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New findings suggest strategy to help generate HIV-neutralizing antibodies

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New discoveries about anti-HIV antibodies may bring researchers a step closer to creating an effective HIV vaccine, according to a new paper co-authored by scientists at the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

Scientists know that an HIV-neutralizing antibody called b12 binds to gp120, an HIV surface protein, at one of the few areas of the virus that does not mutate: the site where gp120 initially attaches to human immune cells. It was thought that exposing the human immune system to this site on gp120 would generate antibodies that, like b12, can neutralize HIV. Studies have found that for unknown reasons, however, the vast majority of antibodies that recognize this site do not block the virus from infecting cells. Now a new study solves this puzzle, suggesting that antibodies must home in precisely on the site of initial gp120 attachment to successfully neutralize HIV.

The gp120 protein usually appears on the surface of HIV and on infected cells in inactive forms of viral debris or non-functional viral spikes. Only rarely do gp120 molecules appear on the surface of the virus in a functional viral spike, which contains a cluster of three gp120 molecules, known as a trimer, in specific alignment. HIV uses this functional viral spike to bind to immune cells and infect them.

The new study shows that most antibodies able to bind to non-functional forms of gp120 cannot bind to gp120 in the functional viral spike and

therefore cannot neutralize HIV. Further, the study demonstrates that the reason most anti-gp120 antibodies similar to b12 cannot bind to the functional viral spike is because of the way these antibodies attach to gp120. A close examination of two such antibodies illustrated that their binding positions on gp120 cause a key portion of the protein either to swing in or flare out in positions incompatible with the trimer structure. In contrast, the position of b12 antibody binding allows gp120 to neatly form its normal trimeric structure.

The scientists conclude that generating HIV neutralizing antibodies will require teaching the immune system to make antibodies that precisely target the site of vulnerability on gp120 as it appears in the functional viral spike rather than targeting the plentiful forms of viral debris such as single gp120 molecules.

More information: L Chen et al. Structural basis of immune evasion at the site of CD4 attachment on HIV-1 gp120. *Science*, DOI 10.1126/science.1175868 (2009).

Source: NIH/National Institute of Allergy and Infectious Diseases (news : web)