

INTERVIEW about

DC/NK cells interaction with HIV infection with

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Why can HIV survive and replicate in the presence of dendritic cells and natural killer cells?

Claudio Fortis: Dendritic cells (DC) and natural killer (NK) cells, the main cellular components of innate immunity, plays a crucial role in controlling HIV infection and disease. As first line of defense, due primarily to its peculiar tissue distribution and rapid activation, the innate immune system may potentially prevent HIV transmission and provide the time and conditions for adaptive immune responses to develop (1). These observations imply that in order for HIV to infect and spread in the human host, it must firstly escape the control of innate immunity. Several impairments of both DC and NK cell function and number have been observed in most HIV-infected individuals. Of note, HIV, in addition to its capacity to productively infect immature (i)DC (2) and to be

transported by DC to lymph node to mediate trans-infection of CD4⁺ T cells (3,4) can block DC maturation (5). This effect may result in T cell anergy and IL-10 dependent suppression (5), and suggests that HIV-infected DC are prone to be more tolerogenic than immunogenic (6). Also NK cell function is impaired during HIV infection (7) both in terms of cytotoxic activity, mainly mediated by a downregulation of activating natural cytotoxicity receptors (NCR) (8), and of the capacity to secrete CCR5-binding chemokines able to block virus entry (9). Thus, the impaired NK cell function results in a reduced capacity of eliminating effectively infected cells and of limiting virus replication, ultimately favoring viral escape from innate immune surveillance (6).

What is the result of NK-cell-mediated cytotoxicity after HBV-infection in HIV-positive patients?

Claudio Fortis: The coinfection with hepatitis B virus (HBV) seems not to affect HIV infection toward a rapid progression and AIDS, even if not totally convincing results have been reported in the literature. We have recently studied the NK cell activity in a group of patients with acute HBV infection both HIV-negative and -positive

(10). In these patients, we have documented a significant decrease of NK cell-mediated cytotoxic activity compared to healthy individuals suggesting that also in acute HBV infection NK cell activity may be impaired, irrespective of HIV infection. However, in one HIV-infected and severely immunocompromised patient, in whom HBV infection

rapidly evolved to fulminant hepatitis (FH) and death, NK cell activity was abnormally and significantly higher than in the remaining patients and healthy individuals. Normally, during the incubation of acute hepatitis B, an increase in the number of NK cells precedes the peak of HBV replication (first phase), and is followed 2-4 weeks later by the appearance of specific adaptive immune responses (second phase) that generally induce complete virus clearance, with a concomitant reduction in number and function of NK cells (11). In this phase, a fundamental role is played by CD4⁺ T cells, which help CD8 T cell specific responses. We have hypothesized that in the patient with severe HIV infection and

HBV-related FH, the induction of the second phase could be compromised (with low CD8 T cell specific responses) as a consequence of the very low number of CD4⁺ T cells (12 cells/ μ l). The consequent negative feed-back that should reduce number and activation level of NK cells does not occur, as documented by the increase in circulating NK cells and by their very high cytotoxic potential. Unlike specific CD8 T cells, NK cells may kill not only HBV-infected, but also bystander hepatocytes, in which the ligands of NK activating receptors could be induced by local inflammatory signals. In this case, cytopathic mechanisms prevail over regenerative mechanisms, inducing the dramatic evolution toward FH.

Is there a special role of infected dendritic cells?

Claudio Fortis: DC express both CD4 and entry chemokine coreceptors CCR5 and CXCR4 at their cell surface and can be productively infected by HIV, although with a lower efficiency than CD4⁺ T cells and macrophages (2). In addition, the HIV-1 envelope glycoprotein gp120 Env can interact with several C-type lectin receptors (CLR) expressed on the surface of DC, like DC-specific intracellular adhesion molecule-grabbin nonintegrin (DC-SIGN, CD209) (3). Once bound to a CLR, HIV is internalized into a low pH non-lysosomal compartment where it retains its infectivity for several days (12), a timeframe compatible with the time required for migration of DC to regional LN, their differentiation into mature DC and their trans-infection of CD4⁺ T cells (4) (Fig. 1). Recently, it has been demonstrated that a bidirectional cross-talk between iDC and resting NK cells leads to activation of both cell types (13). When activated NK cells overwhelm DC

by numbers they became able to kill iDC (14). Thus, the possibility that iDC may escape NK cell-mediated lysis could represent a fundamental event in the pathogenesis of HIV infection, especially during its early phase. To verify this possibility, we recently tested the in vitro susceptibility of iDC to lysis mediated by autologous NK cells in early vs. chronically HIV-infected individuals (15). A reduced killing capacity of NK cells was observed in early HIV-infected individuals and was inversely correlated with the levels of viremia and directly correlated with the percentage of circulating CD4⁺ T cells. The NK cell lytic capacity was lost in chronic patients, irrespective of their current antiretroviral therapy, and of virological and immunological parameters. These findings suggest that a dysregulation in the NK/DC homeostasis occurs early in HIV infection and may represent a potential mechanism through which HIV escapes NK cell-mediated immune surveillance.

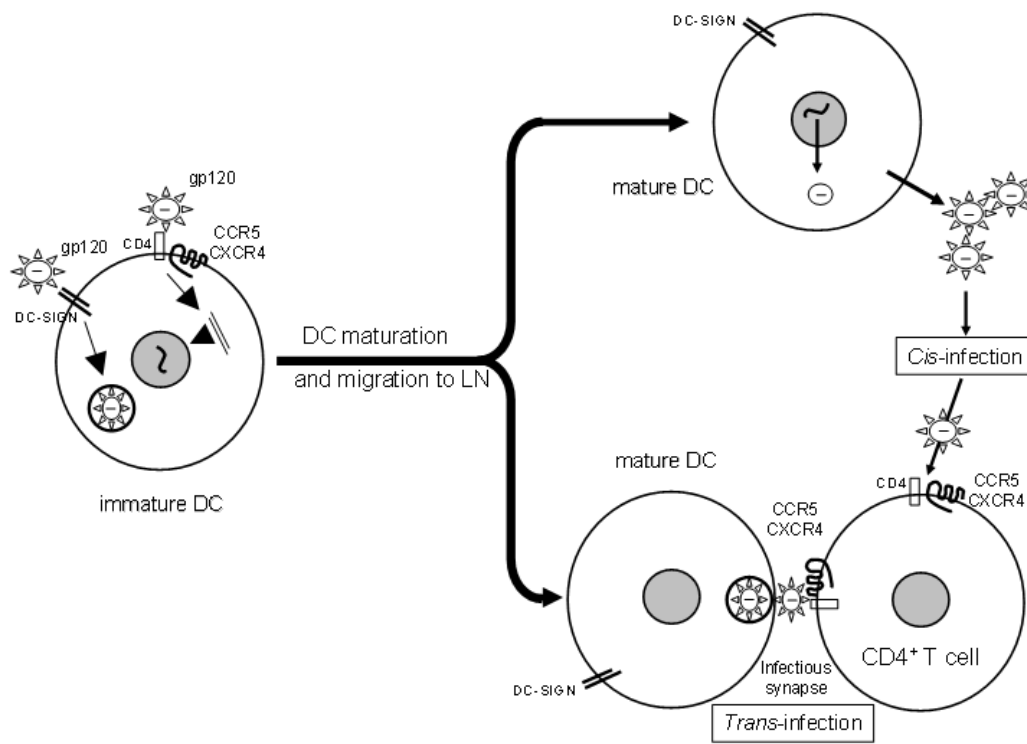
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Figure 1: Model of HIV dissemination from DC to CD4 T lymphocytes. HIV can be captured by iDC either via gp120 Env interaction with CD4 and CCR5 or CXCR4 or with DC-SIGN (or other CLR). Following this latter interaction the virus is internalized in a low pH non-lysosomal compartment where it retains its infectivity for several days and can then infect permissive cells in the lymphoid tissue in trans (from Fortis and Poli. Immunol Rev 2005, 33/1:1-21).
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