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Study models how the immune system might evolve to conquer HIV

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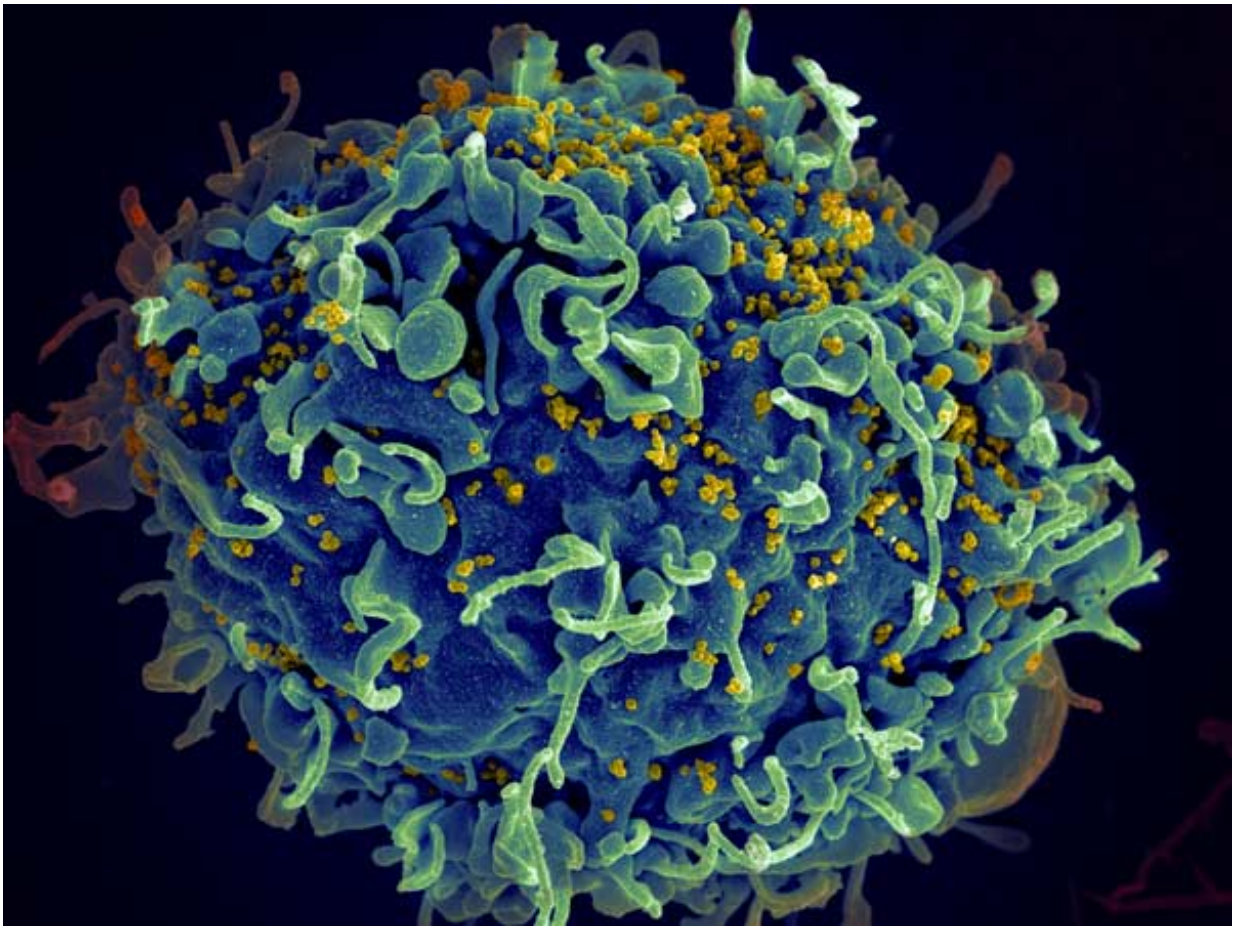

HIV infecting a human cell. Credit: NIH

It has remained frustratingly difficult to develop a vaccine for

HIV/AIDS, in part because the virus, once in our bodies, rapidly reproduces and evolves to escape being killed by the immune system.

"The viruses are constantly producing mutants that evade detection," said Joshua Plotkin, a professor in the University of Pennsylvania's Department of Biology in the School of Arts & Sciences. "A single person with HIV may have millions of strains of the virus circulating in the body."

Yet the body's immune system can also evolve. Antibody-secreting B-cells compete among themselves to survive and proliferate depending on how well they bind to foreign invaders. They dynamically produce diverse types of antibodies during the course of an infection.

In a new paper in *PLOS Genetics*, Plotkin, along with postdoctoral researcher Jakub Otwinowski and Princeton University research scholar Armita Nourmohammad, mathematically modeled these dueling evolutionary processes to understand the conditions that influence how antibodies and viruses interact and adapt to one another over the course of a chronic infection.

Notably, the researchers considered the conditions under which the immune system gives rise to broadly neutralizing antibodies, which can defeat broad swaths of viral strains by targeting the most vital and immutable parts of the viral genome. Their findings, which suggest that presenting the immune system with a large diversity of viral antigens may be the best way to encourage the emergence of such potent antibodies, have implications for designing vaccines against HIV and other chronic infections.

"This isn't a prescription for how to design an HIV vaccine," Plotkin said, "but our work provides some quantitative guidance for how to prompt the immune system to elicit broadly neutralizing antibodies."

The biggest challenge in attempting to model the co-evolution of antibodies and viruses is keeping track of the vast quantity of different genomic sequences that arise in each population during the course of an infection. So the researchers focused on the statistics of the binding interactions between the virus and antibodies.

"This is the key analytical trick to simplify the problem," said Otwinowski. "It would otherwise be impossible to track and write equations for all the interactions."

The researchers constructed a model to examine how mutations would affect the binding affinity between antibodies and viruses. Their model calculated the average binding affinities between the entire population of viral strains and the repertoire of antibodies over time to understand how they co-evolve.

"It's one of the things that is unique about our work," said Nourmohammad. "We're not only looking at one virus binding to one antibody but the whole diversity of interactions that occur over the course of a chronic infection."

What they saw was an S-shaped curve, in which sometimes the immune system appeared to control the infection with high levels of binding, but subsequently a viral mutation would arise that could evade neutralization, and then binding affinities would go down.

"The immune system does well if there is active binding between antibodies and virus," Plotkin said, "and the virus does well if there is not strong binding."

Such a signature is indicative of a system that is out of equilibrium where the viruses are responding to the antibodies and vice versa. The researchers note that this signature is likely common to many

antagonistically co-evolving populations.

To see how well their model matched with data from an actual infection, the researchers looked at time-shifted experimental data from two HIV patients, in which their antibodies were collected at different time points and then "competed" against the viruses that had been in their bodies at different times during their infections.

They saw that these patient data are consistent with their model: Viruses from earlier time points would be largely neutralized by antibodies collected at later time points but could outcompete antibodies collected earlier in infection.

Finally, the researchers used the model to try to understand the conditions under which broadly neutralizing antibodies, which could defeat most strains of virus, would emerge and rise to prominence.

"Despite the effectiveness of broadly neutralizing antibodies, none of the patients with these antibodies has been cured of HIV," Plotkin said. "It's just that by the time they develop them, it's too late and their T-cell repertoire is depleted. This raises the intriguing idea that, if only they could develop these antibodies earlier in infection, they might be prepared to combat an evolving target."

"The model that we built," Nourmohammad said, "was able to show that, if viral diversity is very large, the chance that these broadly neutralizing antibodies outcompete more specifically targeted antibodies and proliferate goes up."

The finding suggests that, in order for a vaccine to elicit these antibodies, it should present a diverse set of viral antigens to the host. That way no one specialist antibody would have a significant fitness advantage, leaving room for the generalist, broadly neutralizing

antibodies to succeed.

The researchers said that there has been little theoretical modeling of co-evolutionary systems such as this one. As such, their work could have implications for other co-evolution scenarios.

"Our theory can also apply to other systems, such as bacteria-phage co-evolution," said Otwinowski, in which viruses infect bacteria, a process that drives bacterial evolution and ecology.

"It could also shed light on the co-evolution of the influenza virus in the context of evolving global immune systems," Nourmohammad said.

More information: Armita Nourmohammad et al, Host-Pathogen Coevolution and the Emergence of Broadly Neutralizing Antibodies in Chronic Infections, *PLOS Genetics* (2016). DOI: 10.1371/journal.pgen.1006171

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