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292. Neurotoxic Properties of Human Endogenous Retrovirus-K Envelope Protein and Detection in Cerebrospinal Fluid of Patients with Amyotrophic Lateral Sclerosis

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Expression of human endogenous retrovirus K (HERV-K) subtype HML-2 envelope (Env) in human neuronal cultures and in transgenic mice results in neurotoxicity and neurodegeneration. Mice expressing HML-2 Env display behavioral and neuromuscular characteristics resembling amyotrophic lateral sclerosis (ALS). Addressing the question of extracellular neurotoxicity of HML-2 Env, we found that HML-2 Env protein could be found in the cerebrospinal fluid (CSF) patients with sporadic ALS. Using recombinant HML-2 envelope protein, we observed a dose and time-dependent neurotoxicity using assays for neuronal cell death, retraction of neurites and neuronal electrical activity using microarray electrodes. Injection of the Env protein into the brains of mice also resulted in neuronal cell deaths. The neurotoxic properties of the Env and the CSF could be rescued with the anti-Env antibody. Using a panel of compounds to screen for their ability to block Env-induced neurotoxicity, we found that GSK-3 β antagonists, retinoic acid receptor agonists and select flavonoids were protective. In conclusion, HERV-K (HML-2) Env is released extracellularly in ALS and causes neurotoxicity via a novel mechanism. Present results pave the way for new treatment strategies in sporadic ALS.