SARS-COV-2 INDUCES DOPAMINERGIC NEURON LOSS IN MIDBRAIN ORGANOIDS

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Abstract. Objectives: COVID-19 presents numerous symptoms mostly associated with the respiratory tract. However, recent evidence showed that the SARS-CoV-2 virus affects the nervous system. We evaluated the effect of the infection in midbrain organoids to determine if cells and pathways related to the onset of Parkinson's disease (PD) are affected.
Methods: The effect of the virus after short- and long-term cultures (4 days, and 1 month) post-infection was analyzed. Features measured included the degree of dopaminergic differentiation (TH), neurite fragmentation, and the level of activated astrocytes (GFAP and S100beta). Bulk RNAseq was performed to determine the effects of the infection on gene expression.
Results: After infection with SARS-CoV-2, the levels of dopaminergic neurons were significantly reduced in both short and long-term culture. Moreover, neurite fragmentation of TH positive neurons in infected organoids significantly increased respective to controls in long-term cultures. Within the same infected organoid TH/SARS-CoV-2 double positive neurons presented an altered morphology and high degree of neurite fragmentation compared to uninfected TH positive neurons. Activation of astrocytes was significantly reduced after infection in the short-term culture. While the levels of S100beta recovered over time, they still remained lower in infected organoids. In both short- and long-term culture, SARS-CoV-2 colocalized more with certain types of cells showing a marked preference for GFAP positive and TH positive cells when normalized to their respective abundance in the organoid. Gene expression analysis revealed a disruption in gene pathways related to vesicle transport, endosomal and autophagy pathways following infection with SARS-CoV-2.
Conclusions: Infection of midbrain organoids with SARS-CoV-2 induced a clear neurodegenerative process of TH positive neurons, while disrupting main pathways known to be involved in Parkinson's disease.