## S2-3

# Modulation of Gene Expression by Viral Protein at Post-transcriptional Levels

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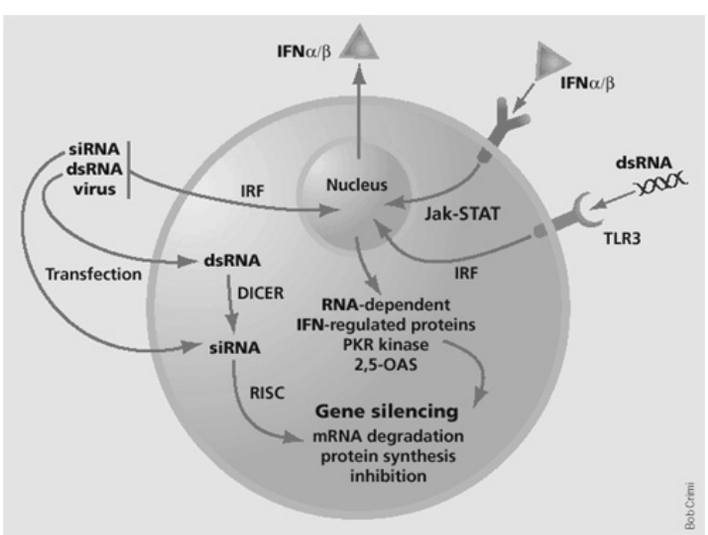
Viruses are obligatory intracellular parasite and use cellular biosynthetic machinery for replication. To replicate and cause diseases, viruses must overcome cellular and humoral immune responses, defeat innate cellular defense systems, usurp cellular factors, and reprogram the normal biology of the cell. Recently, studies of innate antiviral and immune responses, host genetics, cell biology, and neuropathogenesis shave identified host factors that viruses must overcome in order to replicate. The field is now poised to combine these studies to define the molecular mechanisms that underlie important host/virus interactions. Of those, studies of cellular factors and genetic elements that are involved in the innate cellular defense systems has been focused on the interferon-induced, dsRNA-dependent PKR/RNase L activation. It has been known well that the induction of interferon eventually causes non-specific translation initiation through the inactivation of eIF2-α and the degradation of mRNAs. During the course of evolution, viruses devised various tactics to redirect translational machinery and to circumvent host defenses.

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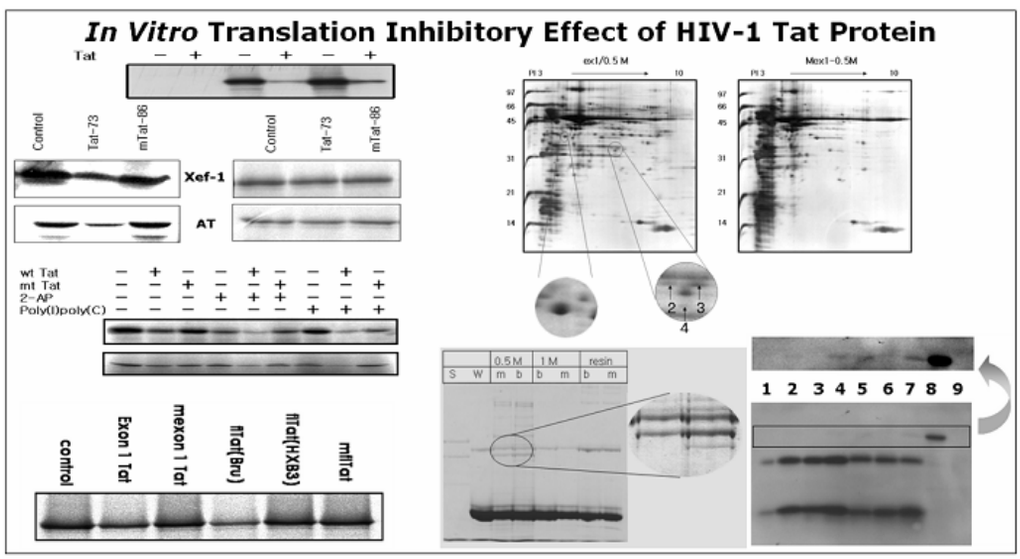
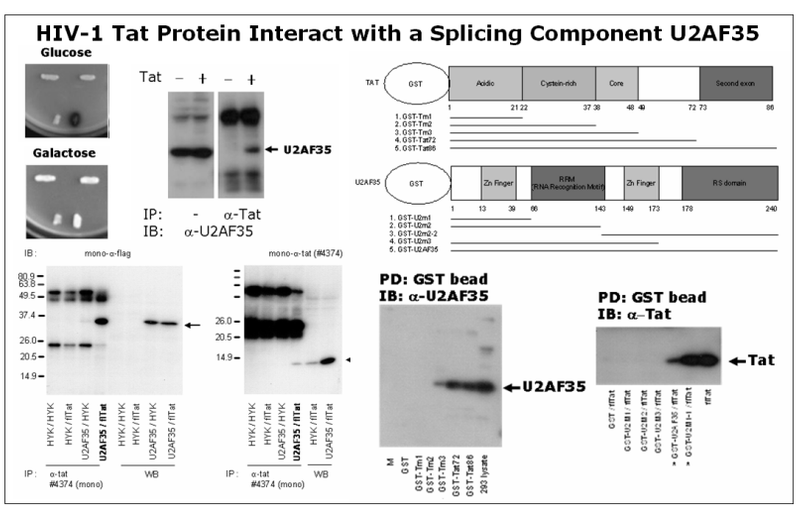
In this study, we found that HIV-1 Tat protein modulates host gene expression PKR-independently at the post-transcriptional levels. The Tat protein of HIV-1 has been known to be critical for viral replication. It binds to TAR RNA at viral long terminal repeat (LTR) region and activates transcription several hundred-fold. In addition to stimulation of HIV-1 gene expression, accumulating evidence suggests that

Tat may exert its effects on various cellular functions as a growth factor, a T-cell activator, a regulator of gene expression, and an inducer or protector of cellular apoptosis. These finding have supported the speculation that Tat has pleiotropic non-transcriptional functions in the cells.

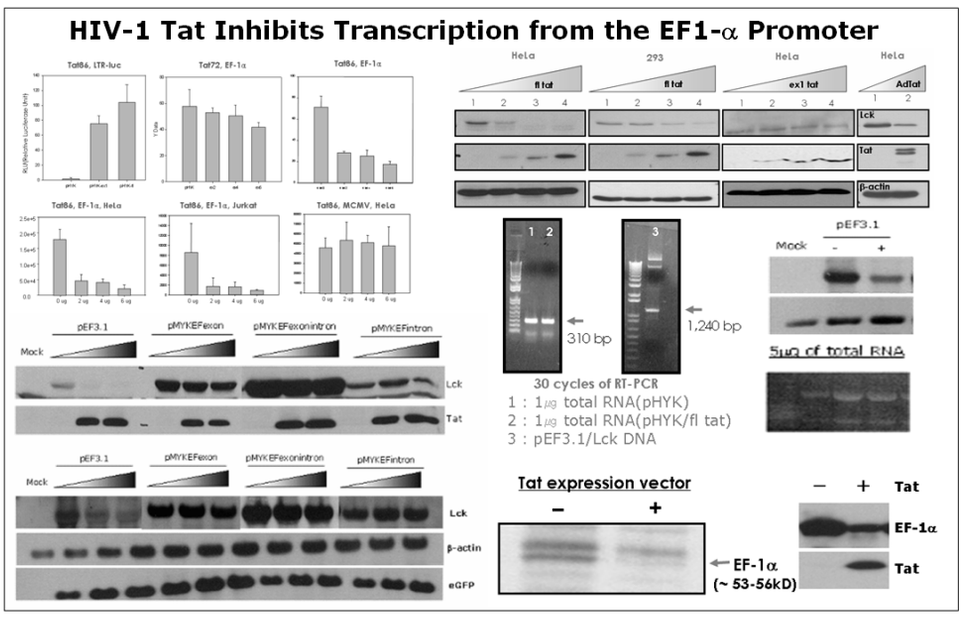
To understand better the biology of the HIV-1 Tat in AIDS-pathogenesis, we have investigated translational effect of HIV-1 Tat protein *in vitro* translation system. Here we report that HIV-$1_{BRU}$ Tat, but not HIV-$1_{HXB3}$ Tat, inhibits translation irrelative to mRNA species.




We also investigated that the HIV-1 Tat downregulates gene expression from EF-1α (eukaryotic elongation factor 1 Alpha) promoter. Decrease of the EF-1α protein by Tat expression resulted in averall inhibition of host protein synthesis. This finding suggests that viral infection could induce a translational inhibitory effect at the translation elongation step as well as translation initiation step. The overall inhibition of host gene expression plays a major role in the ability of the virus to cause disease.



Others have previously demonstrated that Tat regulates alternative splicing using TAR-dependent reporter system. However, the relationship of splicing factors and Tat is not fully defined yet. Here, we show that the alternative splicing was inhibited by Tat protein. By screening of cellular counterpart from a human neuronal cDNA library in the yeast two hybrid system, surprisingly, we identified U2 auxiliary factor 35 (U2AF$^{35}$), a member of non-snRNP splicing factor, as a Tat-binding protein.




During the course of evolution, viruses devised various tactics to redirect translational machinery and to circumvent host defenses. As a consequence, various viral proteins that affect host translation system have been found. In this study, we found that HIV-1 Tat inhibit translation irrelative to mRNA species.