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METH Induced Disruption of Homeostasis and HIV Mediated Neuroinflammation in Microglia Containing Human Cerebral Organoids

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Drugs of abuse such as methamphetamine (METH) can aggravate symptoms of HIV-associated neurocognitive disorders. We developed human iPSC-derived cerebral organoids containing microglia to study impact of HIV-infection and METH by single-cell RNA sequencing (scRNA-seq). Organoids were developed by coculturing neural progenitors (NPCs) with tdTomato-tagged CD34+ microglia precursors. On day 25, organoids were pretreated with water or METH (100 nM, 72 hours). To study HIV mediated effects, the organoids were infected with macrophage R5-tropic NL-AD8 HIV-1. scRNA-seq enabled assessing gene expression changes along with studying METH and HIV-induced perturbations to neuron-astrocyte-microglia interactions using Nichenet ; a computation ligand-receptor analysis tool.

METH altered cytoskeletal, ion transport pathways in astrocytes, dopamine transporter, mitochondrial stress, and lipid metabolism genes in neuron subtypes (excitatory; dopaminergic and glutamatergic neurons). METH modulated ligand-receptor interactions between neurons-astrocytes-microglia and showed amyloid proteins, CX3CL1, S100 family proteins driving inflammatory chemokine and cytokine genes (e.g., CCL3, HLA-DR, IL1β) in microglia. HIV-1 productively infected and spread within the tdTomato+ microglia population. HIV-infected microglia upregulated type I/II interferon response genes alongside reduced homeostatic genes. Under steady-state conditions, microglia-derived ligands (e.g., BDNF, WNT, TGFβ1) promoted neuronal and astrocytic differentiation. In contrast, HIV infected microglia relayed interferon signals upregulating MHC antigen-presentation genes in non-glial cells.

Our model generates cerebral organoids with differentiated microglia to investigate the effects of METH and HIV. METH enhanced neuroinflammation, astrogliosis, and neuronal excitability. Conversely, HIV infection shifted microglia to a reactive state, activating antigen-presentation pathways in non-glial cells, priming them toward a neurodegenerative state that could be exacerbated by METH.