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Targeting the Human CD3γ Gene Promoter By HIV-1 and HTLV-1: Two Distinct Mechanisms Involving A Transcriptional Regulatory Element and Chromatin Remodeling

KE Willard-Gallo*‡[1], BM Badran[1], H Akl[1], M Ravoet[1], G Dorbrita[1], G Manfouo-Foutsop[1], C Equeter[1], A Burny[1], K Kunstman[2], J Stanton[2] and SM Wolinsky[2]

Address: [1]University of Brussels (ULB), Bordet Institute, Brussels, Belgium and [2]Northwestern University Medical School, Chicago, IL

Email: KE Willard-Gallo* - kwillard@dbm.ulb.ac.be

* Corresponding author ‡Presenting author

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Our studies show that HIV-1, HIV-2, and HTLV-I infection all provoke a progressive defect in surface T cell receptor expression. A specific loss of CD3γ transcripts is responsible for the defect after HIV-1 or HIV-2 infection. Alternatively, while CD3γ transcripts are lost first after HTLV-I infection, their reduction is followed several months later by a loss of CD3δ and subsequently CD3ε mRNA. Studies of CD3γ transcriptional control revealed parallels with elements regulating HIV-1 gene expression, including a downstream element reminiscent of HIV TAR. Mutant and deletion CD3γ promoter constructs delimited a 53 bp region downstream from the major transcription start site as critical for positive gene expression. EMSA experiments demonstrate that this sequence functions through an RNA rather than a DNA intermediate, which can bind three specific nuclear protein complexes. Deletion of U at +9 and +37 kills promoter activity. Alternatively, progressive silencing of the CD3 gene locus by HTLV-I functions via chromatin remodeling, characterized by increased binding of Ikaros to the CD3 γ promoter and the CD3δ enhancer. Expression of the CD3 genes can be reactivated in HTLV-I infected cells by the synergistic action of the histone deactylase inhibitor trichostatin A and the DNA methyltransferase inhibitor 5-aza-2'-deoxycytidine. The importance of viral targeting of the CD3 genes will be discussed.