Natural killer cells contribute to immune response against HIV

August 3 2011

A new study shows for the first time that natural killer (NK) cells, which are part of the body's first-line defence against infection, can contribute to the immune response against HIV. In an article in the August 4 issue of *Nature*, a research team based at the Ragon Institute of MGH, MIT and Harvard reports that the HIV strains infecting individuals with particular receptor molecules on their NK cells had variant forms of key viral proteins, implying that the virus had mutated to avoid NK cell activity.

"This study suggests for the first time that NK cells can impose immune pressure on HIV, something that had previously been described only for T cells and antibodies, adding an additional cell to the repertoire of those with anti-HIV activity," says Marcus Altfeld, MD, PhD, of the Ragon Institute and Massachusetts General Hospital (MGH), senior author of the Nature report. "The challenge now will be to translate those findings into new preventive or treatment strategies."

NK cells are part of the innate immune system, which mounts a generalized response against invading organisms. In contrast to the adaptive immune system, which includes T cells and antibodies, innate immune responses are thought to be short-lived and not directed against a particular virus or bacteria. NK cells bind to virus-infected cells or tumor cells and release cell-killing proteins that destroy their targets. Because NK cells have very strong cytotoxic activity, they need to be closely controlled, so their cell membranes are studded with both activating receptors that unleash the cell-killing response and inhibitory

receptors that keep it in check.

Previous research has shown that NK cells multiply during the earliest phase of HIV infection and that the cells can suppress HIV replication in cultured tissues. It also has been observed that infected individuals with particular versions of genes coding for the NK cell receptors called KIRs (killer immunoglobulin-like receptors) are better able to control HIV viral levels. But whether these genes allow NK cells to control HIV replication through direct recognition of infected cells or through another indirect mechanism is unknown. The researchers designed their study to test the hypothesis that mutations in the HIV proteins recognized by particular KIRs could allow the virus to escape NK cell activity, a finding that would support a role for NK cells in HIV control.

The Ragon investigators and colleagues at Microsoft Research began by analyzing the sequences of both HIV proteins and the genes encoding KIR molecules that regulate NK cell activity in samples from 91 infected individuals. Using tools designed to identify drug resistance mutations by detecting alterations in the viral genome found in the presence of drug, they associated particular variants in viral proteins with the presence of specific KIR genes, suggesting that the virus mutates in response to NK-cell-mediated anti-HIV activity.

The researchers also found that viral strains infecting individuals whose NK cells included an inhibitory receptor called KIR2DL2 were more likely to have variant forms of HIV that enhance viral interaction with that receptor, turning off the cell-killing activity. In cell cultures featuring NK cells with this receptor, replication of common forms of HIV was strongly suppressed, but the variant HIV continued to reproduce. Those results imply that, in the presence of NK cells expressing KIR2DL2, HIV mutates into a form that can "flip the off switch" and prevent NK cells from attacking infected cells.

"In those individuals that expressed KIR2DL2, HIV developed mutations that allowed it to evade killing by KIR2DL2-positive NK cells, but those mutations did not develop in participants who did not express that receptor," explains co-lead author Galit Alter, PhD, of Ragon and MGH. "We know that HIV mutates rapidly, and this is one of several ways that it has evolved to escape immune system pressure. But HIV does not have an unlimited ability to change its sequence, so a challenge for the future will be to combine the different anti-HIV arms of the immune system to control HIV or – if vaccines can generate the responses – to prevent infection."

Adds Altfeld, "The results of this study raise a number of interesting new questions. We need to better understand the molecular mechanisms that allow NK cells to recognize HIV-infected cells and learn how to manipulate these cells in humans for therapy or prevention. Recent animal studies have suggested that NK cells may develop immunologic memory responses, and if that ability is found in human cells, inducing such a response through vaccination is an exciting possibility we'd like to explore." Altfeld is an associate professor of Medicine and Alter an assistant professor of Medicine at Harvard Medical School.

Provided by Massachusetts General Hospital

Citation: Natural killer cells contribute to immune response against HIV (2011, August 3) retrieved 26 April 2024 from https://medicalxpress.com/news/2011-08-natural-killer-cells-contribute-immune.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.