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UP-REGULATION OF GLIAL FIBRILLARY ACIDIC
PROTEIN BY HIV-1 TAT PROTEIN AND ITS DIRECT
INVOLVEMENT IN TAT NEUROPATHOGENESIS

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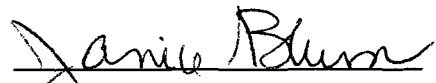


Johnny J. He, Ph.D., Chair



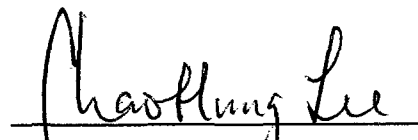
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ABSTRACT

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Up-Regulation of Glial Fibrillary Acidic Protein by HIV-1 Tat Protein and its Direct Involvement in Tat Neuropathogenesis

Human immunodeficiency virus type 1 (HIV-1) infection in central nervous system (CNS) often causes various neurological diseases. HIV-1 Tat protein is an important pathogenic factor in HIV-associated neurological diseases. However, the underlying mechanisms for Tat neurotoxicity are not completely understood. We have shown that Tat expression in astrocytes resulted in increased expression of glial fibrillary acidic protein (GFAP), a cellular marker for astrocytosis. In the current study, we further characterized the interaction between HIV-1 Tat and GFAP, and the role of GFAP up-regulation in Tat neuropathogenesis.

We first determined the mechanisms of Tat-induced GFAP expression. We demonstrated that Tat-induced GFAP expression involved the up-regulation of p300 and early growth response-1 (Egr-1). p300 expression was up-regulated in Tat-expressing or HIV-infected astrocytes. p300 promoter-driven reporter gene assay confirmed that Tat trans-activated p300 promoter. Mutation of the Egr-1 binding sites within the p300 promoter completely abolished Tat effects on p300 promoter, and Egr-1 expression was up-regulated in Tat-expressing cells. Moreover, p300 over-expression alone was sufficient to up-regulate GFAP expression, and p300 knockdown down-modulated both constitutive and Tat-induced GFAP expression. Interestingly, p300 expression significantly enhanced the survival of HIV-infected astrocytes. These results demonstrate that p300 directly up-

regulates Tat-induced GFAP expression and suggest that p300 plays important roles in astrocytosis and HIV latency in astrocytes.

We next determined the role of GFAP up-regulation in Tat neuropathogenesis. With the use of brain-targeted Tat transgenic mice, EGb 761, a standardized formulation of *Ginkgo biloba* extract with neuroprotective functions, was demonstrated to markedly protect these mice from Tat-induced developmental retardation, inflammation, astrocytosis, and neuron loss. EGb 761 down-regulated GFAP expression at protein and mRNA levels. This down-regulation was, at least in part, due to direct effects of EGb 761 on the interactions of AP1 and NF- κ B with the GFAP promoter. Most strikingly, Tat-induced neuropathologies including macrophage/microglia activation, CNS infiltration of T lymphocytes, and neuron death were significantly alleviated in GFAP-null/Tat transgenic mice. Taken together, these results show potential use of EGb 761 for the treatment of HIV-associated neurological diseases, and suggest that GFAP activation or astrocytosis directly contributes to Tat neurotoxicity and HIV-associated neurological disorders.

Johnny J. He, Ph.D., Chair

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