Medical Xpress

HIV-1 protein suppresses immune response more broadly than thought

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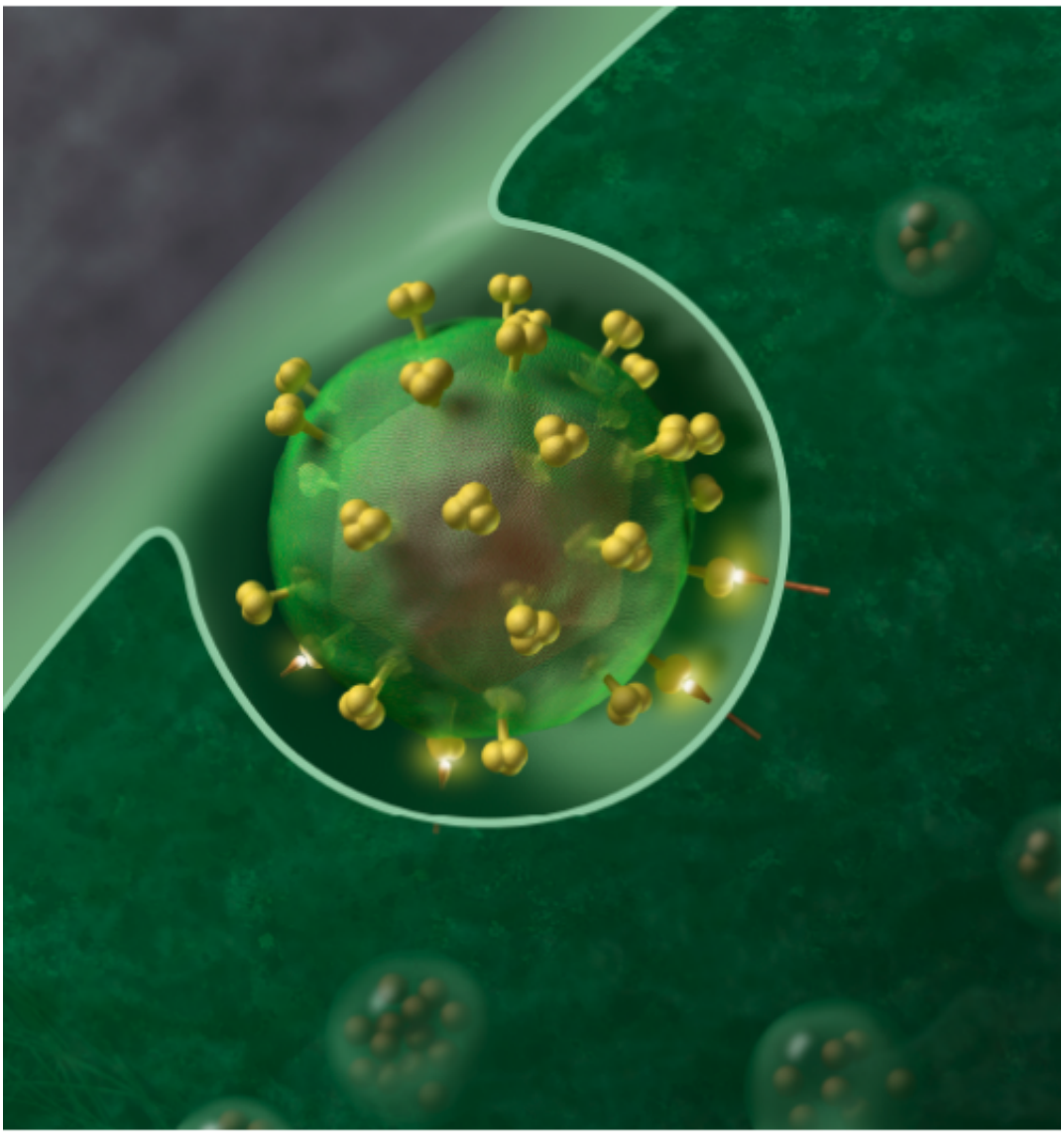

HIV-1 Virus. Credit: J Roberto Trujillo/Wikipedia

Scientists have revealed how a protein produced by HIV-1 plays a broader role in suppressing the immune system's response to infection than previously thought.

Their findings could help inform more effective treatment strategies for HIV, including those aimed at activating the dormant virus in patients before subsequently eliminating it. The study, published in *eLife*, comes from a collaboration between Ulm University, Germany, and the Sanford Burnham Prebys (SBP) Medical Discovery Institute, La Jolla, US.

While the immune system makes a significant effort to fight HIV, the virus is still able to replicate and spread efficiently, infecting about two million people each year. This success can be explained in part by several viral factors that trick the immune system. These include four 'accessory proteins' - Vif, Nef, Vpr and Vpu—that help HIV to persist at high levels in the body.

"When cells are infected by HIV, they can send alarm signals to healthy cells, telling them to fight against viral pathogens and thereby prevent the spread of infection. However, the accessory protein U (Vpu) is able to silence these signals," explains co-author Simon Langer, Postdoctoral Fellow at SBP Medical Discovery Institute, previously at Ulm University Medical Center.

"It was already known that Vpu uses a couple of techniques to suppress the immune response to HIV infection. But accumulating research has suggested that the protein plays a larger role by inhibiting the activation of other proteins called transcription factors," adds co-author Kristina Hopfensperger, Ph.D. student at Ulm University Medical Center. "We wanted to gather more insight into the mechanisms used by Vpu to achieve this."

The team analysed human cells infected with HIV-1 clones that produced intact or defective Vpu. They tested the effects of these HIV variants on the response to infection, release of alarm signals, and production of antiviral factors by the cell.

Their results first revealed that Vpu suppresses the activation of a transcription factor called NF-κB—a 'master regulator' of immune activation in infected individuals. As a result of decreased NF-κB activity, Vpu reduced the production of several cellular factors that play key roles in the antiviral immune response.

"Indeed, we saw that HIV mutants lacking Vpu triggered the release of a larger amount of interferon, which is an important alarm signal for uninfected cells," says co-author Christian Hammer, a scientist at Genentech, South San Francisco, US. "This suggests that the protein inhibits the cross-talk between immune cells during HIV infection."

"Altogether, we've shown that Vpu does play a much wider role in suppressing the immune system than previously believed, especially as it hinders NF-κB-elicited immune responses at the transcriptional level," concludes senior author Daniel Sauter, Junior Professor at Ulm University Medical Center.

"Inactive NF-κB may keep HIV in a dormant state that prevents current drugs from eradicating the virus. Our findings could therefore inform therapeutic approaches aiming to activate dormant HIV for subsequent elimination of the virus."

More information: Simon Langer et al, HIV-1 Vpu is a potent transcriptional suppressor of NF-κB-elicited antiviral immune responses, *eLife* (2019). DOI: 10.7554/eLife.41930