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Extracellular Vesicles and Microrna Crosstalk: Modulators of Neuroinflammation in HIV-1 and Opioid-Associated Neurocognitive Disorders

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HIV-associated neurocognitive disorders (HAND) remain a major challenge, particularly in individuals with opioid abuse, despite the success of combination antiretroviral therapy (cART). The interplay between HIV-1 infection and opioid exposure exacerbates neuroinflammation and neurodegeneration. Emerging evidence suggested that extracellular vesicles (EVs) containing microRNAs (miRNAs) mediated cellular crosstalk between glial cells, neurons, and pericytes, contributing to HAND pathogenesis. Understanding this communication might uncover therapeutic targets to mitigate neuroinflammatory processes in HAND. We hypothesized that HIV-1 Tat protein and opioid exposure (morphine) enhanced the release of miRNA-enriched EVs from glial cells, which modulated neuroinflammation, microglial activation, and blood-brain barrier disruption, contributing to the progression of HAND. Our studies demonstrated that HIV-1 Tat induced the release of miR-9 and miR-7-enriched EVs from astrocytes. MiR-9 targeted PTEN in microglia, promoting their migration, while miR-7 downregulated Neuroligin 2 in neurons, leading to synaptic dysfunction. Morphine exposure induced miR-138-enriched EVs, which activated microglia via the toll-like receptor 7-NFκB signaling pathway. Intranasal administration of a miR-138 inhibitor attenuated microglial activation in morphine-treated mouse models. Additionally, miR-23a-enriched EVs disrupted the blood-brain barrier, facilitating peripheral monocyte entry into the CNS. These findings underscored the critical role of EV-mediated miRNA signaling in HAND, offering promising therapeutic avenues for miRNA-based interventions to reduce neuroinflammation in patients with HIV-1 infection and opioid abuse.

Hyperlink to relevant publication:

1. Yang L, Niu F, Yao H, Liao K, Chen X, Kook Y, Ma R, Hu G, Buch S. Exosomal miR-9 Released from HIV Tat Stimulated Astrocytes Mediates Microglial Migration. J Neuroimmune Pharmacol. 2018;13(3):330-44. Epub 20180301. doi: 10.1007/s11481-018-9779-4. PubMed PMID: 29497921; PMCID: PMC6082702.

2. Yao H, Ma R, Yang L, Hu G, Chen X, Duan M, Kook Y, Niu F, Liao K, Fu M, Hu G, Kolattukudy P, Buch S. MiR-9 promotes microglial activation by targeting MCPIP1. Nat Commun. 2014;5:4386. Epub 20140714. doi: 10.1038/ncomms5386. PubMed PMID: 25019481; PMCID: PMC4104446.

3. Liao K, Niu F, Hu G, Buch S. Morphine-mediated release of astrocyte-derived extracellular vesicle miR-23a induces loss of pericyte coverage at the blood-brain barrier: Implications for neuroinflammation. Front Cell Dev Biol. 2022;10:984375. Epub 20221121. doi: 10.3389/fcell.2022.984375. PubMed PMID: 36478740; PMCID: PMC9720401.

4. Hu G, Niu F, Liao K, Periyasamy P, Sil S, Liu J, Dravid SM, Buch S. HIV-1 Tat-Induced Astrocytic Extracellular Vesicle miR-7 Impairs Synaptic Architecture. J Neuroimmune Pharmacol. 2020;15(3):538-53. Epub 20190810. doi: 10.1007/s11481-019-09869-8. PubMed PMID: 31401755; PMCID: PMC7008083.