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Gene expression changes consistent with neuro AIDS and impaired working memory in HIV-1 transgenic rats

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Background: A thorough investigation of the neurobiology of HIV-induced neuronal dysfunction and its evolving phenotype in the setting of viral suppression has been limited by the lack of validated small animal models to probe the effects of concomitant low level expression of multiple HIV-1 products in disease-relevant cells in the CNS.

Results: We report the results of gene expression profiling of the hippocampus of HIV-1 Tg rats, a rodent model of HIV infection in which multiple HIV-1 proteins are expressed under the control of the viral LTR promoter in disease-relevant cells including microglia and astrocytes. The Gene Set Enrichment Analysis (GSEA) algorithm was used for pathway analysis. Gene expression changes observed are consistent with astrogliosis and microgliosis and include evidence of inflammation and cell proliferation. Among the genes with increased expression in HIV-1 Tg rats was the interferon stimulated gene 15 (ISG-15), which was previously shown to be increased in the cerebrospinal fluid (CSF) of HIV patients and to correlate with neuropsychological impairment and neuropathology, and prostaglandin D2 (PGD2) synthase (Ptgds), which has been associated with immune activation and the induction of astrogliosis and microgliosis. GSEA-based pathway analysis highlighted a broad dysregulation of genes involved in neuronal trophism and neurodegenerative disorders. Among the latter are genesets associated with Huntington's disease, Parkinson's disease, mitochondrial, peroxisome function, and synaptic trophism and plasticity, such as IGF, ErbB and netrin signaling and the PI3K signal transduction pathway, a mediator of neural plasticity and of a vast array of trophic signals. Additionally, gene expression analyses also show altered lipid metabolism and peroxisomes dysfunction. Supporting the functional significance of these gene expression alterations, HIV-1 Tg rats showed working memory impairments in spontaneous alternation behavior in the T-Maze, a paradigm sensitive to prefrontal cortex and hippocampal function. Comparison of gene expression of the hippocampus of HIV-1 Tg rats with the National NeuroAIDS Tissue Consortium (NNTC) human HIV gene expression dataset showed largely consistent results including changes in in genes related to neuronal trophism and degeneration.

Conclusions: Altogether, differentially regulated genes and pathway analysis identify specific pathways that can be targeted therapeutically to increase trophic support, e.g. IGF, ErbB and netrin signaling, and reduce neuroinflammation, e.g. PGD2 synthesis, which may be beneficial in the treatment of chronic forms of HIV-associated neurocognitive disorders in the setting of viral suppression.

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