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Regulation of HIV-1 and IL-2 transcription by inducible CAMP early repressor (ICER)

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HIV-1 infection of human monocytes induces production of prostaglandin E2 (PGE2) *in vitro* and *in vivo*, which has capacity to make the bystander T cells unresponsive (anergic). ICER, a potent transcriptional repressor induced by PGE2 leads to transcriptional attenuation of interleukin-2 (IL-2) and an induction of T cell suppression. We propose that this HIV-1 triggered mechanism may subvert physiologically relevant suppression of IL-2 by regulatory CD4+CD25+ T (Treg) cells. Our preliminary studies suggest that the suppressive mechanism conveyed by Treg cells stems from coexpression of ICER and Foxp3, which inhibits IL-2 expression. Moreover, naïve CD4+CD25- responder T cells retrovirally transduced with Foxp3 can induce the accumulation of ICER and replace natural Treg cells. Importantly, ICER expression is induced in activated responder T cells early and correlates with a sharp decrease of IL-2 expression. Our preliminary studies indicate that ICER inhibits HIV-1 LTR expression and binds the cyclic responsive element (CRE)-like motifs termed DSE positioned downstream of transcription initiation site of HIV-1 LTR. Moreover, in monocytes PGE2 induced transcriptional attenuation of CCR5 expression tightly correlates with upregulation of ICER. We conclude that ICER is a critical component of Treg-mediated inhibitory function that affects transcriptional attenuation of IL-2 production in T cells and that HIV-1 subverts this mechanism via PGE2 and/or Tat-mediated induction of ICER.