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10TH GERMAN AND 16TH AUSTRIAN AIDS-CONGRESS VIENNA

GERMAN AIDS PRIZE AWARDED TO YOUNG SCIENTIST IN BONN

GERMAN AIDS SOCIETY HONOURS TREND-SETTING RESEARCH

The German AIDS Prize of the German AIDS Society (DAIG) has been awarded to a trend-setting contribution on the mode of operation of the HI-virus on 3 June 2005 on the occasion of the German Austrian AIDS Congress in Vienna. The Bonn based scientist *Dr. Jacob Nattermann* received the award for his paper "HIV-1 infection leads to increased HLA-E expression resulting in impaired function of natural killer cells". The Award is endowed with 15.000 Euro by Essex Pharma.

Prof. Dr. Gabriele Arendt of University Clinic Düsseldorf valued the research in her speech on the occasion of the award ceremony in Vienna for "explaining important steps in the fight of the virus against the human immune system and demonstrating how the virus slips through the defence mechanisms of the human organism".

The laureate *Dr. med. Nattermann* (born 10 January 1974 in Halle/Saale) has been working at Medizinischen Klinik und Poliklinik I, Rheinische Friedrich-Wilhelms-Universität Bonn as Assistant Doctor since 2003. He studied medicine in Freiburg/ Breisgau and previously worked at the Howard Hughes Medical Institute, Dallas, among others.

The German AIDS Society has been awarding the German AIDS Prize for a number of years during the biannual AIDS Congress to honour extraordinary scientific accomplishments in the area of HIV/AIDS research. Please, find below a brief summary of this year's work.

N. H. Brockmeyer
President of the German AIDS Society

HIV-1 infection leads to increased HLA-E expression resulting in impaired function of natural killer cells

Jacob Nattermann[1], Hans Dieter Nischalke[1], Valeska Hofmeister[2], Bernd Kupfer[3], Golo Ahlenstiel[1], Georg Feldmann[1], Jürgen Rockstroh[1], Elisabeth H. Weiss[2], Tilman Sauerbruch[1], Ulrich Spengler[1]

[1]Department of Internal Medicine I, Rheinische Friedrich-Wilhelms-Universitaet, 53105 Bonn, Germany;
[2]Institute of Anthropology and Human Genetics, Ludwig-Maximilians-Universitaet, 80333 Munich, Germany;
[3]Institute for Medical Microbiology and Immunology, Rheinische Friedrich-Wilhelms-Universitaet, 53105 Bonn, Germany;

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Abstract: Infection with the human immunodeficiency virus (HIV) progressively impairs both the host's innate and adaptive immune functions. An important mechanism of viral immune evasion is to alter surface expression of classical major histocompatibility complex (MHC) class I molecules. Down-regulation of MHC I prevents lysis of HIV-infected cells by MHC I-restricted cytotoxic T-lymphocytes but may expose infected cells to attack by natural killer (NK) cells.

However, HIV-infected T-cells seem to be resistant to lysis by NK cells despite their reduced MHC class I expression. Importantly, HIV-mediated down-modulation of MHC I molecules is specific in that it affects only HLA-A and –B, but not HLA-C and HLA-E. HLA-E is a non-classical MHC I molecule, which has been shown to be an important regulator of NK cell function by interacting with the inhibitory NK cell receptor (iNKR) complex CD94/NKG2A.

Analyzing HLA-E expression in HIV infection, we found that HIV-positive patients expressed a significantly higher proportion of HLA-E-positive CD4+ cells than HIV-negative individuals ($p = 0.001$). Accordingly, CD4(+) lymphocytes from HIV-infected individuals showed a higher HLA-E-specific mean fluorescence intensity (MFI), which is a marker for surface density of a given molecule, as compared to healthy patients.

Furthermore, we found that in vitro HIV-1 infection resulted in up-regulation of HLA-E expression independently from the type of infecting HIV-1 strain.

In functional tests we confirmed that HIV-infected lymphocytes were resistant to lysis by the human nat-

ural killer cell line NKL despite reduced expression of classical MHC I molecules. Of note, blocking of the inhibitory NKG2A receptor, which specifically interacts with HLA-E, restored cytolytic activity of NKL cells against in vitro HIV-infected lymphocytes.

Commonly, surface expression of HLA-E depends on binding of appropriate peptides. Performing a database search, we identified the well characterized HLA-A2 restricted HIV-epitope HIV $p24_{14-22}$ as a candidate peptide. Using HLA-E transfected K-562 cells we demonstrated that this peptide indeed binds to HLA-E resulting in a enhanced expression of HLA-E and impaired NK cell function. Blocking of the inhibitory NK cell receptor CD94/NKG2A with a NKG2A-specific monoclonal antibody abolished inhibition of cytolysis, showing that cytotoxicity of NKL cells was impaired by the interaction of the HLA-E/ HIV $p24_{14-22}$-complex with the inhibitory NK cell receptor CD94/NKG2A. Likewise, blocking of HLA-E on K-562 HLA-E cells after incubation with HIV p2412-24 restored susceptibility of target cells to NK cell lysis.

In conclusion, we show that HIV-1 can give rise to a class of peptides, that not only correspond to a MHC class I restricted T cell epitope but that can also act as HLA-E ligand and so inhibit NK cell cytotoxicity. Immune recognition of such HIV-derived epitopes via classical and non-classical MHC class I molecules may lead to divergent outcomes, depending on the immunomodulating effects of viral infections that are exerted on classical MHC I and HLA-E expression, respectively.