Protein linked to Alzheimer's disease also has role in HIV progression

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The apolipoprotein (apo) E4 isoform has been implicated in neurodegeneration in Alzheimer's disease, cardiovascular disease, and stroke. Now, investigators at the Gladstone Institutes, the University of California, San Francisco, the University of Texas Health Science Center at San Antonio, and the Infectious Disease Clinical Research Program, Uniformed Services University, Bethesda, Maryland have shown that this troubling protein is a risk factor for AIDS progression rates and promotes entry of HIV into cells. The study was published in today's issue of the *Proceedings of the National Academy of Sciences USA (PNAS).*

"The apoE4 protein is the greatest known genetic risk factor for Alzheimer's disease," said Gladstone president and study author Robert W. Mahley. "However, its role in infectious diseases has been less well-defined."

ApoE has three isoforms that differ by only one amino acid. Yet this seemingly small sequence difference has profound implications for the structure and function of the protein. ApoE4 has an extra intramolecular bond that results in a more compact structure, and it also is more likely to be unstable—characteristics that have been linked to its deleterious effects. Although the apoE3 gene is the most prevalent in all human populations, with frequencies of 50%□□%, the genetic variant that leads to production of apoE4 is also widely distributed; its prevalence is 15%□□%.

The different effects of the apoE isoforms in other settings led the investigators to hypothesize that a similar difference might exist in HIV infection.

To test this hypothesis, Dr. Mahley teamed up with Trevor Burt and Joseph M. McCune of the University of California, San Francisco, Brian Agan and Matthew Dolan of the Infectious Disease Clinical Research Program, and Sunil Ahuja of the University of Texas Health Science Center at San Antonio to examine a large and well-characterized cohort of 1267 HIV-positive subjects of European and African American descent and 1132 ethnically matched seronegative controls. The goal was to study the interactions between apoE and HIV in tissue culture. Several questions were of great interest. Does apoE genotype affect disease progression? Do apoE isoforms influence cell entry by HIV in a manner concordant with the impact of the corresponding APOE alleles on HIV disease progression? Do the genetic variants of apoE convey differential susceptibility to HIV-associated dementia, a condition that shares many pathogenic and clinical features with Alzheimer's disease?

The researchers found a much faster disease course and progression to death in patients with two copies of the apoE4 allele than in patients with two copies of the apoE3 allele. The corresponding apoE4 isoform enhanced in vitro HIV fusion/cell entry of HIV strains that use both the CCR5 and CXCR4 chemokine coreceptors to enter the cell. However, the apoE4 gene did not increase the incidence of HIV-associated dementia.

"A large body of evidence suggests that the amphipathic helical domains of apolipoproteins act as fusion inhibitors," said Dr. Mahley. "We speculate that these domains in apoE inhibit HIV infection in a manner analogous to the clinical HIV fusion inhibitor Enfurvitide. Our findings suggest apoE4 is less efficient than apoE3 at inhibiting fusion of HIV to target cells."

Polymorphisms in host genes significantly affect susceptibility to HIV-1 infection and the rate of disease progression. The study of these polymorphisms has increased the understanding of HIV pathogenesis and informed the development of new antiviral therapeutics.

The findings from this study show that apoE is a determinant of the pathogenesis of HIV/AIDS and raise the possibility that current efforts in the Gladstone Center for

Translational Research to convert apoE4 to an "apoE3-like" molecule for the treatment of Alzheimer's disease might also have clinical applicability in HIV disease.

"Although we suspected that apoE4 had a role in infectious disease, this aspect of the study is very exciting for us because we already have studies under way to find small molecules that make apoE4 more like apoE3," said Dr. Mahley. "Now those potential new drugs may have more value than we originally thought."

Source: Gladstone Institutes