

# HIV-1 TAT-mediated epigenetic downregulation of miR-124 targets MECP2 and promotes microglial activation

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Although the advent of combination antiretroviral therapy has dramatically increased the life expectancy of people living with HIV-1, paradoxically the prevalence of HIV-1-associated neurocognitive disorders (HAND) in people treated with cART, is on the rise. This present study demonstrated HIV-1 TAT-mediated epigenetic downregulation of miR-124 in microglial cells and its possible association with microglial activation. Exposure of microglia to TAT protein decreased the expression of primary miR-124 as well as mature miR-124 in these cells. Also, TAT exposure increased the mRNA and protein expression levels of DNA methylation enzymes, such as DNA methyltransferase (DNMT)-1, DNMT3A, and DNMT3B thereby increased the global DNA methylation levels in microglial cells. Because TAT significantly decreased pri-miR-124 expression levels and, increased both the DNMTs & global DNA methylation levels, the promoter DNA methylation of pri-miR-124 have also increased in TAT exposed cells. Pharmacological and genetic silencing of DNMT1 further validated these findings. Methyl CpG binding protein 2 (MECP2), was identified as a novel 3'-UTR target of miR-124. MECP2 is known to bind to methylated DNA selectively and is a transcriptional repressor, which complexes with several other repressor proteins to silence the promoters of genes. We further confirmed that TAT-mediated downregulation of miR-124 resulted in upregulation of MECP2, which in turn, repressed the expression of miR-124. Besides MECP2, miR-124 also modulated the levels of signal transducer and activator of transcription 3 (STAT3) through targeting 3'-UTR, resulting in microglial activation. Luciferase assays determined the direct binding between miR-124 and 3'-UTRs of both MECP2 and STAT3, respectively. Silencing of MECP2 as well as DNMT1 further upregulated the expression of miR-124 while decreasing microglial activation. Reciprocally, overexpression of miR-124 in microglia blocked TAT-mediated activation of microglia. In summary, our findings demonstrate a novel mechanism of TAT-mediated activation of microglia via downregulation of miR-124, leading ultimately to increased MECP2 and STAT3 activation. Epigenetic modulation of miR-124 could thus be envisioned as a potential therapeutic approach to ameliorate microglial activation and possibly, aid in future development of epigenetic targets as adjunctive therapeutic modalities for treatment of HAND. **Support: DA043138, DA033150, DA035203, DA040397, DA041751, MH106425, DA043164, DA036157**

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