MedicalXpress

Scientists shed new light on how antibodies fight HIV

September 6 2007

By furthering scientists' understanding of the molecular mechanisms that separate the minority of successful HIV antibodies from the majority of ineffective antibodies, the work may have implications for future attempts to design an HIV vaccine.

The study was published on September 6, 2007, in the journal *Nature*. "This study is part of the effort to understand how protection against HIV occurs," says Dennis Burton, a professor at The Scripps Research Institute. "If we really understand this, then we can design tailor-made vaccines in a way that has never been done before."

Although vaccines have long been used with great success to prevent diseases, scientists are still learning about the exact mechanisms of how vaccines work and how the antibodies that vaccines prompt the body to create can neutralize a pathogen. The spread of HIV, which is resistant to most antibodies the body produces against it, has made fully understanding this method of action more urgent.

With this in mind, Burton and colleagues sought to tease apart the action of the b12 antibody-one of the rare antibodies that protects against the HIV virus. The antibody, first identified by Burton, Scripps Research Professor Carlos Barbas III, and colleagues in 1992, originally came from the bone marrow of a 31-year-old male who had been HIV positive without symptoms for six years.

In the current study, researchers created mutated versions of b12 to see

what effect various changes would have on the antibody's effectiveness.

"Hopefully, we can work backwards towards a vaccine, using b12 and the very few other really great, broadly neutralizing antibodies against HIV that have been found," says Scripps Research Senior Research Associate Ann Hessell, who was first author of the Nature paper jointly with Lars Hangartner, a Scripps Research postdoctoral fellow.

Results from the new study suggest the importance of antibody activity against both infected cells and free virus for effective protection. As well as simply binding to HIV, protection was dependent upon the ability of antibodies to interact with immune cell Fc receptors.

Fc receptors are found on the surface of immune cells, such as natural killer cells. The Fc receptor binds to the Fc region of an antibody after an antibody binds to a pathogen, targeting the pathogen for attack by the immune system. Although Fc receptor function was known to be important for the function of antibodies against other diseases, a role in protecting against HIV had never before been demonstrated.

Burton's team examined the ability of two antibodies mutated from b12, dubbed KA and LALA, to prevent infection using the SHIV/macaque model, in which macaques are challenged with a hybrid human-simian virus that infects the model but is recognized by human antibodies. The KA antibody contained a mutation that prevented it from interacting with the complement cascade, a major component of the immune system responsible for destroying invading pathogens. The LALA antibody contained a mutation that rendered it unable to interact with either the complement pathway or the Fc receptor.

In both mutants, the site where the antibody binds to free-floating virus was unaltered, allowing the researchers specifically to investigate the importance of the complement cascade and Fc receptor system for

preventing infection.

“We saw that the KA antibody, which could still bind to the Fc receptors on the immune cells but not to the complement cascade, protected the animals from becoming infected just as the wild type b12 antibody,” says Hessell. “In contrast, the LALA group became infected much like the controls.”

The results provide the first evidence that the Fc receptor, but not the complement cascade, is important to the function of the b12 antibody in preventing HIV infection.

Additional in vitro experiments revealed that the wild type and KA antibodies, but not the LALA antibody, blocked infection more efficiently in the presence of other effector cells of the immune system.

“Our results are fully consistent with the antibody doing two jobs,” says Burton, “job one, stick to the virus; job two, recruit immune cells to come and kill infected cells.”

Source: Scripps Research Institute