HERV-W/MSRV/Syncytin-1 regulation by HIVtat in blood and brain cells is mediated by Toll-like receptor 4 and TNF-alpha: inference for neuroAIDS.

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The multiple sclerosis-associated retrovirus (MSRV, that releases extracellular particles), and ERVWE1 (an element that has inactivating mutations in the gag and pol genes and is not able to form particles) are two components of the HERV-W family, whose envelope proteins (MSRVenv and Syncytin-1, respectively) exert neuro-pathogenic and immune-pathogenic properties *in vivo* and *in vitro*. Due to the sequence similarities between these *env* genes, the effective distinction between the two elements could be obtained by our discriminatory real time RT-PCR assays (Mameli *et al.*, 2009), that can selectively identify either MSRV*env* or Syncytin-1 transcripts, with specific probes designed on the basis of an insertion present only in the cytoplasmic domain of the MSRV*env* gene. At the protein level, no antibody can distinguish the two HERV-W envs. Since 10% of healthy Caucasian release MSRV in the blood, we wondered whether MSRV and Syncytin-1 are activated by HIV-Tat, and therefore could contribute to HIV-related neurodegeneration. To this end, monocyte-macrophages and astrocytes were exposed to HIVtat and/or other treatments. The expression of transcripts and proteins of interest was evaluated by real-time RT-PCR and Western Blotting assays. The results showed that HIV infection and exposure to Tat increase the levels of MSRV*env* mRNAs and HERV-Wenv proteins in astrocytes and in blood cells. In monocyte-macrophages, Tat induces also high levels of CCR2, CD16 and Toll-like receptor4 (TLR4) molecules. Syncytin-1 response to Tat depends on the cell context: in monocytes Tat stimulates MSRV*env* and inhibits Syncytin-1, while in differentiated macrophages and primary astrocytes, Tat stimulates both elements. In U87MG astroglioma cells an opposite regulation of MSRV*env* (upregulation) and Syncytin-1 (downregulation) occurs. This opposite response to the same stimulus of MSRV and Syncytin-1 in U87MG and monocytes was not reported previously, and demonstrates the independent behavior of these retroelements of the same HERV-W family. It is known that TNFα is the most abundant proinflammatory cytokine in the brain of neuro-AIDS patients: in this context of neurodegeneration, MSRV and Syncytin-1 stimulation by the induced TNFα seems a concrete possibility. In primary astrocytes, Tat stimulates MSRV and Syncitin-1 through interaction with TLR4 and induction of TNF-α. The indirect mechanism by which Tat activates the HERV-Ws by TNFα induction could be a new property of this pleiotropic protein. *In vivo* consequence of the study could be that, through increase of CD16 and CCR2, Tat promotes neuroinvasion by HIV-infected monocytes/macrophages, but also by the HERV-Ws, with their neuropathogenic potential. Within the brain, Tat-induced TNFα could induce high levels of the HERV-Ws, in both macrophages and astrocytes, also without HIV replication.