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Cannabinoid modulation of P13K/mTOR pathway to decrease NLRP3 activation and viral transcription in HIV-1 infected monocytes.

There are approximately 39 million people living with HIV-1 (PWH) globally, as of 2022. Of these 39 million PWH, 29.8 million are receiving combined antiretroviral therapy (cART), which stops viral progression at many stages of the viral cycle. cART has extended the life of PWH similar to those without HIV-1 infection, but PWH on cART continue to have HIV-associated neurocognitive disorders (HAND) that range from asymptomatic to dementia. HAND is attributed to chronic inflammation in the brain, which can stem from low level viral transcription that occurs in infected cells even with cART treatment, as there are currently no transcription inhibitors. Viral transcripts such as TAR can be released from the infected cell in the form of extracellular vesicles (EVs). These EVs from infected donors carry TAR and other viral products that stimulate proinflammatory pathways on recipient cells. Interestingly, PLWH who use cannabis have been shown to have a decrease in HAND. This can be attributed in part to cannabidiol (CBD), a non-psychoactive component of cannabis. Our lab has previously shown a significant decrease in viral transcript, TAR, with CBD treatment as well as its synthetic analog HU308. In this abstract, we suggest that CBD and HU308 can be used to attenuate the viral TAR through the activation of autophagy, thus leading to a decrease in NLRP3 inflammasome activation in bystander cells (microglia, astrocytes, neurons). We will show data on the mechanisms of cannabinoid-mediated decrease in viral, cytokine expression, and inflammasome activation; validation of the effectiveness of CBD/HU308 reduction of viral products using 3D min-brain cultures; and how cannabinoid treatment alters HIV-1 gene expression in a humanized mouse.

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