A Viral Cloaking Device: Biologists show how Human Cytomegalovirus hides from the immune system

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(PhysOrg.com) -- Viruses achieve their definition of success when they can thrive without killing their host. Now, biologists Pamela Bjorkman and Zhiru Yang of the California Institute of Technology have uncovered how one such virus, prevalent in humans, evolved over time to hide from the immune system.

The human immune system and the viruses hosted by our bodies are in a continual dance for survival--viruses ever seek new ways to evade detection, and our immune system devises new methods to hunt them down. Human Cytomegalovirus (HCMV), says Bjorkman, Caltech's Delbrück Professor of Biology and a Howard Hughes Medical Institute (HHMI) Investigator, "is the definition of a successful virus--it thrives but it doesn't affect the host."

HCMV is carried by eight in 10 people. Although it generally harms only those who are immunocompromised, it has also been linked with brain tumors like the one for which Ted Kennedy recently had surgery. Understanding how HCMV survives may help in the development of a vaccine, as well as in the fight against other viruses with similar evasive tactics.

"We are interested in mechanisms taken by viruses to escape our immune system," says Caltech biology postdoc and HHMI associate Zhiru Yang. She and Bjorkman published their findings on HCMV

survival mechanisms in the July 15 edition of *Proceedings of the National Academy of Sciences*. They describe the underpinnings of a viral cloaking device, partly made of stolen goods from healthy cells, that helps HCMV to move undetected through the body.

For 20 years, Bjorkman's lab has been dedicated to understanding class 1 major histocompatibility complex (MHC) proteins and the immune response, most recently related to AIDS research. MHC proteins carry peptides, small pieces that are chopped up from the cell's internal proteins, to the cell's surface. If a cell has been infected, MHC presents viral peptides to signal T cells to kill it. So some viruses evolved to evade T cells by keeping MHC from reaching the cell surface. In turn, the immune system recruited other hunters to search for cells that don't show MHC proteins.

Sometime along its treacherous evolutionary path, HCMV stole a class 1 MHC molecule from its host and modified it for supreme stealth. "This is a decoy," Bjorkman says. She and Yang analyzed the structure of the mimic, called UL18, to compare how similar it is to the real thing. They found that despite a mere 23 percent match in genetic sequences, UL18 looks almost exactly the same as a true class 1 MHC.

The same immune cells that search for missing MHC proteins are designed to bind to them when they find them, thereby inhibiting an immune response. Yang and Bjorkman found that UL18 happens to bind 1,000 times tighter to these inhibitory receptors than real MHC molecules do. "This is exactly what the virus wants--to avoid being recognized by T cells, but to engage inhibitory receptors to turn off immune cells," Yang notes. "Only a small number of UL18 molecules are required to have the same inhibitory effect as a large number of MHC class I molecules."

"What I find astounding is that the virus stole this gene and kept it

almost identical but improved upon its binding," Bjorkman says.

UL18 didn't stop there. "It also binds peptides--that's unique to this MHC mimic. We don't know why," Bjorkman adds. The peptide is obscured from killer cells by yet another shield, Yang says. In a trait it shares with HIV proteins, HCMV's UL18 covers itself with carbohydrates, which are unrecognizable to the immune system. A real class 1 MHC molecule has one site for adding carbohydrates; the fake has 13, Bjorkman notes. The only place where it's not covered is where it binds to the inhibitory receptor.

Source: California Institute of Technology