Mechanisms for HIV Subversion of Immune Response: Activation of the IL-10 Promoter and Gene Induction by Tat

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HIV Tat protein has multiple regulatory roles including trans-activation of the HIV genome, mediation of cytokine production, and modulation of intracellular signaling kinases including PKR. PKR is a double-stranded RNA-activated and interferon (IFN)-regulated protein kinase.

Previous reports including ours have demonstrated that PKR is responsible for mediating the effects of IFN and TNF-α, and virus-induced apoptosis. We postulate that Tat and its induced cellular pathways play a critical role in the subversion of host defenses against HIV. We recently demonstrated that PKR mediates the effects of Tat in the induction of cytokines including TNF-α, IL-6 and IL-10 in blood monocytes. We further showed that ERK-1/2 and p38 MAP kinases are downstream of PKR in regulating the Tat-induced events, leading to activation of NF-κB and NF-IL6 activities for cytokine transcription.

IL-10 is a well-described cytokine capable of suppressing immune response including IL-2 synthesis and T cell functions. In order to elucidate the mechanisms of Tat's effects in cell signaling we performed a detailed analysis of the structure and function of the promoter of the human IL-10 gene and generated a series of luciferase reporter plasmids encoding different regions of the promoter. We delineated that the Tat responsive element of the IL-10 gene is located within 652 bp to 640 bp upstream from the transcription start site (+1) by transient transfection of these plasmid constructs. In this region, we identified four potential transcription factor binding elements, namely NF-IL6, Ets-1, Sp-1 and AP-1. By using electrophoretic mobility shift assays and mutational analysis, we determined that Ets-1 and Sp-1 are the transcription factors involved in mediating the Tat-induced transcription. To confirm the role of Ets-1, overexpression of recombinant Ets-1 resulted in induction of the IL-10 promoter activity. We also examined the signaling pathways of Tat-induced transcriptional activation of IL-10, as measured by luciferase activity, using inhibitors of specific kinase pathways including PKR and p38 MAP kinase.

In conclusion, coordinated activities of PKR and p38 MAP kinase play a crucial role in HIV-1 Tat induced IL-10 transcription, which is mediated by the activation of Ets-1 and Sp-1. (Supported by grants to AS Lau from the Hong Kong Research Grants Council and HoTung Paediatrics Fund. Li is a recipient of the American Society for Virology Student Research Award, Annual Meeting 2004, Montreal.)