Cytomegalovirus hijacks human enzyme for replication

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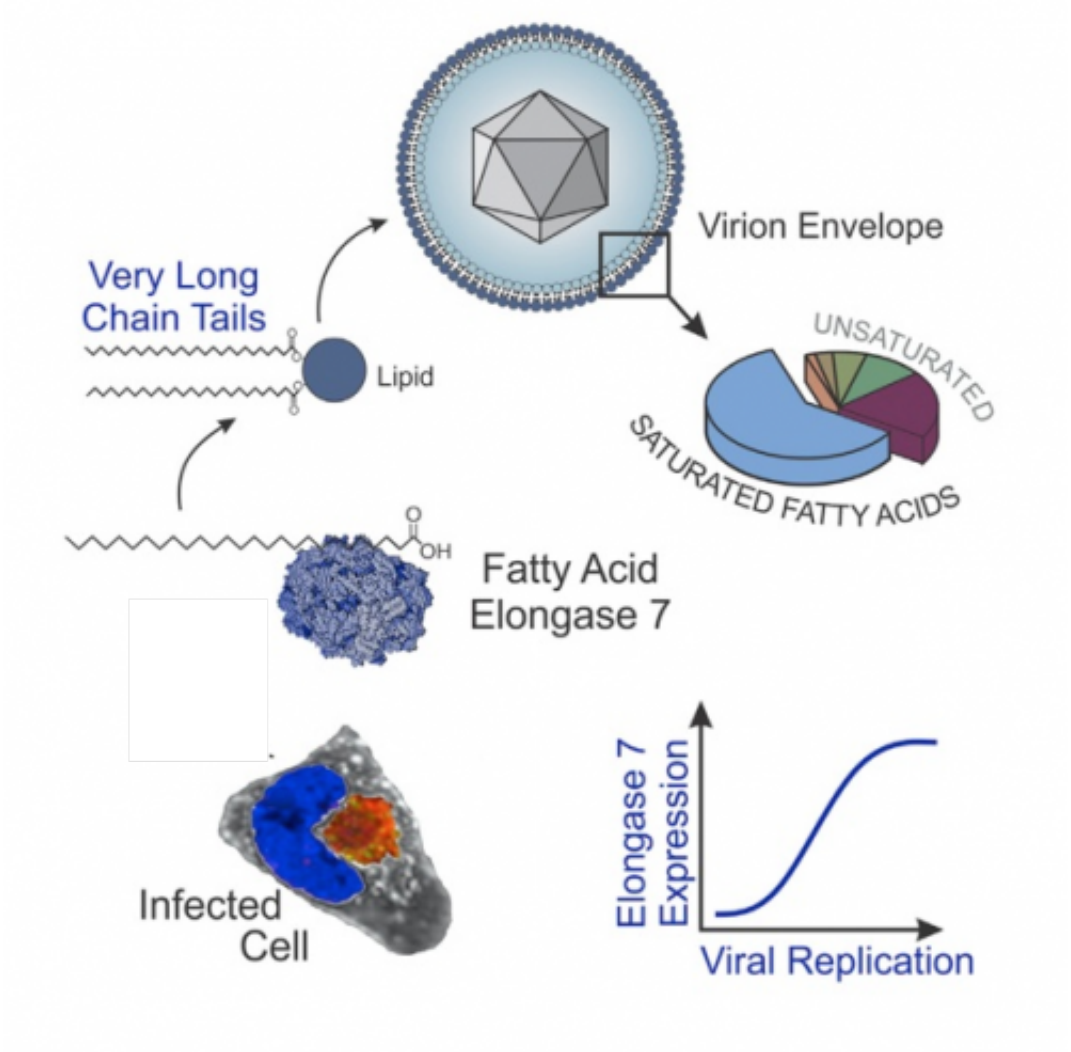

Abstract representation of virus inducing enzyme to produce lipid envelope.
Credit: Rabinowitz lab

More than 60 percent of the world's population is infected with a type of herpes virus called human cytomegalovirus. The virus replicates by commandeering the host cell's metabolism but the details of this maneuver are unclear.

Researchers at Princeton have discovered that cytomegalovirus manipulates a process called fatty acid elongation, which makes the very-long-chain fatty acids necessary for virus replication. Published in the journal *Cell Reports* on March 3, the research team identified a specific human enzyme—elongase enzyme 7—that the virus induces to turn on fatty acid elongation.

"Elongase 7 was just screaming, 'I'm important, study me,'" said John Purdy, a post-doctoral researcher in the Rabinowitz lab and lead author on the study.

He found that once a cell was infected by cytomegalovirus, the level of elongase 7 RNA increased over 150-fold. Purdy then performed a genetic knockdown experiment to silence elongase 7 and established that in its absence the virus was unable to efficiently replicate.

"Elongases are a family of seven related proteins. The particular importance of elongase 7 for cytomegalovirus replication was a pleasant surprise, and enhances its appeal as a drug target," said Joshua Rabinowitz, a professor of chemistry at Princeton and co-author on the paper.

Activation of the elongase enzyme led to an increase in very-long-chain fatty acids, which are used by the virus to build its viral envelope and replicate. The researchers fed infected cells heavy isotope labeled C13-glucose, a molecule that is metabolized by the cell to form substrates for fatty acid elongation. The heavy isotope carbon-13 atoms were incorporated into new products that were detected and identified

by their mass using a specialized mass spectrometry method. This powerful technique provided insight into the amount of fatty acids produced and how they are constructed.

Cytomegalovirus infection mostly threatens populations with compromised immune systems and developing fetuses, and is the leading cause of hearing loss in children. Current treatments target the DNA replication step of the virus and are not very effective. These findings have advanced the understanding of the virus's operations and identified fatty acid elongation as a key process that warrants further study.

More information: Purdy, J. G.; Shenk, T.; Rabinowitz, J. D. "Fatty Acid Elongase 7 Catalyzes the Lipidome Remodeling Essential for Human Cytomegalovirus Replication." *Cell Reports*, 2015, 10, 1375.

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