



Review

CD8⁺ T Cell Suppressor Factors and the Control of Infection, Replication and Transcription of Human Immunodeficiency Virus

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Abstract. CD8⁺ T cells have been shown to produce factors which modulate HIV-1 replication in both T cells and monocytic cells. Examination of the literature reveals that this modulation may occur by the production of β -chemokines which block viral entry. However, another CD8⁺ T cell-derived factor(s) targets the replication of HIV-1 at the level of transcription. CD8⁺ T cell factors strongly suppress replication at the level of transcription in T cells and T cell lines, the factors enhance both replication and transcription in cells of the monocyte/macrophage lineage. The enhancement of transcription and replication, which is pertussis toxin sensitive is induced by increased production of TNF- α by the target cells. Thus, CD8⁺ T cells produce factors which mediate effects on transcription and replication of HIV-1 in a cell type-dependent manner. In this review a summary of the effects of chemokines and CD8-derived factors on HIV-1 transcription and replication is presented focusing on the cellular pathways which may mediate their effects on HIV transcription and replication in different cell types. The virus-host cell interactions that participate in the persistent replication of HIV in macrophages and the suppression of these functions in T cells require definition. The identification of CD8⁺ T cell factors which exert these controls on HIV-1 may lead to promising new therapies for HIV infection.

Key words: CD8⁺ T cell; transcription; replication; HIV-1; macrophage; pertussis toxin.

Introduction

The negative control of HIV-1 replication by CD8⁺ T cells was originally reported in 1986 by WALKER et al.⁵³ and was termed the CD8⁺ T cell antiviral factor (CAF). Since then, CD8⁺ T cell control has been repeatedly shown to be mediated in a non-lytic, MHC class 1-unrestricted manner by soluble factors^{9, 52}, impacting on both virus replication and viral transcription. In addition, this control at the level of virus replication was not shown to be mediated by known cytokines,

suggesting a novel suppressor factor distinct to CD8⁺ T cells³⁹. CD8-mediated control of HIV replication is currently one of the most fast-paced areas of HIV research. In 1995 three β -chemokines, MIP-1 α , MIP-1 β and RANTES, were identified as components of CD8-mediated suppression of virus replication¹⁴. The binding of chemokines to their seven-transmembrane G protein-coupled receptors blocks the entry of HIV into macrophages and T cells. However, despite this interference, MIP-1 α , MIP-1 β and RANTES have clearly been shown to have no modulatory effect on

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HIV long terminal repeat (LTR)-mediated transcription^{16, 32}. In contrast, activated CD8⁺ T cells produce factors which strongly modulate transcription. This review will focus primarily on the current knowledge of the transcriptional effects of CD8⁺ T cell factors in T cells and monocytic cells. An understanding of the mechanisms involved in the CD8-mediated control of transcription may identify other factors with potential value in the treatment of HIV infection.

Chemokines versus CD8⁺ T Cell Factors in HIV Pathogenesis

Following the discovery of RANTES, MIP-1 α and MIP-1 β as CD8-derived suppressors of macrophage-tropic (M-tropic) isolates of HIV, it was reported that the CD4⁺ T cells of highly exposed but uninfected (EU) individuals were resistant to infection with M-tropic isolates⁴⁴. In addition, CD4⁺ T cells of EU individuals produced higher levels of the β -chemokines. Until the discovery of the chemokines, the mechanisms of CD8-mediated suppression were not understood and were assumed to be active at the level of virus replication and/or transcription. The chemokine connection in HIV pathogenesis allowed the first focus on chemokine receptors and their possible role as co-receptors for HIV infection of CD4-expressing cells. Leading the long list of findings was the identification of an α -chemokine receptor, fusin or CXCR4, as a co-receptor for entry of T cell-tropic isolates of HIV-1 into PBMC^{4, 25}. The ligand for fusin was identified as stromal cell-derived factor 1 (SDF-1)^{8, 42}. Following on the heels of the fusin discovery, CCR5^{1, 22, 24}, CCR3^{13, 23} and CCR2b²³ were identified as co-receptors utilized by M-tropic isolates for entry into CD4⁺ T cells. More recently, the requirement of the chemokine receptors STRL33/Bonzo³⁵ and GPR15/BOB⁴⁶ in HIV infection have been described. The importance of CCR5 for entry was further established by reports that individuals homozygous for a 32-base pair deletion in CCR5 were resistant to HIV-1 infection^{21, 36}. Individuals heterozygous for the deletion remained susceptible to infection but demonstrate a somewhat slower rate of disease progression^{21, 29}. In addition to the β -chemokines, it was later shown that the chemoattractant cytokine IL-16, produced specifically by CD8⁺ T cells, strongly inhibited HIV-1 replication at the level of transcription^{36, 56}.

Other studies have reported that the ability of CD8⁺ T cells to suppress HIV-1 replication correlated with a state of clinical good health or lack of disease progression^{6, 28, 30, 40}, including high CD8 suppressor activity in long-term non-progressors (LTNP)¹⁰. Using

a transcription-based system, suppression by CD8⁺ T cells was studied in a cohort of infected individuals¹⁵. No correlations were found between the extent of suppression and either clinical stage of infection or CD4⁺ T cell count. Higher levels of suppression of gene expression were associated with higher CD8⁺ T cell numbers. In addition, a weak correlation was found between MIP-1 α levels in CD8⁺ T cell culture supernatants and the ability of the supernatants to suppress gene expression. Stronger correlations were found between MIP-1 β and RANTES levels and CD8-mediated suppression¹⁵. However, some CD8⁺ T cells which inhibited strongly did not produce correspondingly high levels of MIP-1 α , MIP-1 β or RANTES. Similarly, weakly suppressing supernatants could produce higher chemokine levels than strongly suppressing supernatants¹⁵. In a study of long-term non-progressors, high CD4⁺ T cell numbers were associated with a lack of suppression of virus replication by CD8⁺ T cells²⁶. BARKER et al.³ have identified two distinct CD8⁺ T cell suppressor activities, one which is lost upon disease progression and a second which is maintained at all stages of disease. Further, this study showed that the CD8⁺ T cells of individuals with very low CD4⁺ T cell counts were able to suppress virus replication in an acute infection assay. The latter study employed co-culture of dendritic cells with autologous CD4⁺ T cells, thus eliminating the requirement for exogenous stimulation of the T cells. In addition, RUBBERT et al.⁴⁷ have reported β -chemokine-dependent and -independent effects of CD8⁺ T cell-mediated suppression of HIV replication in T cell-dendritic cell co-culture. These contrasting reports on the association of CD8-mediated suppression of virus replication with clinical well-being may reflect the different systems used, including acute versus endogenous replication assays.

Cellular Source of Suppressor Factors

The suppressive effect of CD8⁺ T cell-derived factors on naturally infected CD4⁺ T cells has been demonstrated for CD8⁺ T cells of both HIV-infected and uninfected individuals⁹. LEVY et al.³³ have previously reported that CD8⁺ T cell suppression of acute infection *in vitro* was dependent upon an individual being infected with HIV or with a potential for exposure to the virus⁵⁴. In contrast, RØSØK et al.⁴⁶ have demonstrated that CD8⁺ T cells from HIV-1 seronegative individuals suppress HIV-1 replication in acutely infected CD4⁺ T cells *in vitro*. We have also demonstrated that both CD4⁺ and CD8⁺ T cells of uninfected individuals produce factors which suppress HIV transcription and acute infection in CD4⁺ T cells³¹. Thus, the CD8 effect

does not appear to require exposure to HIV-1. These contrasting reports may be due to differences in cell culture techniques, such as the mode of CD8⁺ T cell stimulation or the use of lab-adapted strains versus patient-derived isolates of HIV-1. However, variation in CD8 suppressive ability between individuals is likely due to differences in the levels of particular CD8⁺ T cell subsets and the response of subsets to activation⁴⁶, which is required to induce CD8 suppressor factors⁵³. The antiviral activity of CD8⁺ T cells has been reported to correspond to CD29⁺/CD45RA⁻ memory cells³⁰, CD28⁺/HLA-DR⁺ activated cells³⁰ and CD56⁻/CD16⁻ non-NK cells⁹. To date, the specific phenotype of CD8⁺ T cells providing factors that suppress HIV-1 LTR-driven gene expression has not been determined.

CD8⁺ Suppression on HIV-1 Replication in T Cells: Effect of Combination Therapy

In 1994, MACKEWICZ et al.³⁸ demonstrated that zidovudine monotherapy resulted in an augmentation of CAF activity. More recent studies by BISSET et al.⁵ reported that indinavir treatment resulted in increased circulating levels of MIP-1 α , MIP-1 β , RANTES and IL-16 in severely immunodeficient HIV-infected individuals. This was likely due to recovering CD8⁺/HLA-DR⁺ T cells, which are known to specifically produce IL-16¹¹. The ability of protease inhibitor treatment to modulate IL-16 may serve as a protective mechanism and contribute to reduced viral load in severely immunodeficient individuals where SI variants of HIV-1 are likely to be present. The production of IL-16 by CD8⁺ T cells of asymptomatic HIV-infected individuals, LTNP and AIDS patients does not appear to correlate with an improved clinical status^{7, 48}. However, cloned CD8⁺ T cells from LTNP secrete higher levels of IL-16 than clones generated from the CD8⁺ T cells of asymptomatic HIV⁺ or AIDS patients⁷. This suggests that IL-16 production may, in concert with β -chemokines and CAF, contribute to viral suppression in T cells *in vivo*. In individuals undergoing combination therapy, CD8⁺ T cell expansion and activation are reversed², with a concomitant reduction in levels of cytotoxic T lymphocytes⁴³. However, recently it has been shown that combination therapy including a protease inhibitor resulted in an abrogation of the suppression of HIV-1 replication by CD8⁺ T cells of treated individuals⁵⁵. It remains to be determined whether the strong suppression of HIV replication in individuals undergoing combination therapy results in the loss of the CD8 effect. This is likely multifactorial and requires further study, including an examination of the subsets of CD8⁺ T cells which decline during combination therapy.

CD8⁺ T Cell-Mediated Modulation of HIV-1 Transcription

Inhibition of HIV-1 replication in CD4⁺ T cells and T cell lines by CD8⁺ T cells has been reported to be mediated at a point prior to the onset of RNA transcription. Several groups have examined the influence of CD8-derived soluble factors on the course of LTR-mediated gene expression in T cell lines^{12, 19, 20, 37}. In studies employing transient transfection of vectors, in which the HIV-1 LTR directed the expression of chloramphenicol acetyl transferase (CAT) or luciferase, CD8⁺ T cell supernatants were able to inhibit gene expression strongly in T cell lines^{12, 19, 20, 37}. In a closer examination of the HIV-1 LTR, the nuclear factor of activated T cells (NFAT)-1 element was demonstrated to be critical for CD8⁺ T cell-mediated suppression of Tat-activated HIV-1 LTR-driven gene expression in T cells²⁰. In addition, CD8⁺ T cell-mediated inhibition of the HIV-1 LTR-activated by phorbol ester and calcium ionophore was shown to be dependent on the nuclear factor κ B (NF κ B) element¹⁹. Culture of Jurkat cells, acutely infected with HIV-1, with CD8⁺ T cell-derived supernatant has been shown to reduce expression of an integrated HIV-1 LTR-luciferase vector³⁷. The inhibition of LTR-mediated transcription is not restricted to members of the lentivirus family, since CD8⁺ T cell supernatants inhibited expression from the LTR of human T cell leukemia virus (HTLV-1) and of Rous sarcoma virus (RSV)¹⁹. However, the suppression of gene expression induced by CD8⁺ T cells does not appear to involve the chemokines MIP-1 α , MIP-1 β and RANTES. In fact, the suppression of gene expression by CD8⁺ T cell supernatant in Jurkat T cells is not abrogated by a combination of antibodies to MIP-1 α , MIP-1 β and RANTES, nor is there evidence to suggest that chemokines influence LTR-mediated transcription³². This lack of an effect indicates that other factors are involved in suppression at the level of gene expression. This is an argument similar to that proposed by BARKER et al.³, who found two distinct CD8⁺ T cell suppressor activities.

Comparison of CD8⁺ T Cell Influence on Transcription in T Cells versus Monocytes

Further evidence for the involvement of other factors in the modulation of gene expression has been provided by studies involving monocytic cells. Cells of the monocyte/macrophage lineage serve as reservoirs of HIV due to their inherent resistance to the lytic effects of HIV²⁷. In addition, M-tropic HIV-1 isolates can be demonstrated throughout HIV infection⁵¹. Recent re-

Table 1. Evidence suggesting the existence of additional CD8⁺ T cell factors

	T cell		Macrophage	
	replication	transcription	replication	transcription
CD8 ⁺ T cell factors	decrease	decrease	increase	increase
CD4 ⁺ T cell factors	decrease	decrease	increase	increase
Chemokine sensitivity	+	—	+	—
Pertussis toxin-sensitivity				
CD8 ⁺ T cell factors	—	—	+	+
CD4 ⁺ T cell factors	—	—	—	—

ports have indicated that β -chemokines have no effect¹⁶ or stimulate⁵⁰ HIV-1 replication in macrophages. SCHMIDTMAYEROVA et al.⁴⁹ have reported that HIV infection enhances β -chemokine (MIP-1 α and MIP-1 β) levels in monocytes and that the ability of the β -chemokines to inhibit or stimulate HIV replication is cell-type dependent⁵⁰. In contrast, MORIUCHI et al.⁴¹ have demonstrated a suppression of p24 production in GM-CSF-treated human monocytes infected with HIV-1_{BAL} by culture supernatant of a *Herpesvirus saimiri* (HVS)-transformed CD8⁺ T cell clone. Untransformed CD8⁺ T cells were not examined in this study and, further, it is not known if the transformation event by HVS may have significant effects upon factors produced by these cells.

CD8⁺ T cells have been reported to have opposite effects on gene expression in T cells versus monocytic cells¹⁶. The enhancement of gene expression in monocytic cells treated with CD8⁺ T cell culture supernatants correlated strongly with the corresponding level of suppression of gene expression in Jurkat T cells. In U38 monocytic cells, the β -chemokines had no effect on LTR-mediated transcription, nor did a combination of antibodies to these chemokines abrogate the enhancement of virus replication induced by CD8⁺ T cells in infected monocytic cells¹⁶. The enhancement of virus replication in human macrophages and monocytic cells by CD8⁺ T cell-derived factors correlated with the induction of increased levels of TNF- α , while TNF- α levels were not modulated by these CD8⁺-derived factors in Jurkat cells^{17, 18}.

Modulation of Transcription in T Cells versus Monocytic Cells Requires Different Pathways

The enhancement of gene expression in human monocytes and monocytic cell lines by CD8⁺ T cell supernatants was sensitive to the G-protein inhibitor pertussis toxin^{17, 18}, suggesting a G protein-triggered event which could be mediated by a chemokine or cytokine. In addition, enhancement of LTR-mediated gene expression in monocytic cells could be induced by

conditioned supernatants of CD4⁺ T cells. However, this enhancement was not pertussis toxin-sensitive³¹. The same CD4⁺ T cell culture supernatants are strong inhibitors of gene expression in human T cells and T cell lines³¹. This information again suggests that other factors are operative in modulating expression from the LTR. A summary of the suggestive evidence for alternate factors is presented in Table 1.

The enhancement of gene expression and virus replication in monocytic cells induced by CD8⁺ T cells is of particular interest as this enhancement may contribute to the persistence of HIV-1 in cells of this lineage. The ability of macrophages to act as antigen-presenting cells offers an opportunity for the infection of uninfected CD4⁺ T cells, which presumably could increase the frequency of infection given the presence of CD8⁺ T cells, possibly inducing higher levels of virus replication by macrophages. A search for factors other than MIP-1 α , MIP-1 β and RANTES would be timely to allow a full understanding of the mechanisms of CD8⁺ T cell-mediated control of virus replication and viral gene transcription. While the identification of chemokine receptors as co-receptors required in HIV infection remains a milestone in HIV research, further study of the host factors produced by CD8⁺ T cells may contribute to our understanding of HIV pathogenesis and the development of new antiviral therapies.

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