Viruses are sneakier than we thought

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Viruses are molecular marauders, plundering cells for the resources they need to multiply. Of central importance for viruses is the ability to commandeer cellular gene expression machinery. Several human herpesviruses put the breaks on normal cellular gene expression to divert the associated enzymes and resources towards their own viral genes. Kaposi's sarcoma-associated herpesvirus (KSHV), which causes several AIDS-associated cancers, has now been shown to do this in an unexpected way, using a process that is normally protective, called polyadenylation.

Cells decode genetic information in a process called transcription, during which the DNA is unzipped and read by enzymes. The product of this process is a piece of messenger RNA, which then emerges from the cell's nucleus (the section of the cell containing DNA) into the cell cytoplasm (the main cellular compartment) and is translated there into the protein corresponding to the DNA's message. Polyadenylation is the process whereby Poly(A) tails are added to messenger RNAs (mRNAs) in the nucleus before they are transported into the cytoplasm. These tails serve several purposes, including protecting the messages from degradation and enhancing the translation to protein. The effects of KSHV on cells was known to be caused by one of it's proteins - called SOX - but how the protein influences host cells transcription process has previously been unclear.

In a study published in this week's issue of *PLoS Biology*, researchers at UC Berkeley found that the presence of SOX led to an unexpected increase in the length of cellular mRNA poly(A) tails. Mutant KSHV

viruses that can't make SOX protein are unable to block cellular gene expression. SOX mutants fail to increase poly(A) tail length. This suggests that the virus uses a process normally involved in enhancement of gene expression to instead inhibit gene expression.

"We suspect that by aberrantly lengthening the poly(A) tails, the virus is sending the cell a signal that something is wrong with its messages and as a consequence they are held back in the nucleus," says Dr. Britt Glaunsinger, one of the researchers involved in this study. Indeed, similar results have been observed in yeast when mRNAs are improperly made or cannot traffic appropriately.

The researchers showed that SOX has more than one trick to play on cells - as well as preventing the export of new cellular mRNAs, SOX targets the existing messages that were made in a cell before the KSHV could turn on its SOX protein. mRNA poly(A) tails are normally bound by the cell's poly(A) binding protein (PABP), which helps guard them from degradation and facilitates their translation into protein. During KSHV infection, however, SOX removes PABP from the cytoplasm and causes it to instead accumulate in the nucleus. PABP re-localization correlates with destruction of cytoplasmic mRNA in SOX-expressing cells, perhaps because these transcripts have been 'stripped' of an important protector. "I find it fascinating that this single viral protein targets a key mRNA stabilizing element from two different angles to block cellular gene expression," says Glaunsinger. "It's yet another example of how viruses have evolved to interface so exquisitely with their hosts."

More information: Lee YJ, Glaunsinger BA (2009) Aberrant Herpesvirus-Induced Polyadenylation Correlates With Cellular Messenger RNA Destruction. PLoS Biol 7(5):e1000107. doi:10.1371/journal.pbio.1000107, biology.plosjournals.org/perls … journal.pbio.1000107

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