Retrovirology

Poster presentation

C-Maf Cooperates With NFAT2 to Augment HIV-1 Transcription in IL-4 Producing CD4 T Cells

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The human immunodeficiency virus, HIV-1, infects human CD4 T cells, including Th1 and Th2 helper cell subsets. The virus relies on host transcription factors, such as NFkB and NFAT for its transcription and expression. It has previously been shown that HIV-1 preferentially replicates in Th2 cells, but the mechanism of action for this finding remains unknown. c-maf is a Th2-restricted transcription factor that is critically important for differentiation along a Th2, but not Th1 lineage, and for transcription of the prototypic Th2 cytokine, IL-4. c-maf directly binds the proximal IL-4 promoter and acts synergistically with a neighboring NFAT site. We have demonstrated at the individual cell level that IL-4 positive cells (Th2) preferentially support HIV-1 replication compared to IFNg positive (Th1) cells. In studying the HIV-1 long terminal repeat (LTR)/promoter sequence, we identified a MARE (maf-recognition element) located just proximal (5') to the dual NFkB/NFAT binding sites. We show that the HIV-1 MARE binds recombinant maf protein and abuts NFAT binding as detected by DNase I *in vitro* footprinting. In addition, this HIV-1 MARE demonstrates identical mobility shifts compared to the IL-4 promoter MARE in gel-shift assays using nuclear extracts from activated primary human CD4 T cells. Using chromatin immunoprecipitation, we further show that c-maf binds to the HIV-1 LTR *in vivo* in HIV-1 infected primary human CD4 T cells. Although we have previously shown that both NFAT1 and NFAT2 are capable of transactivating the HIV-1 LTR, we now show for the first time preferential binding *in vitro* and *in vivo* of NFAT2 over NFAT1 to the HIV-1 LTR. By comparison, the more abundant NFAT1 family member preferentially binds to the IL-2 promoter. NFAT2 has previously been implicated in Th2 cytokine expression and appears to cooperate with c-maf in binding to the HIV-1 LTR. Functionally, over-expression of c-maf in primary human CD4 T cells cooperatively increases HIV-1 transcription when co-expressed with NFAT1 and 2, and silencing endogenous c-maf expression in primed human CD4 T cells decreases viral transcription. Similarly, over-expression of c-maf alone, or with NFAT1 or 2, increases HIV-1 replication, as measured by intracellular p24/gag expression, in CD4 T cells co-expressing GFP but not in GFP negative/c-maf-negative controls within the same transfected population. Lastly, depletion of c-maf expression by siRNA in primed and HIV-1 infected CD4 T cells decreases p24/gag expression. In summary, the Th2-specific transcription factor, c-maf, binds the HIV-1 promoter in cooperation with NFAT transcription factors, primarily NFAT2, to augment HIV-1 transcription and replication in primary human CD4 T cells. These are the first data to mechanistically explain preferential HIV-1 transcription in IL-4 producing (Th2) cells.