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Early-stage immune system control of HIV may depend on inherited factors

Findings may provide important clues for vaccine development

How well an individual's immune system controls HIV during the earliest phases of infection appears to depend on both the specific versions of key immune-system molecules called HLA Class I that have been inherited, as well as on the fragments of viral protein those molecules display to the T lymphocytes that usually destroy infected cells. In a report in the November issue of PLOS Medicine, researchers from the Partners AIDS Research Center at Massachusetts General Hospital (PARC/MGH) report that specific HLA Class I/HIV viral fragment combinations are associated with a more powerful antiviral response, findings that may help develop vaccines against HIV.

"We found that only a limited number of viral protein fragments from HIV-1 are targeted by the immune system in early infection and that the versions of HLA Class I previously associated with slower HIV-1 disease progression also contribute more to this initial antiviral immune response," says Marcus Altfeld, MD, PhD, of PARC/MGH, the paper's lead author.

An essential aspect of the immune response involves educating T cells to recognize pathogens or other "non-self" proteins. This is done by means of human leukocyte antigen (HLA) receptors that sit on the surface of virtually every cell. Immune system cells that ingest bacteria or parasites digest those pathogens and display protein fragments on their surface membranes via HLA Class II proteins. Virally infected cells display viral proteins on HLA Class I molecules, which activate the CD8 cytotoxic T lymphocytes that usually destroy infected cells. Although the CD8 response against HIV is ultimately ineffective in protecting infection, several studies have suggested that it plays a key role in determining how quickly the disease progresses after initial infection.

HLA ‧also called major histocompatibility complex (MHC) ‧proteins are also the primary markers of tissues as "self." Unique to each individual, these are the factors that need to be

matched as closely as possible in organ transplants, with perfect matches only possible between identical twins. Some studies have found that HIV patients with particular versions of HLA may be better able to control viral levels, but the diversity of HLA molecules ‑each person may have up to six different varieties of Class I proteins ‑has made investigating the role of HLA type in HIV infection challenging.

The current study was designed to determine the contribution of both HLA Class I and the particular viral fragments displayed on those molecules to the activation of HIV-specific CD8 cells. The researchers analyzed blood samples from more than 100 people recently infected with HIV, first determining their specific HLA types by DNA analysis. Then they focused on 173 HIV protein fragments known to bind to those HLA types to see if particular peptides were more powerful in activating the HIV-specific CD8 response.

The researchers found that, for many varieties of HLA, only a few HIV protein fragments were responsible for the activation of CD8 T cells early in infection. In addition, the same HLA types that had been previously identified in people who stay healthy for a longer period of time after initial infection were associated with a more powerful early-stage HIV-specific CD8 activity.

"While we can't say this for sure right now, it is looking like both the HLA Class I molecule and the specific viral sequences being displayed contribute to the strength of immune response against primary HIV infection," says Altfeld. "In addition, the combination of Class I molecules that an individual expresses, something that is genetically determined, seems to have a significant impact on the specificity and strength of that response.

"Identifying the HIV epitopes [viral fragments] that are particularly good at priming an early T cell response may be important to vaccine design, and the impact of an individual's genetic HLA Class I background implies that a successful vaccine would have to overcome genetic factors associated with a less protective response," he adds. Altfeld is an associate professor of Medicine at Harvard Medical School. He and his colleagues are working on a follow-up study with samples from 500 individuals to further investigate the impact of HLA Class I on the control of HIV replication.

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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 nearly $500 million and major research centers in AIDS, cardiovascular research, cancer, computational and integrative biology, cutaneous biology, human genetics, medical imaging, neurodegenerative disorders, regenerative medicine, transplantation biology and photomedicine. MGH and Brigham and Women's Hospital are founding members of Partners HealthCare System, a Boston-based integrated health care delivery system.