Cytomegalovirus particles as seen through an electron microscope: While some of the protein capsules are empty, others contain tightly packaged DNA, visible as dark structures. The diameter of a human hair would cover a line of about 600 virus particles. Credit: Farah Bughio, Felicia Goodrum
By studying how a virus that infects most people at some point in their lives packages its genetic material during infection, an international collaboration of researchers has made discoveries that help scientists better understand virus-host interactions and may open new avenues for therapies.

An international collaboration of researchers including Felicia Goodrum of the University of Arizona's immunobiology department has studied how a human herpes virus carried by the majority of the population packages its genetic information during infection.

The discoveries improve the chances of developing more targeted therapies in place of existing drugs, which do not always work or come with side effects.

Experts estimate that 60 to 90 percent of the world's population carry the human cytomegalovirus, or CMV, which is one of the eight herpes viruses that infect humans.

In healthy individuals, the virus lies dormant and does not cause overt disease. However, it poses a significant risk when contracted by unborn children – whose immune system has not matured yet – and individuals with compromised immune function.

CMV is the leading cause of birth defects resulting from any infectious agent. It affects one in 150 births in the US and most commonly results in hearing loss, but can also cause cognitive or physical anomalies and cerebral palsy. Once infected, the virus stays in the body for life and flares up only when the immune system is suppressed, for example in AIDS patients, transplant patients and cancer patients undergoing intensive chemotherapy.

For the study, published in the scientific journal Proceedings of the
National Academy of Sciences (PNAS), Goodrum teamed up with collaborators in Germany and Israel.

The researchers investigated how a fundamental aspect of the human cell regulates the virus: the mechanism by which genetic information is packaged and stored. Understanding how the viral DNA behaves in the human host cells during dormancy and reactivation of the virus provides the basis for the development of drugs that could prevent the virus from "waking up" and causing disease.

"The human immune system is very sophisticated, and the way this virus has managed to stealthily integrate into our biology to ensure its own survival is no small feat," said Goodrum, also a member of the UA's BIO5 Institute.

"CMV is a master of human cell biology. From transcribing DNA into blueprints for proteins to the manufacturing of those proteins, from cell division to cellular metabolism, there is not a process this virus has not tweaked," Goodrum also said.
Virus factory: The top image shows uninfected, normal human cells with cell nuclei in blue and the cellular protein processing apparatus in red. In the infected cells (bottom image), the virus has produced proteins (green) that take over and reorganize the cellular processing apparatus into a virus factory. Credit: Farah Bughio, Felicia Goodrum
That mastery, she explained, is the reason the virus is so elusive to vaccine, and there currently is no way to eradicate it. Goodrum noted that with other herpes viruses, like Epstein-Barr or Chicken pox, the infection is obvious. But that is not the case with CMV.

"From the perspective of a virus, that is the pinnacle of mastery – to infect without ever making its presence known," Goodrum said.

"To develop more effective antiviral strategies, we must understand the biology of the virus infection and how the virus manages to persist for our lifetimes," she said. "We are trying to understand how our cellular mechanisms are being used by this virus and discover targets for drugs to control it."

Each human cell contains a thread of DNA that is about 6 feet long, stowed away in its nucleus and tightly packaged by proteins called histones. One such package of genetic material is called a chromosome.

"You can imagine histones as a spool, and the thread is DNA that wraps around the spool," Goodrum said. "This accomplishes two important objectives: first, it condenses DNA so that it can be packed into the cell nucleus and second, it provides the cell with a mechanism to regulate the activity of the genes encoded on that DNA."

The association between histones and DNA is very dynamic and acts as a key mechanism used by cells to control which genes are expressed and which are not, Goodrum explained.

For example, when DNA is wound tightly around histones, it is not accessible to enzymes specializing in making copies of genes in a process called transcription, which subsequently serve as blueprints to manufacture proteins.
"When a virus like CMV infects our cells, its DNA is packaged by histones just as if it were the cell's own DNA," Goodrum said.

"The question is, how does this happen, and does the virus have any choice in the matter? Our work maps the deposition of histones across the viral DNA chromosome and shows that the virus encodes a mechanism to reorganize these histones to favor the expression of genes from the viral chromosome."

Michael Nevels of the Institute for Medical Microbiology and Hygiene at the University of Regensburg, Germany, said: "Now that we have determined the positions of the nucleosomes, we can study how transcription is regulated, and from that others can start developing therapies."

For example, if researchers can identify molecules that play key roles in the process, they can design new drugs that target those molecules.

"Since we can't eliminate the virus, the goal is to keep it in check," said Nevels, led the study together with Eran Segal and Einat Zalckvar of the Weizmann Institute of Science in Rehovot, Israel.

"The idea is to target the virus on the level of its DNA structure and to reduce the gene activity back to the dormancy levels," Nevels said.

One such molecular target identified in this study is a viral protein called IE1. Because it regulates the packaging and unpacking of the viral DNA, it could potentially be a target for new therapies.

Cautioning that many more steps will be necessary before this could be achieved, Nevels said that "if we could inhibit IE1, the virus genome would be packed more tightly with histones, which leaves less DNA accessible and prevents genes from becoming active."
Another strategy takes the opposite direction by deliberately awaking the virus from its dormant state so it becomes vulnerable to antiviral drugs. This could be an option for patients about to undergo an organ transplantation, which requires immune-suppressing drugs to prevent the new organ from being rejected. Suppressing the immune system allows the virus to reactivate.

"There are antivirals that target the active, replicating virus but can't target latent virus because in that state, it's really just a piece of DNA in the cell nucleus," Goodrum said. "Before those patients enter a immunosuppressed state, you would target the viral reservoirs and force the virus out of latency."

More information: [www.pnas.org/content/early/2013/07/30/1305548110.abstract](http://www.pnas.org/content/early/2013/07/30/1305548110.abstract)

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