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TLR3 Elicits Constitutive HSV-1 Resistance in Human Cortical Neurons and Inducible Resistance in Trigeminal Neurons

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Background: HSV-1 infections of the central nervous system are associated with life-threatening Herpes Simplex Encephalitis (HSE). Inborn errors in Toll like receptor 3 (TLR3) increase susceptibility to HSE. This study investigates the role of TLR3 in restricting HSV-1 infection using human iPSC-derived neuronal culture models.

Methods: We examined the mechanisms by which TLR3 protects human neurons from HSV-1 infection. Induced pluripotent stem cell derived trigeminal and cortical neurons obtained from TLR3 and STAT-1 deficient patients, and healthy controls, were infected with recombinant strains of HSV-1. Viral entry, retrograde axonal transport, and gene expression were assessed.

Results: Our studies indicate that control cortical neurons exhibit TLR3-dependent constitutive resistance to HSV-1 that manifested from blockades in viral entry and retrograde axonal transport. STAT-1 was dispensable for constitutive resistance to HSV-1. TLR3-deficient cortical neurons revealed that HSV-1 entry occurred by transient endocytosis followed by bafilomycin-sensitive membrane fusion to release capsids into the cytosol. In contrast to cortical neurons, TLR3-dependent resistance in trigeminal neurons required advanced stimulation to establish an antiviral state prior to HSV-1 challenge.

Conclusions: Human iPSC-derived cortical and trigeminal neurons accurately model the selective neurotropic properties of HSV-1 exhibited in vivo. Absence of functional TLR3 results in cortical neuron infection in culture that is consistent with the presentation of HSE in TLR3-deficient patients. We propose that the rapid and constitutive TLR3-based resistance to HSV-1 exhibited in iPSC-derived cortical neurons underlies HSV-1's selective neurotropism for the human peripheral nervous system.