Name: Xu Wang
Email: xuwang@temple.edu
PI Name: Wenzhe Ho
PI Email: wenzheho@temple.edu

TLR3 Activation of Human iPSC-derived Brain Organoids Induces Antiviral Factors

Qian-Hao Xiao, Xu Wang, Priyanka Sarkar, Li Song, and Wen-Zhe Ho

Department of Pathology and Laboratory Medicine, Center for Substance Abuse Research, Temple University Lewis Katz School of Medicine

Human pluripotent stem cell (iPSC)-derived cerebral organoids (COs) have been increasingly used as a brain model for studying various neurotropic viruses, including HIV. Therefore, it is important to determine whether the COs are susceptible to HIV infection and possess innate and functional antiviral components such as the toll-like receptors (TLRs), interferon (IFN), and IFN-stimulated genes (ISGs). We report that human iPSC-derived COs contain the major brain cell types (neurons, astrocytes, microglia, and oligodendrocytes). Importantly, the COs could be productively infected by live HIV, and IFN inhibited HIV infection. We also showed that the COs express TLR3 which could be activated by poly I: C, resulting in the induction of IFNs, ISGs (MX1, MX2, GBP5, SAMHD1, Viperin, and ISG56), the CC chemokines (MIP-1α, MIP-1β and RANTEs) and the chemokines (MCP-1 and TNF-α). This TLR3 activation-mediated induction of the inflammatory factors could be blocked by the pretreatment of the COs with the TLR3/dsRNA complex inhibitor or the IFN receptor-neutralizing antibody. These observations provide the first scientific evidence that human iPSC-derived COs are a suitable in vitro model for studying innate antiviral immunity in the brain. Further studies are necessary to determine whether TLR3 activation can inhibit HIV infection of the brain organoids.