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Scientists identify genetic link that may neutralize HIV

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Scientists from the Gladstone Institute of Virology and Immunology (GIVI) and the National Institutes of Allergy and Infectious Diseases (NIAID) have identified a gene that may influence the production of antibodies that neutralize HIV. This new information will likely spur a new approach for making an HIV vaccine that elicits neutralizing antibodies. Neutralizing antibodies, once produced in the host, can attack and checkmate an infecting virus. The research was reported in the September 5 issue of *Science*.

Scientists have been striving in vain to stimulate strong protective antibodies with an HIV vaccine for years because these antibodies hold great promise for controlling HIV infection in humans. HIV is a type of virus called a "retrovirus," which copies its RNA genetic material into DNA and incorporates it into the DNA of its host.

In 1978, researchers at the National Institutes of Health (NIH) studying a similar retrovirus in mice discovered a gene called Rfv3 that influenced the production of neutralizing antibodies that allowed the animals to recover. By 1999, they had narrowed the location of Rfv3 to a relatively small region on mouse chromosome 15, but that region contained more than 60 genes. The laboratory of GIVI Director Warner C. Greene and a team of scientists from NIAID now demonstrate that Rfv3 is Apobec3, an innate immunity gene with antiretroviral activity.

"This newfound link between Apobec3 and the production of neutralizing antibodies came as a complete surprise," said Dr. Greene,

senior author on the paper.

While the studies involved a different retrovirus infecting mice, the findings may extend to HIV. HIV uses one of its genes, Vif, to specifically disable human Apobec3 proteins and HIV-infected patients rarely make broadly neutralizing antibodies against this virus. This new study raises the possibility that drugs or vaccines that interfere with Vif might allow humans to naturally make better neutralizing antibody responses against HIV.

"We now have a host factor needed for the production of neutralizing antibodies that HIV targets and destroys," said Gladstone scientist Mario Santiago, PhD. "This offers a fresh perspective on how to strengthen this arm of the immune response against HIV, with direct implications for immunotherapy and vaccine development."

The scientists conducted a series of genetic experiments by mating mice with different Rfv3 and Apobec3 profiles. The researchers demonstrated that Apobec3, like Rfv3, contributes to the early control of retroviral infection in mice, and also influences specific retroviral antibody responses. In addition, they discovered that Rfv3 susceptible mouse strains that fail to make antibody responses have a natural defect in Apobec3. These results provide convincing evidence that Rfv3 and Apobec3 are the same gene.

"We set out to solve a 30-year old mystery in retrovirus biology and in the process made a discovery that might impact future development of HIV vaccines. Science really is full of unexpected twists and turns," said Dr. Greene.

The link between Apobec3 and neutralizing antibody responses becomes even more tantalizing in view of other recent studies of people who somehow resist HIV infection despite years of frequent exposure to the

virus. These individuals produce a particular type of antibody recognizing the virus and genetic mapping studies of their resistance points to a chromosomal region where the human Apobec3 genes are clustered.

The research group is now poised to investigate Apobec3 differences in these individuals and is currently screening for compounds that would rescue Apobec3 function during HIV infection.

Citation: Santiago M.L, Montano, M., Benitez,R., Messer, R.J., Yonemoto, W., Chesebro, B., Hasenkrug, K.J., and Greene, WC. Apobec3 encodes Rfv3, a gene influencing neutralizing antibody control of retrovirus infection. *Science*: 1161121.

Source: Gladstone Institutes