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Oral presentation

Characterization of a RNA control element that binds p-TEFb and modulates transcription of the human CD3y gene

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Our studies show that TCR/CD3 surface receptors are downmodulated after HIV-1, HIV-2 and HTLV-1 infection of CD4+ T cells due to a specific defect in CD3y gene transcripts. Studies of CD3 y transcriptional control revealed parallels with elements regulating HIV-1 gene expression, including a stem loop structure similar to HIV TAR.

Analysis of various mutants and deletions in this region revealed that a 43 bp sequence starting from the major transcription start site is critical for positive gene expression. Deletion of ten nucleotides in this region results in a 70% decrease in promoter activity, while deletion of 39 nucleotides completely eliminates promoter activity. EMSA experiments using DNA or RNA probes covering the +1 to +53 region demonstrate that this element functions through an RNA rather than a DNA intermediate. EMSA and Western blots were used to show that this RNA sequence specifically binds the cellular proteins Cyclin-T1 and CDK9 (p-TEFb) as well as the viral transactivator Tat. Deletion of the U at position +9 and U at +37 completely abrogates binding and promoter activity. The p-TEFb-Tat complex is known to promote transcription from the viral LTR, whereas its binding to the CD3y RNA stem loop structure is associated with negative transcriptional regulation. Experiments are currently underway to elucidate mechanisms that regulate the function of these RNA-protein complexes.