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Oral presentation

The human CD3 g gene promoter is controlled by an RNA element that binds P-TEFb and is negatively regulated by HIV-1 Tat

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Our studies show that HIV-1 infection provokes a progressive defect in surface TCR/CD3 receptors due to the specific and escalating loss of CD3 g mRNA. The human CD3 g gene is transcribed from a weak, lymphoid-specific promoter with significant transcription initiation site heterogeneity in normal T cells. However, early after HIV-1 infection CD3 g transcripts preferentially initiate at the +1 and +13 with further focusing over time as +1 transcripts are lost first. Mutant and deletion analysis delimited a 43 bp sequence from the +1 as critical for positive gene expression. DNA probes covering this sequence do not bind nuclear proteins. RNA probes from the +1 or +13 specifically bind the cellular proteins Cyclin T1 and cdk9 (P-TEFb) as well as HIV-1 Tat. The +1 to +43 sequence, defined as the CD3 g RCE (RNA control element), forms a secondary structure containing a uridine bulge, a side loop and a double apical loop with sequence similarity to HIV-1 TAR. Five GGCU repeats present from +18 to +37 form a similar double apical loop structure for +13 transcripts that lack the bulge and side loop. Deletion or mutation in the CD3 g RCE dramatically affects function with a 4 nt apical loop mutation abrogating both promoter activity and nuclear protein binding. Co-transfection of Tat with CD3 g promoter constructs suppresses promoter activity. In infected cells, knocking down tat gene expression restores surface TCR/CD3 whereas treatment with Tat protein accelerates TCR/CD3 downmodulation. Thus, P-TEFb binding to the CD3 g RCE in the presence of Tat is associated with negative transcriptional regulation.