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GLADSTONE INSTITUTE OF VIROLOGY AND IMMUNOLOGY NEWS

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GLADSTONE INVESTIGATORS IDENTIFY A NEW PROTECTIVE ACTION FOR THE POWERFUL ANTI-HIV FACTOR APOBEC3G

Scientists at the Gladstone Institute of Virology and Immunology (GIVI) have identified a previously unknown function of APOBEC3G (A3G), a protein that acts against HIV, a finding that may lead to new approaches for controlling HIV infection.

The work is published today, Oct. 9, 2006, in the *Proceedings of the National Academy of Sciences USA*,

The research, conducted by scientists in the laboratory of GIVI Director Warner C. Greene, MD, PhD, explains why CD4 T cells – the immune system cells targeted by HIV -- are sometimes so susceptible to HIV infection and at other times are highly resistant.

Scientists have known that resistant CD4 called "resting cells," are made up predominantly of CD4 T cells that are in an inactive state, awaiting a stimulus to move into action. In these cells, A3G blocks HIV at an early step in its life cycle. However, when resting CD4 T cells are stimulated by a foreign protein or other signal, A3G is rapidly recruited into large RNA protein complexes within the cells. This change neutralizes the anti-HIV properties of A3G, opening the door to HIV infection.

In the current study, the researchers set out to decipher the protein and RNA components of the A3G RNA protein complexes. In so doing, Ya-Lin Chiu, PhD, a postdoctoral fellow in Greene's laboratory, determined that the complexes help to prevent a threat within cells posed by a class of "jumping genes," or retro-elements, which are sequences of DNA that change position within the genome, causing mutations, activating or inactivating other genes, or duplicating themselves, thereby increasing the quantity of DNA in each cell.

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New Function for APOBEG3G

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As with HIV, the replication and movement of these retro-elements to new chromosomal sites with potentially damaging effect involves copying DNA into RNA and then back into DNA again. The A3G RNA protein complex, Chiu determined, interrupts this retro-element replication cycle by binding the retro-element RNAs and sequestering them in the cytoplasm away from the nuclear machinery required for copying the RNA back into DNA and inserting the retro-element at a new chromosomal site.

Understanding A3G's role in activated CD4 T cells could lead to a new strategy against HIV.

“If we can find a way to partially block A3G assembly into the large complexes during CD4 T cell activation, we could both preserve the potent anti-HIV effect of the small form of A3G and the protective function of the large A3G complex against select mobile genetic elements.” Greene said. Gladstone scientists are now exploring various ways to achieve this desired balance.

Other authors on the study were Gladstone postdoctoral fellows Mario Santiago PhD, and Vanessa B. Soros, PhD, and H. Ewa Witkowska and Steven C. Hall of the University of California, San Francisco, and Cécile Esnault and Thierry Heidmann from the Institut Gustave Roussy in Villejuif, France.

Funding for the study came from the National Institutes of Health, San Francisco Women's HIV Interdisciplinary Network, the American Foundation for AIDS Research, UCSF-GIVI Center for AIDS Research, Ligue Nationale Contre le Cancer, Sandler Family Foundation and the J. David Gladstone Institutes.

The Gladstone Institute of Virology and Immunology is one of three research institutes of The J. David Gladstone Institutes, a private, nonprofit biomedical research institution.

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