PARSING THE HERV-DISEASE LINK

Current research suggests that viral hitchhikers in human DNA may play roles in cancer, inflammation, and neurodegenerative disorders. The mechanisms that underpin these connections between human endogenous retroviruses (HERVs) and disease are just beginning to emerge. Transcription of viral RNA can signal the presence of foreign DNA in cells, triggering defensive immune reactions. Scientists have also proposed that synthesis of the HERV envelope protein—which once enclosed the viral capsid of its retroviral ancestors—exerts pathogenic effects. In other contexts, such as certain cancers, researchers think that the disease state activates HERVs, rather than the other way around.

versity in Denmark, “but we haven’t yet come to the point of showing that it’s actually causative.” Weiss is particularly skeptical of the idea of a cause-effect relationship. “I would say that maybe it’s the autoimmune activation that’s activating the virus, and not the virus that’s causing the autoimmune disease,” he says, though he adds that “the virus in turn may exacerbate the disease.”

The idea that HERVs might play a role in MS was supported by the detection of a HERV-K virus in pathological tissue in ALS, as shown by Nath and others. But a lot more work is needed to establish causation, Nath cautions. Understanding the mechanisms at play “is key not only for establishing its role in ALS,” he says, “but also for developing targeted therapy.”

Mechanistic insights into HERVs

In figuring out the possible mechanisms underlying HERV-disease connections, Nath says he thinks one of the most pressing questions is whether they’re capable of forming infectious retroviral particles. An infectious retrovirus would help explain the progressive nature of ALS symptoms, from motor extremities to the central nervous system. “If it’s not HERV-K being transmitted [from cell to cell], then there’s got to be some other factor that’s being transmitted to activate it,” he says.

So far, there’s no evidence for this type of viral behavior in ALS or in MS. Rather, researchers have focused on HERV envelope proteins, because the homologous proteins in HIV are known to have neurotoxic effects. In 2015, Nath’s team created a transgenic mouse line in which the animals produced the envelope protein of HERV-K. The mice subsequently developed ALS-like symptoms, including spasticity, weakness, and muscle atrophy.8

How this occurred is a mystery. Nath hypothesizes that the HERV-K envelope protein can cause dysfunction in the nucleolus, the membraneless structure within the nucleus that hosts ribosome biogenesis. “And [this] messes up the entire protein synthesis machinery in the cell itself . . . that eventually leads to toxicity,” Nath speculates. (See infographic on page 27.)