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Genetically Modified Human iPSC-Derived Microglia in a Chimeric Mouse Model for Studying CNS HIV-1 Infection and Drug Use

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The central nervous system (CNS) harbors a significant HIV-1 reservoir established early in acute infection, primarily within microglia. HIV-1 induces reprogramming of the microglial transcriptome and 3D genome, promoting up-regulation of genes associated with innate immune activation and inflammation. The mechanisms governing in vivo HIV-1 latency remain elusive due to challenges in identifying transcriptionally silent, latently infected cells. Limited access to human brain tissue and constraints in existing models impede extensive studies on CNS HIV-1 disease. To address these challenges, we developed a chimeric mouse model by xenografting human induced pluripotent stem cells (iPSC)-derived microglia into mouse brains. Genetically modified with a Cre-recombinase-dependent dual fluorescent reporter cassette, our iPSC model enables the permanent marking of cells ever infected with an HIV-1 clone expressing Cre. This molecular tool, termed HIV-1 induced lineage tracing (HILT), allows tracking of infected microglial cells in the mouse brain at a single-cell resolution. HILT serves as a potent investigative tool for understanding the mechanisms governing CNS HIV-1 infection and developing innovative molecular and epigenetic strategies to mitigate the HIV-1 reservoir. Furthermore, our model provides a unique platform to assess the impact of drug interventions on the CNS HIV-1 reservoir, offering valuable insights into the interplay between HIV-1 and drug use.

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