HIV-1 Tat-mediated upregulation of miR-34a activates NF-κB-mediated microglial inflammation via targeting the 3′-UTR of NLRC5

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Although the advent of combination antiretroviral therapy (cART) 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. It has been well documented that despite the effectiveness of cART in suppressing viremia, CNS continues to harbor viral reservoirs with persistence of low-level virus replication. This leads to the presence and persistent accumulation of early viral protein, HIV-1 Tat, that is a well-recognized cytotoxic agent contributing to glial activation. In the current study we demonstrated that exposure of mouse microglia to HIV-1 Tat both dose- and time-dependently upregulated miR-34a expression while concomitantly also downregulating the expression of NLRC5 (a negative regulator of NF-κB signaling). Using bioinformatics analyses, dual-luciferase, and Ago2 immunoprecipitation assays NLRC5 was identified as a novel 3′-UTR target of miR-34a. Transfection of mouse microglia with miR-34a mimic significantly downregulated NLRC5, resulting in nuclear accumulation of NF-κB p65. In contrast, transfection of cells with miR-34a inhibitor notably upregulated NLRC5 levels. Using both gene silencing and pharmacological approaches to block either NLRC5 or NF-κB, our findings demonstrated that HIV-1 Tat-mediated microglial activation involved sequential downregulation of NLRC5 with concomitant activation of NF-κB signaling. Reciprocally, inhibition of miR-34a in microglia blocked HIV-1 Tat-mediated microglial activation. In summary, our findings demonstrate a novel mechanism of HIV-1 Tat-mediated activation of microglia via upregulation of miR-34a, leading ultimately to downregulation of NLRC5 expression with a concomitant upregulation of NF-κB signaling. Modulation of miR-34a 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.