Stochastic choice of expression between IL-2 and HIV-1 in T helper cells as a result of chromosomal interactions between IL-2 promoter and HIV-1 LTR

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When HIV-1 infects T helper (Th) cells, it intercepts the transcriptional regulatory mechanism of IL-2 for its own expression and survival. Transcription of both HIV-1 and IL-2 are stochastic events. The IL-2 promoter and HIV-1- LTR share high sequence homology to which common cellular transcription factors (TFs) bind to either activate or repress their expression. The Ets-2 TF acts as a transcriptional repressor for both IL-2 and HIV-1 in naive Th effector cells. The aim of our study was to investigate whether chromosomal interactions between IL-2 promoter and HIV-1-LTR may be responsible for a stochastic choice of transcriptional expression between IL-2 and HIV-1 in Th cells and whether Ets-2 is involved in these interactions. To this end, Jurkat T cell lines carrying a non-infectious copy of HIV-1 (Jurkat-Lat) or HIV-1-LTR region (Jurkat-LTRG) or none (Jurkat) were cultured for 6h ± mitogens (P/I). IL-2, Ets-2, HIV1-Tat and LTR-GFP reporter gene mRNA was determined by qPCR. In P/I-stimulated cells, IL-2 mRNA levels were increased in all cell lines, whereas HIV-1-LTR mRNA levels were increased in Jurkat-Lat and Jurkat-LTRG cells; Ets-2 mRNA levels were decreased in Jurkat and Jurkat-Lat cells.

CoIP assays showed a strong protein-protein interaction between Ets-2 and Tat mainly in non-stimulated cells. ChIP assays verified the involvement of Ets-2 and Tat in IL-2 and HIV-1 transcriptional regulation by their simultaneous presence on the ARRE-1/TATA and ARRE-2 sequences of the IL-2 promoter and the RATS element of HIV-1-LTR. The presence of Tat on these elements was more pronounced in stimulated cells. Finally, 3C experiments showed that the IL-2 promoter and the HIV-1 LTR were localized in close proximity in the nucleus of unstimulated cells.

Our results suggest that a physical protein-protein interaction between Ets-2 and Tat mediates the interaction between the IL-2 promoter and HIV-1- LTR. This mechanism may be responsible for HIV-1 latency in resting Th cells.