How HIV changes and reproduces

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Years ago, identical twin baby boys received a blood transfusion tainted with HIV. Today, one twin is relatively healthy with a near-normal immune system, but his brother is five years behind on the growth chart and has developed many complications.

A BYU research team studied how the virus evolved differently in each patient and published one of three recent BYU studies on the deadly virus. Another study analyzed the genetic changes in the virus during a failed trial for an AIDS vaccine in Thailand, and the third demonstrated how a naturally occurring protein can stop HIV from multiplying.

Twins with HIV

Keith Crandall, chair of the Department of Biology, and a BYU team

collaborated with researchers at the National Cancer Institute to see what can explain such different outcomes when genetically identical copies of the same virus infect genetically identical people.

It comes down to chance, Crandall says. Some genetic variants of the virus survived in one twin that did not in the other. The variants in the offspring of the virus are a random sample of those of their parent viruses. It's impossible to predict fully which viral types will survive and reproduce.

"One of the problems with HIV early on was that people did not appreciate the evolutionary nature of the virus," Crandall said. "It evolves and continues to develop resistance to drugs we develop to combat it."

The study, published in the journal *BMC Evolutionary Biology*, highlights the fact that effects of this reproductive randomness are more significant in small samples of the virus, such as those that are transmitted from one person to another, even when, overall, there is a large population of HIV.

And that, Crandall says, is why genetic analyses of vaccine studies are so important.

When HIV vaccines don't work

An HIV vaccine was put to the test in Thailand and unfortunately failed to limit infections. But as part of the vaccine trial, researchers took regular blood samples from the study subjects, both before and after some of them contracted HIV. After accessing these data, Crandall and a different team could observe how HIV evolves soon after it infects a person.

Their analysis showed that the HIV-infected community in Thailand is relatively tight-knit compared to other places that have had vaccine trails, such as North America. For example, the analysis spotted subjects that were infected by the same virus, possibly by sharing the same needle during drug use. That limits the power of a trial, which needs diversity to establish whether a vaccine is working or not.

“We are trying to inform future vaccine trials in terms of the genetic diversity of the populations and things you need to look out for,” Crandall said.

The paper was published in the scientific journal *PLoS One*.

How to stop HIV from copying itself

Another BYU researcher has found that an increase of a naturally occurring protein stops HIV from multiplying — and equally important, he knows how it blocks virus replication.

Greg Burton, chair of BYU’s Department of Chemistry and Biochemistry, and his student Xueyuan Zhou report in the Journal of Immunology that an increase in the protein called a-1-antitrypsin (AAT) throws a wrench in HIV’s ability to make more virus. AAT is already clinically approved as a treatment for chronic obstructive pulmonary disease and is harvested from blood plasma donations.

“That’s the neat thing about it — that it’s naturally occurring in the human body,” Burton said. “All we did was boost it a little higher than the normal level for a healthy human being.”

Burton’s research involved taking blood samples from healthy individuals. A pretreatment of AAT didn’t completely prevent infection when the virus was introduced, but it did stop the virus from making

copies of itself and multiplying.

This finding mirrors a recent human trial with AAT conducted by researchers in Europe. But the BYU study goes one step further and shows how AAT blocks virus replication. At the right levels, AAT alters the structure of a separate protein that HIV uses to transcribe its genetic code in the replication process. Those alterations to the other protein make it unrecognizable to the virus.

“The human trial performed in Europe produced a dramatic difference,” Burton said. “Even though our work was independent of those researchers, our study explains the mechanism behind their findings.”

Burton is also excited to explore whether these new findings could lead to the discovery of an “off switch” for other autoimmune diseases and allergies. Stay tuned for that.

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