MOTOR NEURON DISEASE

Human endogenous retrovirus-K activation is implicated in amyotrophic lateral sclerosis

Expression of human endogenous retrovirus-K (HERV-K) genes could be a risk factor for amyotrophic lateral sclerosis (ALS), according to new research from Avindra Nath and colleagues, published in *Science Translational Medicine*. HERVs are retroviral elements in the human genome that are normally inactive owing to a build-up of nonsense mutations, but evidence is accumulating that parts of the viral genome can be reactivated under pathological conditions.

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“In 2006, I saw a patient who had HIV infection and developed an ALS-like syndrome, and when we treated him with antiretroviral drugs his HIV and the ALS both got better,” explains Nath.

“Some investigators had found evidence of reverse transcriptase in the blood of patients with ALS, but were unable to find exogenous retroviruses—I reasoned that the reverse transcriptase might arise from an endogenous retrovirus.”

Nath’s team examined postmortem brain tissue from 11 patients with ALS, and 16 controls without evidence of neurological disease. They discovered neuron-specific upregulation of HERV-K genes in the ALS patient samples. “The expression of HERV-K was specific to ALS, and we did not find it in other neurological diseases such as Parkinson disease or Alzheimer disease,” says Nath.

The researchers used the CRISPR–Cas9 gene-editing system to activate HERV-K in cultured human neurons. This intervention led to neurite retraction and a reduction in neuronal numbers, indicating a neurotoxic effect. Moreover, mice that were transgenic for the HERV-K envelope protein (*env*) gene showed loss of upper

and lower motor neurons and exhibited progressive motor dysfunction, thereby mimicking the human ALS phenotype.

Intriguingly, TAR DNA-binding protein 43 (TDP-43), which has long been implicated in ALS, was found to activate HERV-K. Nath and colleagues propose, therefore, that TDP-43 could exacerbate neurodegeneration by modulating HERV-K gene expression.

The investigators plan to further explore the mechanisms via which HERV-K causes neuronal injury, and to assess whether ALS is associated with specific variants in the viral genome. They also aim to develop antiviral drugs that target HERV-K, in the hope of treating or averting at least a subset of cases of ALS.

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