

Researchers link HIV susceptibility to little-understood immune cell class

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High diversity among certain cells that help fight viruses and tumors is strongly associated with the likelihood of subsequent infection by HIV, Stanford University School of Medicine researchers have found.

Natural killer cells, or NK cells, are lymphocytes, a type of white blood cell. NK cells' increased diversity, the scientists learned, may stem from prior exposures to viruses.

The findings, described in a study that will be published July 22 in *Science Translational Medicine*, could spur the development of blood tests capable of flagging individuals' susceptibility to viral infection. The study also offers insights into the workings of NK cells, a somewhat poorly understood but crucial group of [immune cells](#).

"This puts NK-cell diversity on the map as a metric of immune function," said Catherine Blish, MD, PhD, assistant professor of infectious diseases and geographical medicine and the study's senior author. "But it was a first foray. Before we can say definitively that NK-cell diversity predicts a person's susceptibility to infection, we need to validate these findings by looking at large numbers of individuals in a different population.

"NK cells are particularly suited to detecting and demolishing virally infected or [cancerous cells](#)," Blish added. "They arrive on the scene quickly, and they act quickly. An NK cell can kill an infected cell in 10 minutes."

Unexpected finding

Unexpectedly, it was higher, rather than lower, diversity in this immune-cell population that turned out to be associated with increased HIV susceptibility in the study. The investigators had figured that, as is the case with B cells and T cells—the two other, better-known types of lymphocytes—diversity in NK cells would be a strength, not a detriment, Blish said.

"Our hypothesis was wrong," she said. "We didn't think NK-cell diversity would be a bad thing, or that NK cells' diversification would occur to the extent that it does with viral exposure."

Using a cutting-edge, single-cell analytic technology called mass cytometry, Blish and her colleagues, including the study's lead author, graduate student Dara Strauss-Albee, showed that overall diversity in people's NK-cell repertoires is low at birth and steadily accumulates over the course of a lifetime.

An individual T cell has surface receptors that recognize unique protein snippets, called peptides, on other cells' surfaces. The structures of these receptors, which can discern "healthy" versus "suspect" peptides, differs from T cell to T cell. So a healthy person's legion of T cells can surveil and sort out hundreds of millions of different peptides representing possible invaders.

Unlike their T cell cousins, NK cells don't have surface receptors that recognize unique peptides. Instead, these lymphocytes harbor various combinations of generic receptors. Some receptors recognize signs of other cells' normalcy, and others recognize signs that a cell is stressed—due, say, to viral infection or cancerous mutation. On recognizing their targeted features on other cells' surfaces, an NK cell's "normalcy" receptors tend to inhibit it, while its stress-recognizing

receptors activate it.

All told, NK cells can have many thousands of different combinations of these receptors on their surfaces, with each combination yielding a slightly different overall activation threshold. An NK cell's surface features also vary depending on its degree of maturation.

Mass cytometry analysis of NK cells exposed in a dish to HIV—as well as to West Nile virus, which differs substantially from HIV in its makeup and its modus operandi—showed that exposure to virus-infected cells leads to differentiation of NK cells and to an increased diversity among them. But diversification in the NK-cell population, the experiments indicated, was associated with a diminished ability of these cells' ability to replicate and kill.

The researchers also showed that while healthy human adults differ considerably from one another in the diversity of their NK-cell populations, a given adult's NK-cell population remains quite stable, changing little over periods of many months. An examination of NK cells extracted from umbilical-cord blood showed that newborns' NK-cell population is much less diverse.

Blish said she believes that viral exposure during one's lifetime is the driving force behind the maturation, differentiation and diversification of NK cells.

HIV link

In order to assess the impact of NK-cell diversity on adult humans' viral susceptibility, Blish and her associates turned to blood samples that had been drawn during the Mama Salama Study, a longitudinal study of just over 1,300 healthy pregnant or postpartum Kenyan women. In that study, 25 of the women were found to have HIV. For 13 of these women, blood

drawn both before and after infection was available.

Using mass cytometry, the researchers carried out a precise analysis of NK [cells](#) in the women's blood and observed a strong positive correlation between the diversity of a woman's NK cell population and her likelihood of becoming infected with HIV. This correlation held up when the scientists controlled for age, marital status, knowledge of sexual partners' HIV status and history of trading sex for money or goods. The two groups of women were also statistically indistinguishable with respect to their sexually transmitted disease status or their reported frequency of recent unprotected sex.

The NK-diversity-dependent difference in these women's likelihood of HIV infection was huge. Those with the most NK-cell diversity were 10 times as likely as those with the least diversity to become infected.

A 10-fold risk increase based solely on NK-cell diversity is far from negligible, said Blish. "By way of comparison, having syphilis increases the risk of contracting HIV two- to four-fold, while circumcised men's HIV risk is reduced by a factor of 2.5 or 3," she said.

The observations could have clinical potential, most immediately by spotlighting people who need to be closely monitored for possible viral infections and, perhaps, prophylactically treated. But Blish cautioned that the study remains preliminary.

Provided by Stanford University Medical Center

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