Old protein, new tricks: Study connects a protein to antibody immunity for the first time

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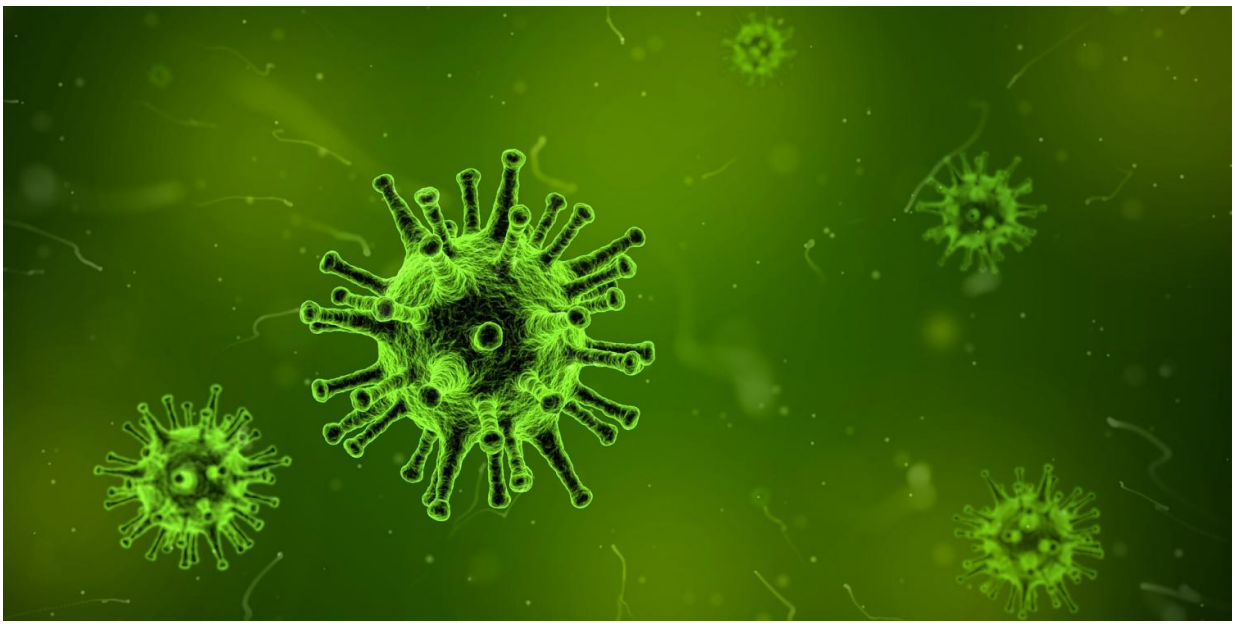

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Human cytomegalovirus (HCMV) may not be a household name as far as viruses go, but according to Xiaoping Zhu, professor and chair in Veterinary Medicine at UMD, half of the population walking around campus is likely to be a carrier. Once contracted, it lays dormant in your body for the rest of your life and can flare up whenever your immune system is severely compromised, giving you flu-like symptoms. This

becomes a severe problem for people who already have weakened immune systems, for example the very young, old, pregnant women, organ transplant recipients, or HIV/AIDS patients. More concerning, however, is that HCMV is the number one infectious cause of congenital birth defects in the world, including developmental disabilities and deafness. But how can a protein be a major contributor in the development of birth defects, and also hold the potential to provide symptom relief from autoimmune diseases like lupus? In a new paper published in *Nature Communications*, Zhu and his colleagues are helping to answer this question and uncover the mechanisms that will lead to multi-faceted prevention and treatment.

"HCMV stays asleep inside our cells," explains Zhu. "Then one day, you get stressed, you have too much going on, and your immunity decreases allowing the virus to spring up again." This is the case with all strains of the herpes virus like HCMV, chickenpox, and herpes simplex. HCMV can present similar symptoms to the flu virus. But unlike the flu, it persists in your body, and your immune system has to work harder than normal to combat the virus and keep it at bay.

It can also be passed through the placenta to a pregnant mother's unborn child, not only affecting the child's immune system, but also potentially causing birth defects. "When the mother gets infected, the virus spreads from mother to baby and can cause mental disabilities, vision loss, and deafness. People are aware of this concern with Zika virus for instance, but Zika doesn't stay in your system for life like HCMV, and it isn't present in 50 to 80 percent of the population globally depending on where you live," says Zhu.

This makes the study of HCMV and the mechanisms that contribute to its persistence and transmission a high priority for the medical community, with National Institutes of Health (NIH) funding Zhu's work. The immune system has two arms of immunity, at the cellular and

antibody levels, to specifically destroy bugs. The mechanisms of the US11 protein that allow HCMV to evade white blood cells that kill viruses on the cellular level are well known, but in this latest publication from Zhu, he and his colleagues discuss a newly discovered function of the same protein that impairs antibody immunity. Antibody immunity normally prevents viruses from entering and infecting uninfected cells and labels the infected cells to be destroyed by the white blood cells. But US11 attacks a specific receptor that not only naturally bolsters your immunity, but also directs protective antibodies from the mother to be transferred to the fetus. With this receptor impaired, HCMV may reduce transmission of these critical antibodies, resulting in vulnerability to all sorts of birth defects, and at the very least compromising the child's immunity throughout their life.

"This is the first time that we discovered that this virus, or any pathogen, has this strategy to destroy this receptor function and reduce antibody functionality," says Zhu. "Antibodies are also used to treat diseases like AIDS, cancer, and make vaccines, and this mechanism makes that less effective. By understanding this function, we can hopefully figure out methods to block that mechanism in the future."

Beyond prevention for birth defects and immune system dysfunction, Zhu sees another potential treatment benefit for this mechanism for patients struggling with autoimmune diseases. "Humans have many autoimmune diseases, and in these cases like with lupus, it is actually our immune response that causes the disease, which is regulated by antibodies," explains Zhu. "In these patients, we are concerned with how to reduce autoimmune antibodies, because their overproduction causes damage on our own tissues and cells, swelling in the joints, and substantial pain. Since this protein US11 can facilitate antibody degradation and suppress antibody function, it could be used in humans to treat autoimmune disease and target these disease-causing antibodies to indirectly benefit patients with immune diseases."

This therapeutic prospect is being patented by UMD through Zhu and Xiaoyang Liu, who stress the importance of directly translating basic research like this into applied outcomes and treatment options, not just for humans, but for animals that are infected with similar viruses as well. "Human and animal health research is interconnected," says Zhu. "Similar knowledge can be used to promote animal and human health, and diseases pass directly from animals to humans and vice versa."

With humans and animals standing to benefit from this work in many different ways, the applications of this discovery are widespread. The full paper, entitled "Human cytomegalovirus evades antibody-mediated immunity through endoplasmic reticulum-associated degradation of the FcRn receptor," is available through *Nature Communications*.

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