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Transcription of host noncoding DNA elements signals viral intrusion but is hijacked by gammaherpesvirus

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Mammalian DNA, including the human genome, contains about 1 million SINEs (short interspersed nuclear elements), noncoding mobile genetic elements that make up about 10% of the total genome. SINEs are normally silent, though in some cases viral infection can promote their transcription into RNA. A study published on November 19th in *PLOS Pathogens* reports that SINE transcription following gammaherpesvirus infection has two very different consequences: on one hand, it activates a non-specific immune response defending the attacked host; on the other, it supports the propagation of the viral intruder.

Britt Glaunsinger and her colleagues from the University of California in Berkeley, are interested in potential roles for SINE RNA transcripts during viral infection. They study a mouse gammaherpesvirus called MHV68, a relative of several human cancer-promoting viruses that include Kaposi's sarcoma herpesvirus. After infection of mouse cells with MHV68, the researchers observed rapidly induced SINE transcription. This activation of SINE expression is a biphasic response, with an initial phase arising as a result of either viral attachment or entry in to cells, and a second wave that requires progression of the infection past entry and expression of immediate early and early viral genes.

The researchers show that the resulting host-derived SINE RNAs are robust activators of a key signaling molecule in the non-specific (or innate) immune response called the IKKβ kinase. Although the main

pathway controlled by activation of the IKKβ kinase (called the NF-κB signaling pathway) is normally detrimental to viral replication, MHV68 co-opts IKKβ kinase activation to boost its own viral transcription activator, using a viral protein called RTA, thereby enhancing viral gene expression and virus production.

"Collectively", the researchers conclude, "we reveal the first example of a role for SINE RNAs in the host-pathogen interaction and identify them as key immune signaling molecules early during infection. Though SINE RNAs activate the innate immune response, MHV68 has co-opted SINE-mediated innate immune activation to enhance the viral lifecycle." Noting that SINE RNAs are also activated upon infection with several other human and mouse viruses, they suggest that "whether in other systems SINE RNAs serve as anti-viral signaling components, as well as if and how they are co-opted by the diversity of viral and non-viral pathogens remain exciting avenues for future research".

More information: Karijolich J, Abernathy E, Glaunsinger BA (2015) Infection-Induced Retrotransposon-Derived Noncoding RNAs Enhance Herpesviral Gene Expression via the NF-κB Pathway. *PLoS Pathog* 11(11): e1005260. DOI: 10.1371/journal.ppat.1005260