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HCMV researchers utilize novel techniques to show preferential repair of the viral genome

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A new study about Human Cytomegalovirus (HCMV), a leading cause of birth defects, reveals how the virus co-opts cells' abilities to repair themselves. In the paper published on November 29 in the Open Access journal *PLOS Pathogens*, O'Dowd et al. describe their utilization of a novel technique for the simultaneous evaluation of both the viral and host genomes in an infected cell.

Approximately 1% of babies born annually in the United States – about 40,000 – are infected with HCMV. Among them, some 4,000 are born with such conditions as loss of vision and hearing, cerebral palsy, mental retardation and microcephaly (small head size). Another 4,000 develop problems, such as progressive hearing loss, during childhood.

When HCMV infects a cell, it sets up centers inside the nucleus to replicate itself. The proteins that repair cellular damage – including one known as the "guardian of the genome" – become trapped in these centers.

"If we could figure out how the virus interacted with these cellular proteins to keep them from repairing the cellular DNA, then we could target those viral proteins specifically," says the study's senior corresponding author, associate professor of biological sciences at University of Idaho, Lee Fortunato, "Then the cellular DNA would be fine."

Fortunato hypothesized that the virus was taking over the cell's repair mechanisms and using them for itself, leaving the cells unable to fix themselves if they incurred damage or kill themselves to stop the spread of the virus. To confirm her hypothesis, Fortunato exposed infected cells to ultraviolet (UV) irradiation, which equally damaged the cellular and viral DNA. She then used an agarose gel assay in a novel way to understand what happened as the cells' repair machinery tried to operate.

In these assays, damaged DNA runs as a long smear when passing through the gel due to the presence of small fragments. As repair occurs, these small fragments come back together to form larger strands of DNA that stay near the top of the gel. But unlike typical studies that examine total DNA, both cellular and viral, in an infected cell together, Fortunato's test tracked viral and cellular DNA repair separately in each sample.

The test showed the cellular machinery repaired the viral DNA far more quickly and efficiently than cellular DNA. In fact, a day after being exposed to UV rays, viral DNA had been repaired and was back to normal. But the cellular DNA was still damaged.

"We've shown that, at least with UV radiation to an infected cell, the viral genome is preferentially repaired, but the cellular genome is not repaired," Fortunato said. "That could have ramifications for an infected fetus."

Fortunato's work could lead to an antiviral therapy and new understanding of the ways infections caused by various disease-causing organisms defeat cells' defenses.

More information: O'Dowd JM, Zavala AG, Brown CJ, Mori T, Fortunato EA (2012) HCMV-Infected Cells Maintain Efficient Nucleotide Excision Repair of the Viral Genome while Abrogating

Repair of the Host Genome. PLoS Pathog 8(11): e1003038.
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