD4+ T cells remain virus free even in the presence of high-level viremia [31].

During primary HIV-1 infection, a massive infection of both resting and activated CD4+ T cells in gut-associated lymphoid tissue occurs, destroying up to 60% of these cells in the early days after infection [32]. HIV-1–specific CD4+ T cell responses emerge simultaneously or even earlier than CD8+ T cell responses during primary HIV-1 infection but decrease after the first months of infection. This contraction of the CD4+ T cell response pool has been suggested to be due to preferential infection, but studies of other chronic viral infections suggest that CD4+ T cell responses often naturally contract after the initial burst of viremia. Moreover, as for CTL epitopes, escape mutations in CD4+ T cell targeted epitopes develop, showing that CD4+ T cells can exert selection pressure on the virus, especially during the early phase of infection [29, 33]. Although studies showed convincingly that HIV-1 replication can be predominantly controlled by CD8+ T cells [1–5, 34, 35], the effectiveness of these CD8+ T cell responses appears to be fundamentally affected by the presence or absence of CD4+ T helper cells [36–42]. Interestingly, antigen-specific CD8+ T cells can be generated in the absence of CD4+ T cell help, but the secondary expansion on antigen reencounter is inefficient [36, 42–44]. A robust and effective CD8+ T cell response in elite controllers has been associated with the presence and preservation of HIV-1–specific CD4+ T helper cell responses [28, 45]. These cells might be also preserved through the initiation of highly active antiretroviral therapy during primary HIV-1 infection [28], thereby maximizing HIV-1–specific CD8+ T cell responses. However, so far very little is known about to what extent CD4+ T cell help is critical for CD8+ T cell–mediated control and which mechanisms are required. Whereas some findings have suggested that interleukin (IL) 2 signals are important for CD8+ T cell proliferation [46], recent studies in the lymphochoriomeningitis virus model suggest that IL-21–secreting CD4+ T cell responses are also critical to prevent CD8+ T cells from becoming rapidly exhausted [47–49], a factor that certainly plays a role in HIV-1 infection. However, whether IL-21+ CD4+ T

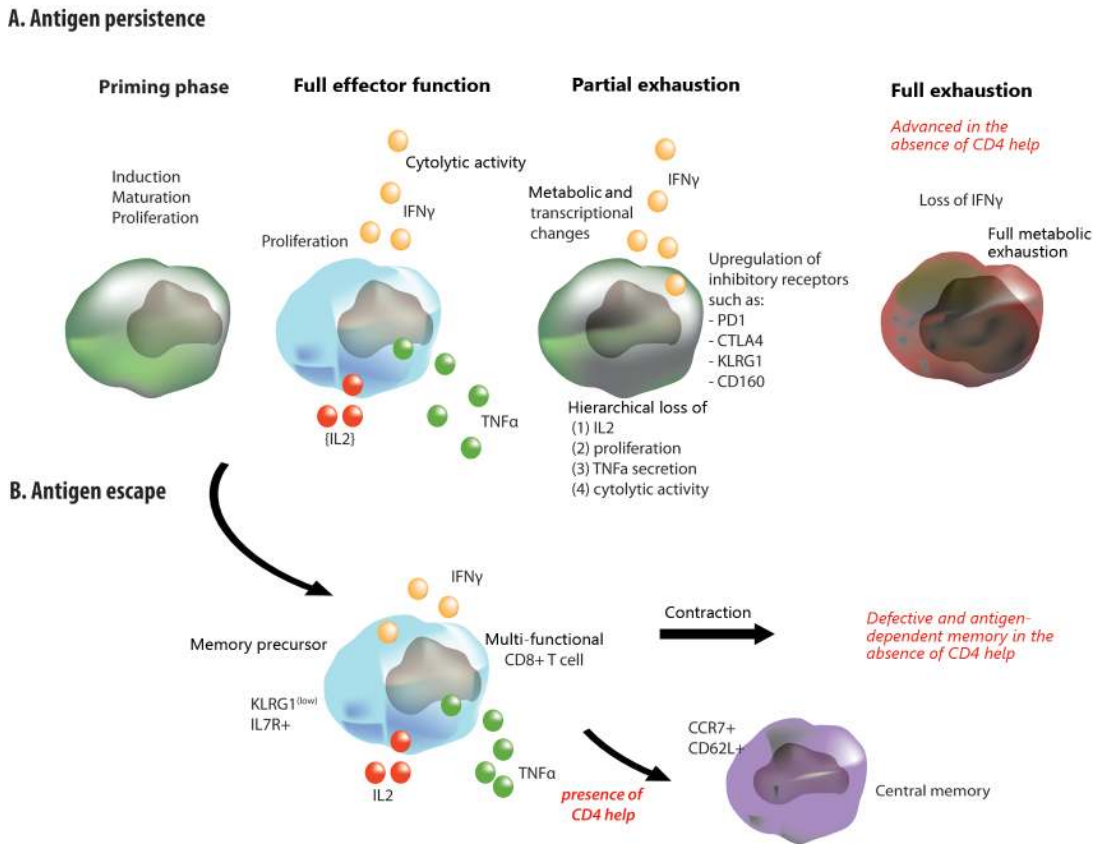

Figure 2. Schematic model for progressive CD8+ T cell exhaustion and memory development. CCR7, chemokine (C-C motif) receptor 7; CTL, cytotoxic T lymphocyte; IFN, interferon; IL, interleukin; PD, programmed death; TNF, tumor necrosis factor.

cells are also involved in antiviral immunity in humans has not been determined thus far.

The role of other $CD4^+$ T cell subsets and their contribution to the control of viral replication are also controversial. T helper 17 (Th17) cells have been implicated as being proinflammatory, causing immune activation, which might not be beneficial in the case of HIV-1. Conflicting results exist concerning the presence of HIV-1–specific Th17 cells, and their contribution to immunpathogenesis remains to be determined. Similarly, only a little is known about the role, presence, and specificity of HIV-1–specific Th2 or T follicular helper cell responses, which provide important helper signals for the maturation and antibody generation of B and plasma cells. The importance of this understudied area of HIV-1 research is stressed by the recent results of the immunogenicity data of the RV144 Thai trial, suggesting a potential critical interplay of induced Env-specific $CD4^+$ T cell responses and HIV-1–specific antibody responses.

PROGRESSIVE EXHAUSTION PREVENTS BETTER CONTROL

$CD8^+$ T cell responses primed in acute HIV-1 infection have a better metabolic starting position than $CD8^+$ T cells generated under persistent viral infection with abundance of antigen. When naive $CD8^+$ T cells recognize their antigen, they mature to effector cells, recognizing and killing the respective target cells. After clearance of an acute viral infection, this population contracts, and only a minor fraction of the effector cells develop into a long-lived memory pool. However, in chronic persistent infections and under persistent levels of antigenemia, $CD8^+$ T cells become progressively exhausted. This exhaustion follows a clear hierarchical pattern face (Figure 2) [50]: the cells first lose the ability to proliferate, to secrete different cytokines and chemokines, and their cytolytic activity, and finally they enter a stage of full exhaustion. This metabolic loss of functional abilities is followed by physical deletion. The different stages of exhaustion are reflected by the up-regulation of different inhibitory molecules on the cell surface, such as programmed death 1, CTLA-4, KLRG1, TIM-3, or CD160. Although these receptors are generally up-regulated under repetitive antigenic stimulation, they appear to be differently regulated, suggesting a distinct modulation of these inhibitory pathways [51]. It is also important to note that although there is a general up-regulation of inhibitory receptors, this might be distinctly different at the epitope level. Studies in humans and mice demonstrated that once a CTL escape mutation in the targeted epitope develops, these receptors down-regulate from the cell surface at different rates [52, 53]. Similarly, the functionality of the $CD8^+$ T cells appears to improve upon escape mutations in the targeted epitope (Figure 2). However, it is not known whether the inhibitory receptors indeed decrease and the functionality of the cells generally increases or whether the pool of the different clonal $CD8^+$ T cell population appears less exhausted because the more exhausted T cells have already entered apoptosis. Thus, to analyze the functionality and phenotype of the antigen-specific $CD8^+$ T cells, it is important to simultaneously analyze the corresponding viral sequences.

One hallmark of HIV-1 infection is a chronic activation of the immune system that not only increases the number of activated $CCR5^+CD4^+$ target cells but also directly impairs the immune system through activation-induced cell death. Although the immune system has developed several strategies to counteract this abundant activation, it has been shown to be one of the strongest contributors to $CD4^+$ T cell loss in the case of HIV-1 infection. One specific mechanism of evasion from hyperactivation is a specific expansion of inducible $FoxP3^+CD25^+$ regulatory T cells after acute HIV-1 infection. Interestingly, subjects with chronic progressive infection showed significantly higher levels of these cells than subjects able to control viral replication [54]. These cells have been shown to have the ability to effectively inhibit several arms of the immune system, but the mechanism by which they act is currently unknown. Both contact-mediated activity and activity through soluble factors, such as transforming growth factor β or IL-10, have been suggested. Indeed, increased IL-10 plasma levels in chronic HIV-1 infection have been demonstrated and suggested to contribute to the general dysfunction of $CD8^+$ T cell responses [55]. Overall, HIV-1–specific $CD8^+$ T cells generated in the chronic phase of infection face an immune system that is prone to reduce rather than foster immune responses. Thus, the ability of these cells to decrease the level of viral replication more efficiently might be impaired owing to an inhibitory cellular and cytokine milieu.

CONCLUSIONS

Emerging studies suggest that immune responses induced during the early stages of HIV-1 infections substantially influence disease outcome. Differences in functionality and cosignals through $CD4^+$ T helper cells appear to be critical for the effectiveness of $CD8^+$ T cell responses generated in acute HIV-1 infection, compared with "impaired" responses in the chronic phase of infection. In particular, the role of $CD4^+$ T cells in the control of viral replication has not been sufficiently assessed and might be fundamentally important for a broader understanding of the immunpathogenesis of this disease.

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