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Molecule of the month HIV-1 Tat and miRNA

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miRNAs are a well-established RNA phenomenon derived from the non-coding major portion of the human genome. miRNAs cannot be ignored because they are so heavily involved in the control of gene expression **[1]**. The study of neurological and neuropsychiatric disease also has miRNA components that are commencing to be mapped and characterized. Due to their high stability, for example miRNA can be found in cerebrospinal fluid (CSF) as well as within cells. In a recent publication, comparisons of miRNAs were made among individuals that were HIV positive, without and with HIV encephalitis (HIVE), in individuals with HIV-Associated Neurological Disorders (HAND), and HIV negative controls. CSF and frontal cortex were studied. Comparing HIV positives with HIV negatives, a total of 66 miRNAs were found differentially upregulated for HIV positive individuals. The HIV negative cases were a type of disease control in that they had non-viral acute encephalomyelitis. Of the 66 upregulated miRNAs, statistical analyses demonstrated that 11 miRNAs were upregulated significantly **[2].**

HIV-1 Tat is an important virus coded regulator protein produced during HIV-1 infection **[3].** HIV-1 Tat disrupts neuronal function via miRNAs. Specifically, miRNA expression becomes altered in neuron cultures exposed to HIV-1 tat. Tat is a high inducer of miR-34a as well as other miRNAs. However, tat also decreased levels of target genes including CREB involving miR-34a **[4].**

Earlier studies on the effects of Tat specifically and HIV-1 in general need to be reinterpreted in terms of the involvement of miRNAs. For example, PC12 (neuronal) cell cultures demonstrate a rapid (*ca.* 5 minutes) increase in cAMP and CREB transcription factor levels upon exposure to HIV-1 Tat. The serine-133 (Ser-133) amino acid is phosphorylated on CREB. However, when this experiment is done at later times of addition of Tat (*ca.* 1-2 hours), there is a continued decline of cAMP and reduction of phosphorylated CREB. The dephosphorylation was shown to be due to activation of a phosphatidyl-inositol-3-kinase, AKT, and cyclic nucleoside phosphodiesterase pathway. In addition, there was increased apoptosis of the treated cells. These findings may be relevant for the mechanisms of pathogenesis for HIV-1-associated dementia (HAD) **[5]** as well as HAND.

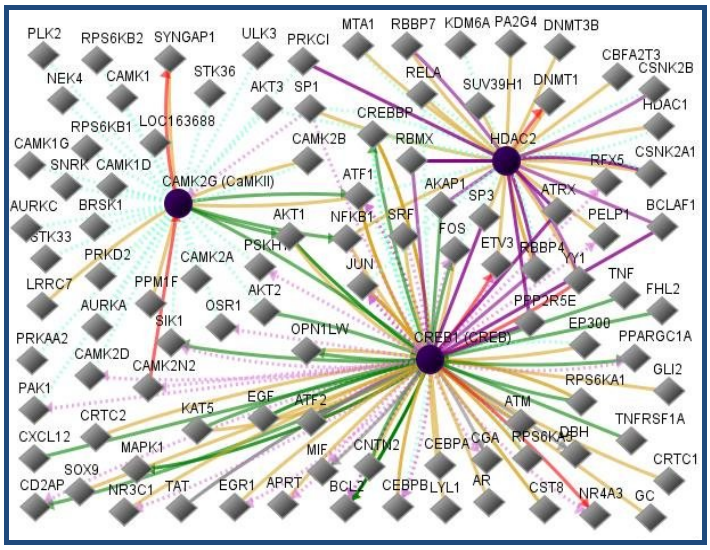

Figure 1: CREB HDAC2 CaMKII Network. The graph shows interactions among proteins CREB, HDAC2, and CaMKII. As mentioned in the text, the expression of these proteins may be modulated by miRNAs that are consequent to HIV-1 infection. In this figure, line-colors and various interactions with other genes are red Down-regulation, green Up-regulation, beige Regulation, purple Co-expression, brown Physical Interaction, turquoise dotted Predicted Protein Interaction, and mauve dotted Predicted TFactor Regulation (GenePro SA Biosciences, http://www.sabiosciences.com/).

In related studies, HIV-1 Tat protein was shown to affect histone deacetylases (HDACs) (that are central in transcriptional epigenetics and remodeling of chromatin). Tat protein upregulates HDAC2 in neuronal cells. This may result in inhibition of transcription in neurons and down regulation for Ca2+/calmodulin-dependent protein kinase II (CaMKII) as well as CREB gene expression. These genes are involved in neuronal function and synaptic plasticity. Moreover, as indicated by findings described above, miRNAs may be involved. These pathways may be components of dysfunction that lead to HAD and HAND. Consequently, specific HDAC2 inhibitors may be of use in NeuroAIDS **[6].**The manipulation of miRNA expression may become an important component of the attack on disease. The figure illustrates various gene interactions. It is left as a puzzle for the interested reader to identify the various genes and their functions in the **(Figure 1) [7, 8].**

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