HERV epigenetic dysregulation and transactivation by environmental viruses

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Human endogenous retroviruses (HERV) are a consistent part of our genome (average 8% of human DNA). Their expression is dependent on multiple factors. A pre-requisite is the HERV availability to be transcribed, i.e. the chromatin state where the retroelement is located. DNA methylation and histone modifications are key factors in the epigenetic control also of the transcription of HERVs. Another pre-requisite is that HERV sequences must retain functional long terminal repeats, and at least one intact open reading frame. Several triggers may modify the epigenetic control of HERVs. Cells of different tissues vary for the nuclear microenvironment, the chromatin state of tissue-specific coding regions, and the pool of available transcription factors. Hence, a baseline predisposition of an HERV to be activated may be tissue-, cell- or differentiation-specific. Many HERVs are expressed in highly proliferating tissues, as placenta, embryo tissues, and cancer cells. In the placenta, elevated expression of HERV-W, HERV-FRD, HERV-R, and HERV-E, and HERV sensitivity to hormones have been reported. The interplay between HERVs and pluripotent embryo stem cells varies among HERVs. Specific HERVs are expressed during early embryogenesis in a stage-specific manner. Importantly, activation in differentiated human cells of specific HERVs (HERV-H, HERV-K, HERV-E, HERV-W) has been associated with development of malignant tumors, and proposed to have role in cancer progression and metastasis. Inflammatory stimuli may activate HERVs, when epigenetically dysregulated: transcription of HERV-W sequences is upregulated by pro-inflammatory cytokines (as TNFα, IL-6, and interferonγ), but inhibited by interferon-β. The latter exerts a dual effect, with dominant inhibition involving HERV-W promoter and stimulatory effects mediated by its viral, LTR, moiety. Different HERV-Ws may be regulated in opposite ways within same or different cells and with monocyte/macrophage differentiation. It is worth to note that several viruses, whose infection was shown to precede the onset of neurological and neuropsychiatric diseases as diverse as multiple sclerosis, schizophrenia, bipolar disorders, Parkinson's disease, induce robust pro-inflammatory responses. Several HERV families were reported to be transactivated by exposure to viral proteins or infection with herpes simplex virus-1 (HSV-1), varicella-zoster virus (VZV), cytomegalovirus (CMV), human herpes virus type 6 (HHV-6), and Epstein Barr virus (EBV) in various histotypes of human cell lines and in cells from patients. The triggers of HERV activation by herpesviruses were the HSV-1 ICP0 and ICP4 immediate early proteins (to induce HERV-W), the EBV latent membrane proteins 1 and 2A (to induce HERV-K18 in B cells), the interaction of EBV gp350 envelope protein with its CD21 cell receptor (to induce HERV-K18 in tonsil cells, and HERV-W/MSRV/Syncytin-1 in PBMC and astrocytes). In PBMC EBVgp350 stimulated HERV-W/MSRV*env/* Syncytin-1 in B cells and monocytes, but not in T cells, nor in the highly expressing NK cells. The NK cells, but not the T cells, were activated by proinflammatory cytokines, indicating that HERV-W elements can be stimulated also in NK cells, when the proper stimuli are given. The monocyte/macrophages were the most responsive to EBVgp350, reaching HERV-Wenv levels higher than those detected in B cells, particularly after differentiation into macrophages. The activated monocytes can easily pass across the blood-brain barrier, thus the HERV-W expression (and release) by monocyte-macrophages was proposed to account for the bulk of expression (and effects) of these elements within the brain of patients affected by multiple sclerosis (MS). Since the main links between EBV and MS onset (history of infectious mononucleosis and high IgG titers against EBV nuclear antigen-1) are paralleled by HERV-W/MSRV activation, a "dual virus hypothesis" was formulated, indicating EBV as initial trigger of future MS, years later, and HERV-W/MSRV as effector of neuropathogenesis before and during MS.

Other viruses reported to transactivate HERVs are HTLV-1 and HIV-1 exogenous retroviruses. HTLV-1 Tax potently increased the LTR activity of HERV-W, HERV-H, HERV-K and HERV-E families in T cells. HERV-K(II)env was found highly expressed in human neurons, and further increased by HIV, exerting protective effects on neuronal cells. HIV effects on HERV-K and on HERV-W are reproduced by cell exposure to the Tat protein, which indirectly activates HERV-W through Toll-like receptor-4 (TLR4), TNFα and NF-κB. This implies many targets, mostly non HIV-infected cells. Therefore, in the blood Tat could promote neuroinvasion by monocytes/macrophages expressing the HERV-Ws, with their neuropathogenic potential; within the brain Tat and Tat-induced TNFα could induce high levels of the HERV-Ws, in macrophages and astrocytes, also without HIV replication. This model might apply also to other HERVs, such the HERV-K involved in HIV-associated ALS (amyotrophic lateral sclerosis). This indirect mechanism indicates a different activation pathway than that of Herpesviridae, which is followed by self-sustained HERV expression under appropriate triggering events, which can activate pathogenic cascades in several diseases.