HIV dearms protective protein in cells

April 15 2009

The AIDS-causing HIV specifically counteracts the mechanisms of human cells that protect these against viral infections - a special viral protein marks protective cellular proteins for their rapid destruction and thus diminishes the cell's supply. A team of researchers in Heidelberg under supervision of virologist Dr. Oliver Keppler demonstrated this mechanism for the first time in cell cultures, thus discovering a target for a novel treatment strategy.

Another important discovery of the Heidelberg virologists - this strategy of the human HIV is not effective in a rat model for AIDS. The protective protein in rats is immune to HIV counteraction. Consequently, HIV cannot propagate itself as easily in the animal model as in humans - one limitation of the current rat model. However, this new knowledge may enable an improvement of the small animal model developed by the Heidelberg researchers. The study was published in the journal *Cell Host & Microbe* in March 2009.

Newly formed viruses are retained at the cell surface

In addition to the immune system, the body can activate other protective mechanisms to fight or stop virus infections - the infected cells themselves dispose of several proteins that inhibit various steps of virus reproduction. In the presence of the protective protein CD317, newly formed viruses are tethered to the cell surface when they are in the process of leaving the cell and this prevents them from infecting other cells of the body. HIV overcomes this restriction by its protein Vpu by specifically counteracting this protective mechanism, which,

interestingly, is effective against many types of viruses.

Dr. Keppler's team of virologists from the Department of Virology at the Hygiene Institute of Heidelberg University Hospital (Medical Director: Professor Dr. Hans-Georg Kräusslich) studied how Vpu disrupts protection by CD317. They determined that in human cells in which Vpu was formed after infection with HIV, the pool of CD317 was reduced to about one quarter of the original amount. "When Vpu is present, CD317 is rapidly degraded by a cellular system. Vpu presumably binds to the CD317 and marks it for rapid destruction," explains Dr. Keppler.

The less CD317 is present in the cell, the more viruses can escape interception. "Disrupting this interaction between Vpu and CD317 to increase the cells' own protective mechanisms could thus be a promising strategy for therapy," says Dr. Keppler.

Rats and mice also have this protective protein; it has the same function and is able to block HIV. However, there is a significant difference - the Heidelberg virologists discovered that in rat cells, Vpu has no effect on CD317. "HIV is adapted to humans and the disruptive mechanism of Vpu does not affect protection against infection in animals," said Dr. Christine Goffinet, first author of the study.

Rat model now to be improved

This detail is important when one wants to imitate and study HIV infection in rats in an animal model - the infection in rats does not follow the same course as in humans, since fewer viruses are released due to the intact protective mechanisms. Based on the new research results, the Heidelberg scientists now hope to improve the current transgenic rat model of HIV infection. The goal is to suppress CD317 in rats through genetic engineering and thus achieve a degree of HIV infection that is more similar to that in humans.

As early as 2007, the researchers in Heidelberg first succeeded in making rats susceptible to HIV infection by specifically modifying their genetic material. They successfully tested drugs against HIV infection in humans in these transgenic rats. Using this small animal model, it is possible to test the efficacy of medications against the AIDS virus HIV rapidly and on a larger scale prior to clinical studies in humans and thus to accelerate the further development of virostatics.

More information: Christine Goffinet, Hans-Georg Kräusslich, and Oliver T. Keppler: HIV-1 Antagonism of CD317 Is Species Specific and Involves Vpu-Mediated Proteasomal Degradation of the Restriction Factor. *Cell Host & Microbe* 5, 285, March 19, 2009. DOI 10.1016/j.chom.2009.01.009

Source: University Hospital Heidelberg (news : web)