How HIV cripples immune cells

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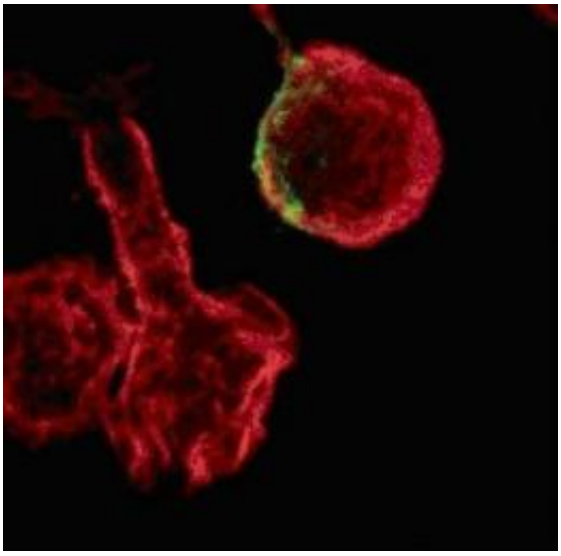

This is the actin cytoskeleton of human T-lymphocytes (red) in the presence of the stimulus CCL-19. An HIV-1 infection (HIV-1 protein CA in green) leads to the loss of actin reorganization and therefore of cell motility. Credit: Source: Hygiene Institute, Heidelberg University Hospital.

In order to be able to ward off disease pathogens, immune cells must be mobile and be able to establish contact with each other. The working group around Professor Dr. Oliver Fackler in the Virology Department of the Hygiene Institute of the Heidelberg University Hospital has discovered a mechanism in an animal model revealing how HIV, the AIDS pathogen, cripples immune cells: Cell mobility is inhibited by the HIV Nef protein. The study was published in the highly respected journal "*Cell Host & Microbe*". This discovery may have pointed the way

towards a new treatment approach.

Over 30 million persons worldwide are infected with HIV. Typically, after the initial infection accompanied by acute symptoms, there is a latency period of several years before the acquired immune deficiency syndrome (AIDS) manifests. The human immunodeficiency virus (HIV) has developed numerous strategies for eluding the body's defenses and the medications administered. The prerequisite for efficient reproduction of the virus in the patient's body is the virus's own Nef protein. Without Nef, the development of AIDS is significantly slowed or even stopped completely. The underlying mechanism of this observation was a complete mystery up to now, however.

HIV modifies the cell structure system of the host cells

Viruses alter the support structures of affected cells, enabling them to enter the cells more easily. The cell structure element actin, which also gives muscles their mobility, aids in the motility of immune cells. This is necessary for immune cells to be able to establish contact with each other and combat the virus. After each movement, actin must be returned to its original state in order to be available once again. HIV especially attacks immune cells of the T-helper type. These cells support not only direct "defense against the enemy", but are also necessary for building sufficient antibodies against the invader. For this, they must rely on their mobility.

Short-circuiting of two different signal paths in the cell by Nef

The researchers examined the movement of cells in living zebra fish embryos and were able to show that cell mobility is inhibited by the HIV

Nef protein. As they continued their experiments on cell cultures, they were able to explain the underlying mechanism: Nef causes an enzyme that normally has nothing to do with cell mobility to deactivate a regulator for actin regeneration. Nef therefore causes a short-circuit of two cellular mechanisms, thus inhibiting the reorganization of the cell structure element actin and the cell's ability to move. Thus, the affected immune cells can no longer fulfill their function.

"We speculate that the negative effect of Nef on the mobility of T-helper cells has far reaching consequences for the efficient formation of antibodies by B-lymphocytes in the patient. The mechanism we have described could be involved in the increasingly observed malfunction of B-lymphocytes in AIDS patients", explains Professor Fackler. Up to now, Nef has not been a target of antiviral therapy. Since one of the first molecular mechanisms has now been decoded, however, and the importance of Nef for the disease has become clearer, this could change in the future.

More information: HIV-1 Nef Interferes with Host Cell Motility by Deregulation of Cofilin. Bettina Stolp, Michal Reichman-Fried, Libin Abraham, Xiaoyu Pan, Simone I. Giese, Sebastian Hannemann, Polyxeni Goulimari, Erez Raz, Robert Grosse, Oliver T. Fackler. *Cell Host & Microbe*, 2009 Aug 20;6(2):174-86. DOI:10.1016/j.chom.2009.06.004

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