Herpes virus hijackers

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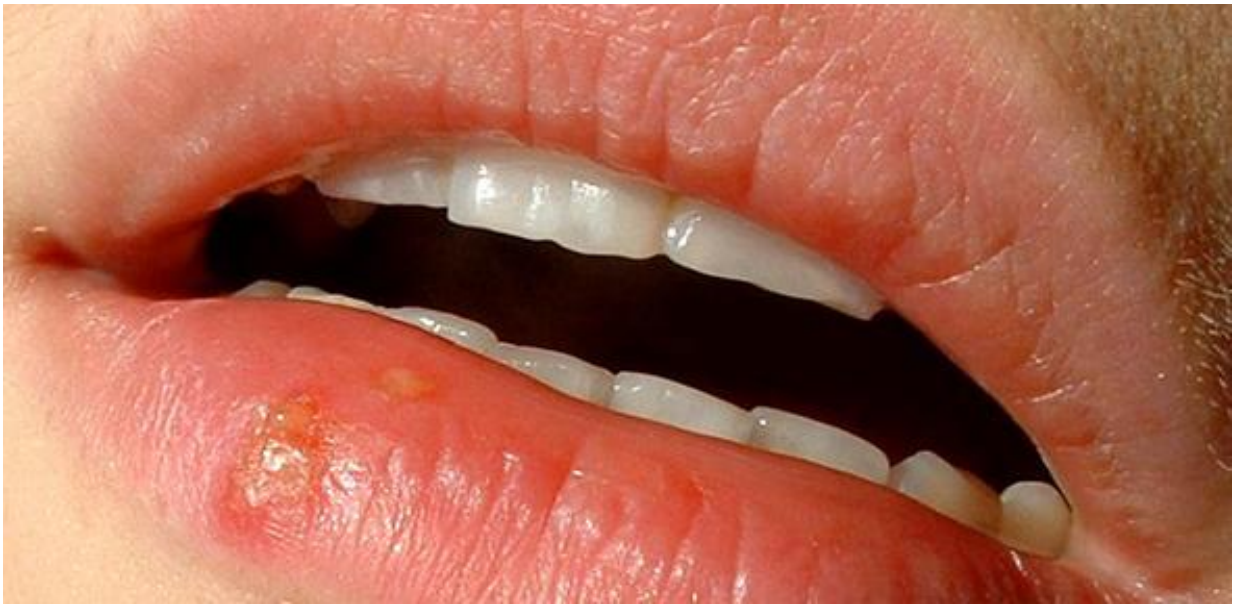

Cold sore. Credit: Metju12

The virus responsible for the common cold sore hijacks the machinery within our cells, causing them to break down and help shield the virus from our immune system, researchers from the University of Cambridge and colleagues in Germany have discovered.

The common cold sore, caused by herpes simplex virus 1 (HSV-1), is relatively harmless to most people, but for others it can cause life-threatening disease. In intensive care units, for example, the virus commonly leads to severe lung infections. Even in healthy people, in rare

cases it can spontaneously cause inflammation of the brain, which can lead to irreversible brain damage.

The genetic material of the virus consists of DNA, like in humans. As soon as HSV-1 has penetrated human cells, it smuggles its DNA into the cell nucleus, where the molecular machinery is located that is used to read the genetic information contained in the DNA and to transcribe it into RNA molecules. This RNA then determines which proteins are produced by the cell.

In the cell nucleus, the virus takes full control of this machinery within a few hours of infection. It uses it to produce its own proteins and produce new virus particles on a massive scale. Formation of the cellular proteins soon becomes almost an irrelevance. In the end, the host cell dies off and thousands of new viruses are released that again infect other cells.

Professor Lars Dölken from the Department of Medicine at the University of Cambridge and the Institut für Virologie, Würzburg, Germany, together with the bioinformatics team at LMU Munich, led by Professor Caroline Friedel have looked in greater detail at the process of infection. Today in the journal Nature Communications, they report using cell cultures to see how HSV-1 infects human connective tissue cells (fibroblasts) and examine what happens with all the RNA molecules in the cells during the process. The researchers used fibroblasts as this enabled them to look at what the virus does with the cell rather than how the innate immune system responds to the virus.

Just three to four hours after the virus enters the cells it does something quite unexpected. Usually, the process of transcribing DNA into RNA stops when it reaches the end of the genes being transcribed. But in this case, the human cell DNA continued to be transcribed for tens-of-thousands of nucleotides – the A, C, G and Ts of DNA – and often across several neighboring genes. This creates masses of unusable RNA

products that can no longer properly translate into proteins.

"It's like someone transcribing a short story, but instead of stopping at 'The End', they carry on and transcribe all the copyright and publication details and ISBN numbers at the beginning and end of the book," explains Professor Dölken. "This produces lots of meaningless, confusing and useless information."

Interestingly, the viral DNA is accurately transcribed throughout infection. By interfering with the transcription processes in our own cellular genes, the virus is acting to benefit itself – it causes the cell to shut itself off, preventing the immune system from attacking the virus. It also increases the synthesis of viral proteins and thus aids the production of new virus particles.

This newly discovered mechanism can give the impression that the virus also activates a large number of genes in the cell, but this is actually not the case and may have led previous studies to incorrectly interpret experimental data. According to the findings, hundreds of cellular genes seemingly activated by the viruses are not translated into proteins at all.

"Unlike previous studies which only studied single genes, we also found no indication that the virus generally impedes the processing of RNA in the cell nucleus, known as splicing," says Dölken. "Instead, it causes unusual splicing events, many of which have never before been observed."

The research team from Cambridge, Würzburg and Munich set a milestone in methodology with this work: With a single experimental approach it is possible to record all the changes that occur when transcribing and processing RNA as well as their impact on protein production.

More information: "Widespread disruption of host transcription termination in HSV-1 infection." *Nature Communications* 6, Article number: 7126 DOI: 10.1038/ncomms8126

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