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Animal Model : Transgenic Mice Expressing Human Immunodeficiency Virus Type 1 Tat protein

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The human immunodeficiency virus type 1 (HIV-1) Tat protein is a key pathogenic factor in a variety of acquired immune deficiency syndrome (AIDS)-associated disorders. A number of studies have documented the neurotoxic property of Tat protein, and Tat has therefore been proposed to contribute to AIDS-associated neurological diseases. We attempted to establish a transgenic mouse model in which Tat expression was regulated by both the astrocyte-specific glial fibrillary acidic protein promoter and a doxycycline (Dox)-inducible promoter. In the present study, we characterized the phenotypic and neuropathogenic features of these mice. Both in vitro and in vivo assays confirmed that Tat expression occurred exclusively in astrocytes and was Dox-dependent. Tat expression in the brain caused failure to thrive, hunched gesture, tremor, ataxia, and slow cognitive and motor movement, seizures, and premature death. Neuropathologies of these mice were characterized by breakdown of cerebellum and cortex, brain edema, astrocytosis, degenerationof neuronal dendrites, neuronal apoptosis, and increased infiltration of activated monocytes and T lymphocytes. These results together demonstrate that Tat expression in the absence of HIV-1 infection is sufficient to cause neuropathologies similar to most of those noted in the brain of AIDS patients, and provide the first evidence in the context of a whole organism to support a critical role of Tat protein in HIV-1 neuropathogenesis. More importantly, our data suggest that the Dox inducible, brain-targeted Tat transgenic mice offer an in vivo model for delineating the molecular mechanisms of Tat neurotoxicity and for developing therapeutic strategies for treating HIV-associated neurological disorders.