inside blood

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Comment on Groot et al, page 1957

Opposing roles of dendritic cell subsets in HIV-1 infection

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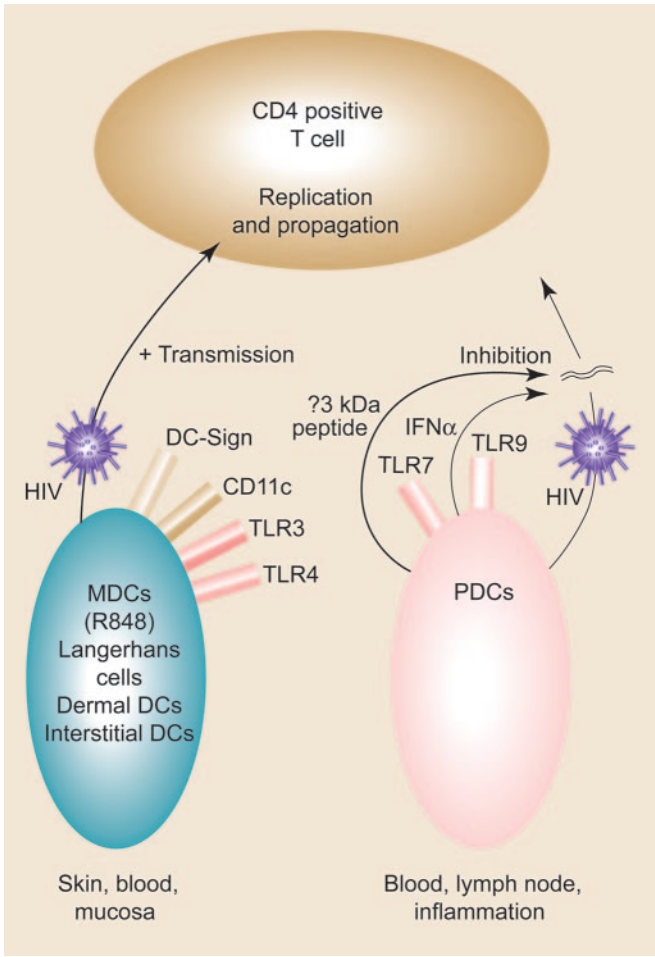
In this issue of *Blood*, Groot and colleagues clarify the function of the 2 major types of dendritic cells in the transmission, propagation, and—importantly—the inhibition of infection with HIV-1.

Groot and colleagues have identified a new small anti-HIV factor secreted by one of the 2 major types of dendritic cells (DCs), adding to the armamentarium of natural antiviral compounds. Bench-to-bedside drug discovery programs have yet to take advantage of these innate constitutive and/or inducible molecules, despite their obvious attractiveness in terms of presumed efficacy and toxicity profiles.

Previous data have shown that during HIV infection both myeloid DCs (MDCs; interleukin-12 [IL-12]–producing) and plasmacytoid DCs (PDC; interferon-α [IFN-α–producing) are reduced in number,[1] that their function is impaired, and that through C-type lectins such as DC-specific intercellular adhesion molecule 3–grabbing nonintegrin (DC-SIGN) they capture and transmit the virus at the DC–T-cell interface, the infectious synapse.[2,3]

This study, which uses isolated donor-matched DCs rather than monocyte-derived cells, adds a number of new observations with functional consequences. MDCs enhance and PDCs inhibit HIV replication in T cells, a process mediated by different mechanisms for each DC subset: (1) MDCs actively transmit HIV to T cells, and factors that are secreted during MDC maturation or after T-cell encounter probably do not influence this process; and (2) secreted factors during PDC activation were completely responsible for the inhibition of HIV-1 infection of T cells. Here, PDC activation appears entirely responsible for the inhibition of HIV-1 replication.

MDCs, on the other hand, have differing transmission efficiencies (R-848 being the most superior), and this is not due to differences in expression of integrins (ICAM-1, -2, -3, or LFA-1), CD83/CD86 expression, or the amount of HIV capture. Furthermore, PDCs secrete high amounts of IFN-α, which inhibits HIV replication, but most interestingly, they secrete a small molecule less than 3 kDa in size that inhibits HIV replication. Since it is sensitive to heat, this molecule is likely to be a polypeptide. This molecule was found by passing supernatants through centrifugal filters and testing their capacity to inhibit HIV-1 infection in a single-cycle replication assay with LuSIV cells. The smallest fraction contained no IFN-α, and the addition of neutralizing antibodies against type 1 IFNs did not change inhibition.



Opposing roles of DC subsets in HIV infection. MDCs enhance HIV-1, with transmission of HIV-1 across the infectious synapse; PDCs inhibit this process via IFN-α and a new small molecule. Illustration by Paulette Dennis.

Not only do Groot and colleagues discuss opposing roles of CD11c-positive and -negative DCs, their discovery of a novel, small, naturally occurring host molecule might lead to the discovery of a new unknown anti-HIV compound. While cause and effect remains to be established (is the molecule secreted as a consequence of HIV infection or is it constitutively produced?), it is notable that the passions and polemic surrounding similar discoveries in the past have not yet led to the identity of some naturally occurring anti-HIV secreted

factors[4] (though they tend to have a much higher molecular weight than the compound here). However, this is unquestionably a worthwhile endeavor. We learn an enormous amount from individuals and animals that become infected and do not develop uncontrollable viremia with suppression of $CD4^+$ T cells.[5] One appropriate step would be to identify this small molecule and determine its role in the long-term nonprogressor process. In addition, there are probably enough data now for a randomised DC-based therapeutic vaccine trial in HIV. Based on the paper herein by Groot et al, this should be based on the PDC model. ■

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TRANSPLANTATION

Comment on Amrolia et al, page 1797

Weeding out dangerous alloresponses by graft engineering

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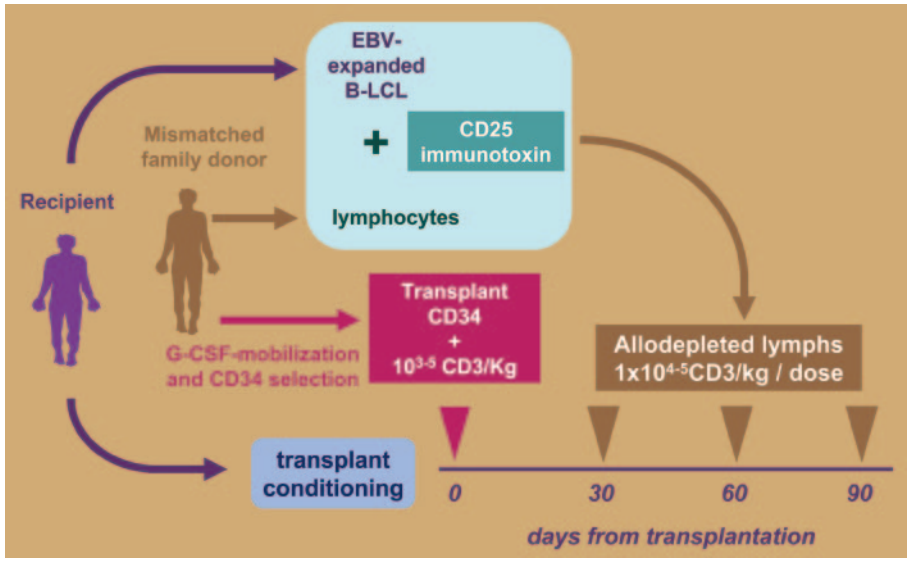
Hematopoietic stem cell grafts engineered to eliminate graft-versus-host alloreactivity rapidly restore cell-mediated immunity in human leukocyte antigen–mismatched pediatric transplant patients.

There is a high mortality rate from treatment failure in patients receiving stem cell transplants from human leukocyte antigen–haploidentical family donors. With immunosuppression and profound T-cell depletion, acute graft-versus-host disease (GVHD) can be avoided, but the price paid is severely delayed immune recovery, high mortality from infection, and reduction in any T-cell–mediated graft-versus-leukemia (GVL) effect. The paper by Amrolia and colleagues in this issue of *Blood* describes a way to break this impasse between GVHD control and compromised immune recovery. Following T-cell–depleted stem cell transplantation (SCT), patients were infused with up to 10^5/kg donor T cells depleted of alloimmune responsiveness at monthly intervals after transplantation. The process of allodepletion involved a 72-hour in vitro exposure of donor lymphocytes to the recipient's irradiated antigen-presenting cells (APCs). Activated donor T cells up-regulating the CD25 interleukin-2 receptor were eliminated by adding a ricin-conjugated anti-CD25. The allodepleted washed product was then transfused (see figure). In a clinical trial, 16 pediatric recipients of T-cell–depleted mismatched stem cell transplants received allodepleted T cells. Only 2 developed grade II or higher acute GVHD. Doses of 10^5/kg, but not 10^4/kg, allodepleted T cells resulted in impressive early numerical and functional lymphocyte recovery derived from the peripheral expansion of memory T cells. The strength of this article is the authors' meticulous description of immune recovery, using Vβ spectratyping T-cell repertoire analysis, naive effector–memory phenotyping, T-cell–receptor excision circle (TREC) analysis, and viral-specific T-cell responses to cytomegalovirus, Epstein-Barr virus (EBV), and adenovirus. This study is an important step toward the goal of engineering stem cell transplants to rapidly reconstitute immunity without causing GVHD. Results extend observations from other trials using the CD25 immunotoxin, confirming that allodepletion can reduce GVHD while supplying postthymic T cells for immunity reconstitution.[1-3] However, there is still a long way to go with this approach. Not surprisingly, only 5 of these high-risk refractory patients survived disease free; 9 died from relapsed leukemia or infection.

Much remains to be understood about the mechanism of allodepletion and ways to optimize it: residual unmanipulated T cells in the graft may have contributed to both GVHD and immune recovery, and we can only guess at the identity of the antigenic targets stimulating the donor alloresponse. Furthermore, CD25 depletion might even risk enhancing



Graft engineering to prevent graft-versus-host disease. Mismatched T-cell–depleted stem cell transplantation followed by transfusion of allodepleted donor lymphocytes.