

International Research Gives Insight to Immunity, HIV

Since the advent of the HIV/AIDS pandemic more than 20 years ago, scientists have wondered why the immune systems of some people with HIV are better able to resist the damaging virus than others. A study conducted jointly by U.S., British and African research teams now offers some clues.

"This study identifies the genetic battleground where the struggle between HIV and the human immune response occurs," says Dr. Philip Goulder of the Partners AIDS Research Center at Massachusetts General Hospital (MGH) --the study's principal investigator -- in a MGH December 8 press release.

Scientists involved in this work are looking at the fundamental mechanics of the immune system to see how cells either ward off attacks by viruses or are overwhelmed by the invaders. They've found that particular cells -- Class 1 molecules -- alert the body's defensive T cells that a virus is present, and the immune system needs to mount an attack.

But some Class 1 molecules are more effective than others. The research from MGH, the University of Oxford and the University of KwaZulu-Natal finds that several genes can encode the Class 1 molecules, and one known as HLA-B makes a significant difference in how well a given individual copes with HIV infection.

The presence of HLA-B -- its importance to the immune response and, by extension, survival itself -- is also likely to affect human evolution, according to the press release. "This is an exciting time for infectious disease research because we are witnessing the evolutionary fight between the human immune system and the HIV virus happening right now, rather than over a period of thousands of years," says Goulder, who also has an appointment in pathogen research at Oxford.

The text of the press release follows:

(begin text)

MASSACHUSETTS GENERAL HOSPITAL
News and Information

Study identifies key aspect of immune response against HIV
Results illuminate evolutionary interaction between virus and human immune system

BOSTON - December 8, 2004 - An international research team has identified immune-system genes that appear to play a key role in the body's defense against HIV, the virus that causes AIDS. The findings may lead to ways of circumventing the virus's ability to avoid vaccines by rapid mutation. The study in the Dec. 9 issue of Nature also describes how HIV infection is driving human evolution, since individuals with protective versions of the identified genes are more likely to survive and pass those genes along to children. Including researchers from the University of Oxford and the University of KwaZulu-Natal in South Africa, the investigation is a

result of a program established by the Partners AIDS Research Center at Massachusetts General Hospital (MGH).

"This study identifies the genetic battleground where the struggle between HIV and the human immune response occurs," says Philip Goulder, MD, PhD, of the Partners AIDS Research Center at MGH, the study's principal investigator. "The findings will help in understanding precisely how the immune system can succeed or fail against HIV, a prerequisite for a rational approach towards design of an HIV vaccine." Goulder also has an appointment at the Peter Medawar Building for Pathogen Research at Oxford.

The human immune system learns to recognize and attack virus-infected cells through the activity of human leukocyte antigen (HLA) Class 1 molecules, which sit on the surface of cells. When new viruses are being produced within an infected cell, Class 1 molecules grab fragments of viral proteins from within the cell and display them at the cell surface, thereby alerting the body's "killer" T cells that something foreign is within the cell and it should be destroyed. Three genes called HLA-A, HLA-B, and HLA-C encode Class 1 molecules, and it is known that the HLA-B genes are extremely diverse, with more than 560 versions or "alleles" having been identified. The current study was designed to test the theory that the diversity of HLA Class 1 molecules could reflect differences in the killer T cell activity controlled by those molecules.

The researchers analyzed blood samples from 375 HIV-infected patients at the Doris Duke Medical Research Institute at the University of KwaZulu-Natal to determine whether particular HLA Class 1 molecules control the killer T cell response against the virus. They found that an individual's version of HLA-B made a significant difference in how well the immune system responds against HIV, whereas the version of HLA-A or HLA-C inherited did not matter.

To examine the impact of Class 1 molecules on blood viral levels, the team studied more than 700 chronically infected African patients and again found that particular versions of HLA-B were associated with high or low plasma virus levels. Additional tests that looked at levels of the helper T cells that are destroyed by HIV and that analyzed samples from Australian patients infected with a different strain of virus all supported the conclusion that the form of the HLA-B molecule patients inherit makes a significant difference in how well their immune systems cope with HIV infection.

Evidence of the virus's impact on human evolution was found in an analysis of HLA-B alleles in HIV-infected mothers and their infants. Not only are HIV-infected women who have a protective version of HLA-B more likely to survive, they are also less likely to pass the virus along to their children. From an evolutionary standpoint, that finding suggests a trend towards greater frequency of the protective alleles in a population over time.

"We have known for some time that HLA-B molecules are evolving more rapidly than other types, but it has been unclear why this is happening," says Goulder. "These data suggest an explanation for the more rapid evolution of HLA-B in response to other infectious diseases, not only HIV. This is an exciting time for infectious disease research because we are witnessing the evolutionary fight between the human immune system and the HIV virus happening right now, rather than over a period of thousands of years." Goulder is an assistant professor of Medicine at Harvard Medical School.

"The AIDS crisis will only be solved with the development of an effective vaccine," says Bruce Walker, MD, director of the Partners AIDS Research Center at MGH and a co-author of the current study. "This study's results help to focus this effort by telling us what the most effective immune responses are." Walker is also a Howard Hughes Medical Institute researcher and a professor of Medicine at Harvard Medical School.

In addition to Goulder and Walker, authors of the Nature study are first author Photini Kiepiela, and Isobella Honeyborne, Danni Ramduth, Christina Thobakgale, Senica Chetty, Prenisha Rathnavalu and Hoosen Coovadia of the Doris Duke Medical Research Institute at UKZN; Alasdair Leslie, Katja Pfafferott, Louise Hilton, Peter Zimbwa, Cheryl Day, and Paul Klenerman of the Medawar Building for Pathogen Research at Oxford; Corey Moore, Ian James and Simon Mallal of Royal Perth Hospital in Australia; Sarah Moore, University of Washington; Michael Bunce, Dynal Biotech Ltd, Wirral, UK; Linda Barber, Royal Free Hospital, London; Bette Korber, Santa Fe Institute; and Todd Allen, Christian Brander, Marylyn Addo, and Marcus Altfeld of the Partners AIDS Research Center at MGH. The study was supported by grants from the National Institutes of Health, the Doris Duke Charitable Foundation, the Wellcome Trust, and the Elizabeth Glaser Pediatric AIDS Foundation.

The Partners AIDS Research Center (PARC) was established in 1995 in response to the continuing world-wide AIDS pandemic. The center serves both MGH and Brigham and Women's Hospital, the founding members of Partners HealthCare, and is a natural progression of the more than twenty-year commitment by the clinicians and scientists at those institutions to HIV and AIDS research and care. The Doris Duke Medical Research Institute at the University of KwaZulu-Natal (UKZN) opened in 2003 and was established through a collaboration between PARC-MGH and UKZN. The institute is focused on interdisciplinary research into AIDS and other health issues affecting South Africa and the entire African continent.

Massachusetts General Hospital, established in 1811, is the original and largest teaching hospital of Harvard Medical School. The MGH conducts the largest hospital-based research program in the United States, with an annual research budget of more than \$400 million and major research centers in AIDS, cardiovascular research, cancer, cutaneous biology, medical imaging, neurodegenerative disorders, transplantation biology and photomedicine. In 1994, MGH and Brigham and Women's Hospital joined to form Partners HealthCare System, an integrated health care delivery system comprising the two academic medical centers, specialty and community hospitals, a network of physician groups, and nonacute and home health services.

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