receptor NKp30 is essential for the killing of DCs; however, inhibition of NKp30 has no effect on the DC-induced expansion of NK cells. The other groups also failed to identify the DC factors that mediate NK-cell activation.

Together, these studies describe a new regulatory relationship in innate immunity. In a commentary in the same issue, Lawrence Zitvogel outlines the ways in which this two-way negative and positive cross-regulation might co-ordinate the initiation and dampening down of innate responses to infection.

Jennifer Bell

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The splenocytes of the mice treated with Tim-3 antibody showed higher basal proliferation and the spleens contained higher numbers of activated macrophages compared with control animals. The enhanced background proliferation in the Tim-3-treated mice was dependent on an interaction between anti-Tim-3-treated T cells and macrophages. These data indicate that engagement of Tim-3 during T-cell activation affects interactions between T cells and macrophages, and results in macrophage expansion and activation, which is probably responsible for the increased severity of this autoimmune disease.

The authors conclude that, because T_H1 and T_H2 cells cross-regulate each other's function, expression of Tim-3 on T_H1 cells might, in addition to its role in development of autoimmunity, also have therapeutic implications for asthma and allergy.

Jenny Buckland

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T lymphocyte: Helpers

HIV

A SIGN for HIV

Cellular entry of HIV is dependent on interactions between the viral envelope glycoprotein, host CD4 molecules and chemokine receptors (CCR5 and CXCR4). Much of the work on mechanisms of HIV entry has been performed *in vitro*, and additonal factors that could be important for infections *in vivo* remain poorly characterized. Recent work on HIV infection has focused on the role of the dendritic cell (DC)-specific lectin DC-SIGN (dendritic-cell-specific intercellular adhesion molecule (ICAM)-3-grabbing non-integrin). Two papers in *Immunity* now show that the HIV-1 protein Nef upregulates DC-SIGN expression on DCs and that binding of DC-SIGN mediates internalization of virus particles into a non-lysosomal compartment, which enhances infectivity.

DC-SIGN was previously shown to bind to glycoprotein 120 (gp120) of HIV. DCs that express DC-SIGN can retain virions in an infectious state for several days and augment infection of T cells, although HIV is known to replicate inefficiently in DCs. It has been proposed that DC-mediated transport of virus from mucosal sites to secondary lymphoid tissues is important for the efficient transfer of virus to T cells, but whether the virus is actually internalized in DCs remains unclear.

The study from Olivier Schwartz' group examined the role of HIV-1 Nef in viral infectivity. DC-SIGN was found to be upregulated at the surface of infected, but not uninfected, cells. Upregulation was dependent on Nef, given that DCs infected with Nef-deficient virus showed DC-SIGN staining patterns similar to uninfected cells. Two putative internalization signals — a tyrosine-based motif and a dileucine motif — are located in the cytoplasmic tail of DC-SIGN. The role of these motifs was examined using DC-SIGN-negative HeLa cells transfected with plasmids encoding DC-SIGN or Nef, or both. HeLa cells expressing wild-type DC-SIGN had very little surface expression but a high rate of endocytosis. By contrast, dileucine mutants of DC-SIGN showed high levels of surface expression with little or no internalization. Co-transfection with wild-type DC-SIGN and Nef resulted in stable expression of DC-SIGN at the plasma membrane. These results show that Nef upregulates DC-SIGN surface expression by preventing internalization, which enhances the ability of DCs to form clusters with lymphocytes and facilitates viral transmission.

The study from Dan Littman's group focused on the role of DC-SIGN in internalization and infectivity of HIV-1. DC-SIGN was shown to mediate the internalization of gp120 in a monocyte cell line transduced with a DC-SIGN-encoding virus. Fluorescence confocal microscopy showed that whole viral particles could be internalized by human DCs. After 45 minutes, most of the viral particles were localized in a non-lysosomal compartment, and these could be transmitted to a second target cell. Low pH in this compartment was important for maintenance of infectivity, given that neutralization of pH abolished the ability of DC-SIGN-positive cells to enhance infection of T cells.

Taken together, these results suggest that HIV has evolved to exploit the function of DCs and enhance viral transmissibility and infectivity. Although several questions — such as how HIV returns to the cell surface and what regulates this process — remain to be answered, this new work has implications for our understanding of HIV pathogenesis.

Elaine Bell

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WEB SITE
Dan Littman's lab: http://www.med.nyu.edu/people/D.Littman.html

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